Appendix C.2 May 2021 Risk Dossiers

BORIC ACID (CAS NO. [redacted]
SODIUM TETRABORATE DECAHYDRATE (BORAX) (CAS NO. [redacted]

This dossier presents the most critical studies pertinent to the risk assessment of two boron compounds (boric acid and borax) in their use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): boric acid

CAS RN: [redacted]

Molecular formula: BH_3O_3

Molecular weight: 61.84 g/mol

Synonyms: orthoboric acid; boracic acid; borofax; boron hydroxide; boron trihydroxide

SMILES: B(O)(O)O

Chemical Name (IUPAC): disodium bicyclo[3.3.1]tetraboroxane-3,7-bis(olate)

CAS RN: [redacted]

Molecular formula: $B_4Na_2O_7$

Molecular weight: 381.4 g/mol

Synonyms: sodium tetraborate decahydrate; borax; monosodium metaborate; sodium borate; sodium borate (NaBO2); sodium diborate; sodium meta borate; sodium metaborate; sodium tetraborate

SMILES: B1(OB2OB(OB(O1)O2)[O-])[O-].O.O.O.O.O.O.O.O.O.O.[Na+].[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Limited measured data are available for borax. In the environment, borax is expected to dissociate and/or hydrolyse to release boric acid at neutral pH. Therefore, measured data available for boric acid have been presented as analogue data for this substance.

Key physical and chemical properties for boric acid are shown in Table 1.

Table 1: Overview of the Physico-chemical Properties of Boric Acid

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, odourless, crystalline solid	2	ECHA
Melting Point	> 100°C (decomposes)	1	ECHA
Boiling Point	Not Applicable	-	ECHA
Density	1,489 kg/m^3 @ 20°C	1	ECHA
Vapour Pressure	0 Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})	Not Applicable, substance is inorganic	-	ECHA
Water Solubility	48.8 g/L @ 20°C	1	ECHA
Dissociation Constant (pKa)	8.94 @ 20°C	1	ECHA

Boron is almost exclusively found in the environment in the form of boron-oxygen (B-O) compounds, which are often referred to as borates. The high strength of the B-O bond relative to those between boron and other elements makes boron oxide compounds stable compared to nearly all non-oxide boron materials. Indeed, the B-O bond is among the strongest found in the chemistry of naturally occurring inorganic substances (ECHA).

In the environment, borates and compounds of boric acid will dissociate and/or hydrolyse to form the same boron species. For example, when borax dissolves in dilute solutions, it dissociates into Na^+ ions and the tetraborate anion ($B_4O_5(OH)_4^{2-}$). Boric acid ($B(OH)_3$) is formed following acid catalysed hydrolysis of the tetraborate anion. Under alkaline conditions, dilute solutions of the tetraborate anion depolymerise rapidly to the mononuclear borate anion ($B(OH)_4^-$) (NICNAS, 2019).

Boric acid is a Lewis acid that acts as a weak monoprotic acid by accepting OH^- and not as a proton donor (pKa 9.14). Therefore, at the near neutral pH of most environmental systems and at low concentrations (< 0.025 mol B/L), the neutral mononuclear species ($B(OH)_3$) will dominate and only a small proportion of boron will exist as the borate monoanion, $B(OH)_4^-$. Therefore, in the environment boric acid is in equilibrium with borate anions. Both species are very stable as they do not undergo biotransformation or redox reactions under normal environmental conditions (NICNAS, 2019).

Exposure to borates are often expressed in terms of boron (B) equivalents based on the fraction of boron in the source substance on a molecular weight basis. The B equivalents used are a generic designation rather than a designation of the element boron. The factor for converting boric acid to B-equivalents is 0.1748. The factor for converting borax to B-equivalents is 0.2149.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Borax will transform into boric acid in the aquatic environment. In the environment boric acid is in equilibrium with borate anions. Degradation is not applicable to inorganic borates.

Boric acid is highly soluble in water. Some partitioning to soil and sediment does occur, but this adsorption is pH dependent. It has a low potential for bioaccumulation.

B. Partitioning

Borax will transform into boric acid in the aquatic environment. In the environment boric acid is in equilibrium with borate anions. Both species are very stable as they do not undergo biotransformation or redox reactions under normal environmental conditions. Boric acid is highly water soluble and it tends to remain in surface waters. Although some partitioning from water to soil and sediment does occur, the adsorption is pH dependent with the greatest adsorption occurring under alkaline conditions (pH 7.5 to 9.0) (NICNAS, 2019).

C. Biodegradation

Degradation is not applicable to inorganic borates. It is not subject to hydrolysis, photodegradation or biodegradation (ECHA). Inorganic borates are subject to chemical transformation processes (adsorption, complexation, precipitation, fixation) once released into the environment (ECHA).

D. Environmental Distribution

The Kp value for boron compounds was calculated as the median of all measured Kp values from the GEMAS project (Geochemical Mapping of Agricultural and Grazing Land Soil project): 2.19 L/kg dry weight (ECHA) [KI score = 2]. The chemistry of boron in soils and aquatic systems is simplified by the absence of oxidation-reduction reactions or volatilisation. Redox processes can mobilise Fe oxides and Mn oxides, which may lead to a release of boron in aquatic systems. Generally, sediments are characterised with higher pH values than the soil matrix, which increases the boron sorption capacity (ECHA).

If released to soil, based on this low Kp value, low vapour pressure and high water solubility, boric acid and borax are considered relatively mobile in the environment, under certain conditions (ECHA).

E. Bioaccumulation

The WHO review of boron (WHO, 1998) noted that “highly water soluble materials are unlikely to bioaccumulate to any significant degree and that borate species are all present essentially as un-dissociated and highly soluble boric acid at neutral pH”. BCFs of < 0.1 to 10.5 L/kg have been reported from laboratory tests of fish and oysters (Hamilton and Wiedmeyer, 1990; Thompson et al., 1976).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Borax exhibits low acute toxicity by the oral and dermal routes. Boric acid exhibits low acute toxicity by the oral, dermal and inhalation routes. Neither substance is a skin or eye irritant, nor a skin sensitiser. In aqueous media at physiological pH, borax will predominantly exist as un-dissociated boric acid. The developing foetus and the testes are the two most sensitive targets of boron toxicity in multiple species. The testicular effects include reduced organ weight and organ to body weight ratio, atrophy, degeneration of the spermatogenic

epithelium, impaired spermatogenesis, reduced fertility and sterility. The developmental effects from boron exposure include high prenatal mortality, reduced foetal body weight, malformations and variations. Repeated inhalation exposure to read-across substance boron oxide resulted in slight irritation to the respiratory tract, but no systemic toxicity. Boric acid was not genotoxic, and boric acid and borax was not carcinogenic to rodents.

B. Toxicokinetics

Boric acid is not metabolised in either animals or humans, owing to the high energy level required (523 kJ/mol) to break the B-O bond. Other inorganic borates convert to boric acid at physiological pH in the aqueous layer overlying the mucosal surfaces prior to absorption. Most of the simple inorganic borates exist predominantly as undissociated boric acid in dilute aqueous solution at physiological and environmental pH, leading to the conclusion that the main species in the plasma of mammals is un-dissociated boric acid. Since other borates dissociate to form boric acid in aqueous solutions, they too can be considered to exist as un-dissociated boric acid under the same conditions. Additional support for this derives from studies in which more than 90% of administered doses of inorganic borates are excreted in the urine as boric acid. Absorption of borates via the oral route is nearly 100%. For the inhalation route also, 100% absorption is assumed as worst-case scenario. Dermal absorption through intact skin is very low with a percent dose absorbed of 0.226 ± 0.125 in humans. Using the % dose absorbed plus standard deviation (SD) for boric acid, a dermal absorption for borates of 0.5% (rounded from 0.45%) can be assumed as a worse-case estimate (ECHA).

In the blood boric acid is the main species present and is not further metabolised. Boric acid is distributed rapidly and evenly through the body, with concentrations in bone 2 to 3 times higher than in other tissues. Boric acid is excreted rapidly, with elimination half-lives of 1 hour in the mouse, 3 hours in the rat and < 27.8 hours in humans, and has low potential for accumulation. Boric acid is mainly excreted in the urine (ECHA).

C. Acute Toxicity

The oral LD_{50} of borax in rats is > 2,500 mg/kg (ECHA) [KI score = 1]. The oral LD_{50} of boric acid in rats is 3,450 mg/kg (ECHA) [KI score = 1].

There are no acute inhalation studies on borax. In a read-across study for borax, the 4-hour inhalation LC_{50} value for disodium tetraborate pentahydrate in rats is > 2.04 mg/L (ECHA) [KI score = 1]. The 4-hour inhalation LC_{50} value for boric acid in rats is > 2.01 mg/L. The mass median aerodynamic diameter (MMAD) was 2.8 µm (ECHA) [KI score = 1]. In another study, the 4-hour inhalation LC_{50} value for boric acid in rats was > 2.03 mg/L (ECHA) [KI score = 1].

The dermal LD_{50} of borax in rabbits is > 2,000 mg/kg (ECHA) [KI score = 2]. The dermal LD_{50} of boric acid in rabbits is > 2,000 mg/kg (ECHA) [KI score = 1].

D. Irritation

Application of 0.5 g of borax to the skin of rabbits for 4 hours under occlusive conditions was not irritating. The mean erythema and oedema scores were 0.00 (ECHA) [KI scores = 2]. Application of 0.5 g. of boric acid to the skin of rabbits for 24 hours under occlusive conditions was not irritating. The mean of the 24 and 72-hour scores were 0.13 for erythema and 0.00 for oedema (ECHA) [KI scores = 1].

Disodium tetraborates are eye irritants. Instillation of 0.08 mL of read-across substance disodium tetraborate pentahydrate into the eyes of rabbits was slightly irritating. The mean of 24, 48, and 72 hours scores were 0.22 for corneal opacity; 0.22 for iridial lesions; 2.8 for conjunctival redness; and 1.89 for chemosis. The effects were fully reversible (ECHA) [KI score = 1].

Boric acid induced mild conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days (ECHA). Instillation of 100 mg of boric acid into the eyes of rabbits was slightly irritating. The mean of 24, 48, and 72-hour scores were 0.00 for corneal opacity; 0.11 for iridial lesions; 0.94 for conjunctival redness; and 0.56 for chemosis (ECHA) [KI score = 1].

E. Sensitisation

There are no skin sensitisation studies on Borax. Read-across substances disodium tetraborate pentahydrate was not a skin sensitiser to guinea pigs in a Buehler test (ECHA) [KI score = 1].

Boric acid was not a skin sensitiser to guinea pigs in a Buehler test (ECHA) [KI score = 1]. Sodium tetraborate pentahydrate was not a skin sensitiser to guinea pigs in a Buehler test (ECHA) [KI score = 1]. Sodium tetraborate decahydrate was not a skin sensitiser to guinea pigs in a Buehler test (ECHA) [KI score = 1].

F. Repeated Dose Toxicity

<u>Oral</u>

Male and female SD rats were given in their feed boric acid at doses of 0, 52.5, 175, 525, 1,750 or 5,250 ppm B equivalents for 90 days. The average intake has been estimated to be approximately 0, 2.6, 8.8, 26, 87.5 or 262.5 mg B/kg/day, respectively (USEPA, 2004). By week 6, all animals in the highest dose died. Clinical signs in the top two dose levels were rapid respiration, inflamed eyes, swollen paws and desquamated skin on the paws and tails. There was also reduced food consumption and body weight gain. The 1,750 ppm females showed reduced liver, spleen ovary and adrenal weights; the 1,750 ppm males showed reduced liver, spleen, kidney, testes and adrenal weights. The adrenals of 4 of the 1,750 ppm males showed minor increases in lipid content and size of the cells in the zona reticularis. Atrophied testis (complete atrophy of the spermatogenic epithelium and decreased in the size of the seminiferous tubules) was seen in all of the 1,750 ppm males. One 525 ppm male had partial testicular atrophy. The NOAEL for this study is 175 ppm boron or 8.8 mg B/kg/day (Weir and Fisher, 1972) [KI score = 2].

Male and female SD rats were given in their diet borax at doses of 0, 52.5, 175, 525, 1,750 or 5,250 ppm B equivalents for 90 days. The average intake has been estimated to be approximately 0, 2.6, 8.8, 26, 87.5 or 262.5 mg B/kg/day, respectively (USEPA, 2004). By week 6, all the animals in the highest dose died. Clinical signs in the top two dose levels were rapid respiration, inflamed eyes, swollen paws and desquamated skin on the paws and tails. There was also reduced food consumption and body weight gain. The 1,750 ppm females showed reduced liver, spleen and ovary weights; the 1,750 ppm males showed reduced liver, spleen, kidney, testes and brain weights. The adrenals of the majority of the 1,750 ppm males and females showed slight to moderate increases in lipid content and size of the cells in the zona reticularis. Atrophied testis (complete atrophy of the spermatogenic epithelium

and decreased in the size of the seminiferous tubules) was seen in all the 1,750 ppm males. Four 525 ppm males had partial testicular atrophy. Spermatogenic arrest was found in one 525 ppm male. The NOAEL for this study is 175 ppm boron or 8.8 mg B/kg/day (Weir and Fisher, 1972) [KI score = 2].

Male and female B6CF1_1 mice were given in the diet 0, 1,200, 2,500, 5,000, 10,000 or 20,000 ppm boric acid for 13 weeks (control and highest dose group) or 16 weeks (remaining dose groups). These dietary levels correspond to approximately 0, 34, 70, 141, 281 and 563 mg B/kg/day for males, respectively: and 0, 47, 97, 194, 388 and 776 mg B/kg/day for females, respectively (USEPA, 2004). There was mortality (8/10 males; 6/10 females) in the 20,000 ppm group, as well as hyperkeratosis and acanthosis. One male also died in 10,000 ppm group. Degeneration or atrophy of the seminiferous tubules occurred in the ≥ 5,000 ppm males. Minimal to mild extramedullary haematopoiesis of the spleen was observed in all dose groups. The LOAEL for this study is 1,200 ppm, corresponding to 34 and 47 mg B/kg/day for males and females, respectively (NTP, 1987) [KI score = 2].

Male and female SD rats were given in their diet 0, 117, 350 or 1,170 ppm boric acid for two years. The average intake has been estimated to be approximately 0, 5.9, 17.5 or 58.5 mg B/kg/day, respectively (USEPA, 2004). The 1,170 ppm rats had decreased food consumption during the first 13 weeks of the study and suppressed growth throughout the study. Signs of toxicity in the 1,170 ppm animals included swelling and desquamation of the paws, scaly tails, inflammation of the eyelids and bloody discharge from the eyes. All the 1,170 ppm males had testicular atrophy at the 6, 12 and 24-month time points. The seminiferous epithelium was atrophied, and the tubular size in the testes was decreased. There were significant decreases in the absolute and relative testes weights. Brain and relative thyroid weights were increased. The NOAEL for this study is 350 ppm B equivalents or 17.5 mg B/kg/day (Weir and Fisher, 1972) [KI score = 2].

Male and female B6C3F_1 mice were given up to 20,000 ppm boric acid in their feed for 13 weeks (NTP, 1987). Eight out of the 10 males and 6 out of the 10 females from the 20,000 ppm group died and 1 of the 10 males from the 10,000 ppm group died before the end of the study. Symptoms included nervousness, haunched appearance, dehydration, foot lesions and scaly tails. Incidences of extra medullary haematopoiesis of the spleen were observed of varying severity in all dose groups for both males and females and hyperkeratosis and/or acanthosis of the stomach observed at the highest dose only in both males and females. At doses > 5,000 ppm (142 mg B/kg bw for the male), degeneration or atrophy of the seminiferous tubules was observed. The NOAEL for this study is 34 mg B/kg/day (NTP, 1987) [KI score = 2].

Inhalation

Male and female rats were exposed by inhalation to 0, 77, 175 or 470 mg/m^3 boron oxide. The exposures were 6 hours/day, 5 days/week for 24, 12, and 10 weeks for the 77, 175, and 470 mg/m^3 concentrations groups, respectively. The MMAD were 2.5, 1.9 and 2.4 µm for the 77, 175 and 479 mg/m^3 concentrations groups, respectively. There was no evidence of systemic toxicity. Some of the 470 mg/m^3 had reddish exudate from the nose. As these animals were covered with dust, this effect may have been local irritation of the nose and from the animals scratching the nose. The NOAEL for systemic toxicity is 470 mg/m^3, the highest exposure concentration tested. The NOAEL for localised effects (irritation) is 175 mg/m^3 (ECHA) [KI score = 2].

Dermal

No studies are available.

G. Genotoxicity

In Vitro Studies

There are no *in vitro* genotoxicity studies on borax. Table 2 presents the results of the *in vitro* genotoxicity studies on boric acid.

Table 2: *In vitro* Genotoxicity Studies on Boric Acid

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	ECHA
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	-	1	ECHA
Chromosomal aberrations (Chinese Hamster Ovary cells)	-	-	1	ECHA
Chromosomal aberrations (Chinese Hamster Ovary cells)	-	-	1	ECHA
Chromosomal aberrations (Human peripheral lymphocytes)	NS	+	2	ECHA
Unscheduled DNA synthesis (rat liver cells)	NA	-	1	ECHA

*+, positive; -, negative; NA, not applicable; NS, not specified.

In Vivo Studies

No studies are available on borax.

Male and female Swiss Webster mice were given two daily doses of 0, 225, 450, 900, 1,800 or 3,500 mg/kg boric acid. The frequency of micronucleated polychromatic erythrocytes were not increased at any dose level (ECHA) [KI score = 1].

H. Carcinogenicity

Oral

Male and female SD rats were given in their diet disodium tetraborate decahydrate (Borax) or boric acid at doses of 0, 117, 350 or 1,170 ppm as B equivalents (approximately 0, 5.9, 17.5 or 58.5 mg B/kg/day) for two years. There was no mention of tumours in the report. Nevertheless, NTP (1987) concluded that this study provided adequate data on the lack of carcinogenic effects of boric acid in rats (Weir and Fisher, 1972; USEPA, 2004).

Male and female B6C3F_1 mice were given in their diet 0, 2,500 or 5,000 ppm boric acid for 103 weeks. The dietary levels are equivalent to 0, 446 or 1,150 mg/kg/day boric acid or 0,

78.1 or 201.3 mg B/kg/day. There was no evidence of carcinogenicity (NTP, 1987) [Kl score = 2].

I. Reproductive Toxicity

A three-generation reproductive toxicity study was conducted in Sprague-Dawley rats with boric acid. Male and female rats were fed a diet containing 0, 117, 350 or 1,170 ppm boron (approximately 0, 5.9, 17.5 or 58.5 mg B/kg/day, respectively). In the lower two dose groups, there were no treatment-related effects on reproduction. Litter size, progeny weights, fertility, live birth indices, lactation and appearance were similar to the controls. No gross abnormalities were noted in these two dose groups. The 1,170-ppm dose group were found to be sterile, and there were no litters from mating the treated females with control males. Lack of viable sperm was found in the atrophied testes of all 1,170 ppm males. Decreased ovulation was also seen in the majority of the ovaries of the 1,170 ppm females. The NOAEL for this study is 350 ppm boron or approximately 17.5 mg B/kg/day (Weir and Fisher, 1972) [Kl score = 2].

A three-generation reproductive toxicity study was conducted in Sprague-Dawley rats with borax. Male and female rats were fed a diet containing 0, 117, 350 or 1,170 ppm boron (approximately 0, 5.9, 17.5 or 58.5 mg B/kg/day, respectively). In the lower two dose groups, there were no treatment-related effects on reproduction. Litter size, progeny weights, fertility, live birth indices, lactation, appearance were similar to the controls. No gross abnormalities were noted in these two dose groups. The 1,170-ppm dose group were found to be sterile, and there were no litters from mating the treated females with control males. Lack of viable sperm was found in the atrophied testes of all 1,170 ppm males. Decreased ovulation was also seen in the majority of the ovaries of the 1,170 ppm females. The NOAEL for this study is 350 ppm boron or approximately 17.5 mg B/kg/day (Weir and Fisher, 1972) [Kl score = 2].

In a continuous breeding protocol, male and female CD-1 mice were given in their diet 0, 1,000, 4,500 or 9,000 ppm boric acid in their feed. The authors estimated that the average daily intakes were 0, 26.6, 111 and 220 mg B/kg/day to males; and 0, 31.8, 152 and 257 mg B/kg/day to females. Boric acid consumption did not differ among the groups. There were no litters in the 9,000 ppm breeding pairs. At 4,500 ppm, there was a successful first litter, after which there was a progressive decrease in fertility; only one pair produced a fourth and fifth litter. All fertility indices were affected in the 4,500 ppm group. A complete crossover mating trial was conducted using control mice and the 4,500 ppm mice. The results showed that the probable cause of the reduced fertility was a decrement in male fertility. A dose-related decrease in body, testicular and epididymal weights was observed in the 4,500 and 9,000 ppm F_0 males. Sperm count was significantly decreased in these two dose groups, and percent motile sperm was decreased in all dose groups. Testicular histopathology showed seminiferous tubular atrophy in the 9,000 ppm males and partial atrophy of the seminiferous tubules in the 4,500 ppm males. There were no histopathologic changes in the 4,500 ppm females. No statistically significant decreases in mating index, fertility index or live pups/litter in the 4,500 ppm females, but the number of days to litter in this dose group was increased. Oestrous cyclicity was unaffected. Reproductive organ weights were unaffected, but relative maternal liver and kidney/adrenal weights were reduced. An F_1 fertility trial was performed using offspring from the 1,000 ppm groups. There were no decreases in mating, fertility or reproductive performance. The F_2 adjusted live pup weight was slightly, but significantly, reduced from controls. A clear NOAEL for reproductive toxicity in males was not seen in this study. The 1,000 ppm males had decreased sperm motility in

the F_0 generation and decreased sperm concentration in the F_1 generation. Decreased F_2 pup relative body weight was statistically significant from controls. The NOAEL in this study for females is 1,000 ppm boric acid or 32 mg B/kg/day). The LOAEL in this study for males is 1,000 ppm or 27 mg B/kg/day; a NOAEL was not established (Fail et al*.,* 1991) [Kl score = 2].

J. Developmental Toxicity

No studies are available on borax.

Pregnant female SD rats were given 0, 0.1, 0.2 or 0.4% boric acid in their feed on gestational days (GD) 0 to 20 or 0.8% boric acid on GD 6 to 15. The average amounts of boric acid ingested were estimated to be 0, 78, 163, 330 or 539 mg/kg/day (0, 13.6, 28.5 or 57.7 mg B/kg/day), respectively. Effects on the pregnant rats were altered food and/or water intake at ≥ 0.2% boric acid, increased liver and kidney weights relative to body weights at ≥ 0.2%, reduced weight gain at ≥ 0.4%, and increased corrected weight gain at 0.4% boric acid. There was a reduction in foetal body weights in all treated groups (94, 87, 63 and 47% of control weight, respectively). Increased malformations occurred at ≥ 0.2%, and prenatal mortality was increased at 0.8%. There was a dose-response for altered skeletal morphology in rats (≥ 0.1%), and specific findings were significantly elevated above controls at ≥ 0.2%. Specifically, there was an increased incidence of short rib XIII (a malformation) and a decreased incidence or rudimentary or full rib(s) at lumbar I (an anatomical variation) (Heindel et al., 1992) [Kl score = 2].

Pregnant female SD rats were given in their feed 0, 0.025, 0.005, 0.075, 0.1 or 0.2% boric acid on GD 0 to 20. Approximately half of the dams were terminated on GD 20, and the remaining dams delivered their litters. Pup growth and viability were monitored until postnatal day (PND) 21. The average amounts of boron ingested on GD 20 were: 0, 3.3, 6.3, 9.6, 13.3 and 25 mg B/kg/day, respectively. The average amounts of boron ingested on PND 21 were 0, 3.2, 6.5, 9.7, 12.9 and 25.3 mg B/kg/day, respectively. There were no maternal deaths and no treatment-related clinical signs. Maternal body weights were similar across all groups during gestation. However, decreased maternal body weights (GD 19 and 20 at sacrifice) and decreased maternal body weight gain (GD 15-18 and GD 0-20) were statistically significant in trend tests. There was a 10% reduction in gravid uterine weight (statistically significant) in the 0.2% group. Corrected maternal weight (maternal gestational weight minus reduced gravid uterine weight) was unaffected by treatment. Feed intake in the 1,000 ppm dams was minimally affected and only during the first three days of dosing. Water consumption was higher in the treated groups after GD 15. The number of corpora lutea and uterine implantation sites, and the percentage of preimplantation loss were similar across all groups. Increased relative kidney weights were increased in the 0.2% group. There were no differences in the viability of the offspring between treated and controls. On GD 20, foetal body weight was 94% and 88% of controls in the 0.1% and 0.2% groups, respectively; recovery was complete at birth (~GD 22). The incidence of short rib XIII was increased on GD 20 in the ≥ 0.1% groups, but only in the 0.2% group at PND 21. The incidence of wavy rib was increased on GD 20 in the ≥ 0.1% group; the reversibility of this effect was confirmed on PND 21. There was a slight decrease in extra lumbar ribs in the 0.2% group on GD 20, and extra lumbar ribs were seen in the 0.2% group on PND 21. The developmental NOAEL was considered to be 0.075% boric acid or 9.6 mg B/kg/day on GD 20; and 0.1% boric acid or 12.9 mg B/kg/day on PND 21 (Price et al., 1996a) [Kl score = 1].

Pregnant Swiss mice were given in their diet 0, 0.1, 0.2 or 0.4% boric acid on gestational days (GD) 0 to 17. The average amounts of boric acid ingested were estimated to be 248, 452 or

1,003 mg/kg/day (0, 43.4, 79.0 or 175.3 mg/B/kg/day), respectively. Maternal toxicity consisted of mild kidney lesions (≥ 0.1%), increased water intake and relative kidney weights (0.4%), and decreased water intake during treatment. Foetal body weights were reduced in the ≥ 0.2% groups, and there were increased incidences of resorptions and malformed foetuses per litter in the 0.4% group. The LOAEL for maternal toxicity is 248 mg/kg/day boric acid or 43.4 mg B/kg/day; a NOAEL was not established. The NOAEL for developmental toxicity is 248 mg/kg/day boric acid or 43.4 mg B/kg/day (Heindel et al., 1992) [KI score = 2].

Pregnant female New Zealand rabbits were dosed by oral gavage with 0, 62.5, 125 or 250 mg/kg boric acid (0, 10.9, 21.9 or 43.7 mg B/kg) during GD 6-19. Feed intake was in the 250 mg/kg maternal animals during the exposure period, but it was increased in the ≥ 125 mg/kg dose groups. In the 250 mg/kg group, maternal body weights during GD 9-30, weight gain during GD 6-19, gravid uterine weight and number of corpora lutea per dam were significantly reduced. In the ≥ 125 mg/kg groups, maternal corrected gestational weight gain was increased compared to controls. Maternal liver weights were unaffected by treatment. In the 250 mg/kg group, relative, but not absolute, kidney weights were increased, although no effects in the kidney were noted in the histopathological examination. Prenatal mortality was increased in the 250 mg/kg group (90% resorptions/litter versus 6% for controls); the proportion of pregnant females with no live foetuses was increased (73% versus 0%), and live litter size was reduced (2.3 foetuses versus 8.8). Thus, there were only 14 live foetuses (6 live litters) available for evaluation in the 250 mg/kg group. The percentage malformed foetuses/litter was increased in the 250 mg/kg group, primarily due to cardiovascular defects (72% versus 3% of controls). There was no definitive maternal or developmental toxicity in the 62.5 or 125 mg/kg dose groups. The NOAEL for maternal and developmental toxicity is 125 mg/kg/day boric acid or 21.9 mg B/kg/day (Price et al., 1996b) [KI score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for boric acid follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021)).

A. Non-Cancer

An oral reference dose was not derived for boric acid or borax.

The Australian drinking water guideline value for boron (4 mg/L) may be applicable (ADWG 2011 updated 2021). The health-based ADWG value was based on a tolerable daily intake (TDI) of 0.16 mg/kg bw. This TDI is based on the NOAEL of 9.6 mg/kg/bw/day for foetal bodyweight effects in a rat developmental study (Price et al., 1996a) with an uncertainty factor of 60 (10 for interspecies and 6 for human intraspecies).

B. Cancer

There was no evidence of carcinogenicity in rat and mouse chronic studies conducted on borax and/or boric acid. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Borax and boric acid do not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Borax and boric acid have low acute and chronic toxicity to aquatic organisms.

B. Aquatic Toxicity

In ecotoxicological tests for boron, the exposure concentrations are expressed as boron equivalents, i.e., mg B/L. This is because boric acid and borate salts will have the same boron speciation when dissolved in environmental matrices. Therefore, in the following sections toxicological values are given as mg B/L regardless of the form of boron that was tested.

Acute Studies

Borax will transform into boric acid in the aquatic environment. Table 3 lists the results of acute aquatic toxicity studies conducted on boric acid.

Table 3: Acute Aquatic Toxicity Studies on Boric Acid

Test Species	Endpoint	Results (mg B/L)	Klimisch score	Reference
Fathead minnow	96-hour LC_{50}	79.7	2	ECHA
Legumia recta (Black sandshell mussel)	96-hour LC_{50}	147	2	ECHA
Hyalella azteca	96-hour LC_{50}	64	2	ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50}	52.4 mg B/L	1	ECHA

Chronic Studies

Long-term effects (LC_{10}) on freshwater fish ranged from 3.5 to 47 mg B/L. Adequate long-term LC_{10} of 21.6 mg B/L was found for the freshwater fish *P. promelas* in a study according to USEPA OPPTS 850.1400 (ECHA) [KI score = 2].

Long-term effects (LC_{10}/NOEC) on reproduction on freshwater vertebrates ranged from 6.6 to 32 mg B/L based on several well-accepted guideline studies (ECHA) [KI scores =1 or 2].

Boric acid has been evaluated for its toxicity towards the freshwater alga *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) in an Alga growth inhibition test according to OECD 201 under GLP requirements. The exposure duration was 72 hours under static conditions. The NOEC growth rate determined from the study was 17.5 mg B/L (ECHA) [KI score = 1].

The ANZG water quality guideline (2021) derived a very high reliability default guideline value (DGVs) for (dissolved) boron in freshwater from 22 chronic (long-term) toxicity data, comprising eight fish, two amphibians, three crustaceans, one bivalve, three macrophytes, one green microalga, three diatoms and one blue–green alga. The summary of representative data used by ANZG to develop a water quality guideline for boron is presented in Table 4. These values are noted to be consistent with those reported in ECHA. Additional chronic aquatic toxicity data is found in the ANZG Technical Brief (ANZG, 2021).

Table 4: Chronic Aquatic Toxicity Studies on Boron[1]

Test Species	Endpoint	Results (mg B/L)
Danio rerio	34-day NOEC (Biomass)	1.8
Pimephales promelas	32-day NOEC (Mortality)	11
Daphnia magna	14-day NOEC (Reproduction)	2.4
Pseudokirchneriella subcapitata	4-day NOEC (Growth)	2.8

1 - The DGVs are based on toxicity data for boron as either boric acid, H_3BO_3 (CAS [redacted] or borax, $Na_2B_4O_710H_2O$ (CAS [redacted] in freshwater.

In the chronic toxicity data set, fish sensitivity to boron ranged from the least sensitive species in the dataset (*Melanotaenia splendida*, LC_{10} 102 mg/L) to the third most sensitive species in the dataset (*Danio rerio*, NOEC 1.8 mg/L). Of the crustaceans, *D. magna* was best represented in the literature, with 18 published NOEC values (ranging from 2.4 mg/L to 29 mg/L) for six different endpoints from six different publications. The final NOEC of 2.4 mg/L used in the DGV derivation was lower than that for *C. dubia* (NOEC 5.6 mg/L) and for the amphipod *H. azteca* (NOEC 6.6 mg/L). For *P. subcapitata*, there were three separate studies available with toxicity data for boron. The toxicity values from these studies ranged from a NOEC of 2.8 mg/L to a NEC of 27 mg/L, varying with endpoint, duration and test medium used. Boron was least toxic to *P. subcapitata* when tested in algal growth medium with added $NaHCO_3$, suggesting that carbonate addition may have influenced boron toxicity. Therefore, although NECs are preferred to NOECs or EC10s, in this instance, a reliable NOEC of 2.8 mg/L was the most sensitive toxicity value for *P. subcapitata* (ANZG, 2021).

C. Sediment Toxicity

Limited sediment toxicity data are available for boric acid and boron containing compounds in general (NICNAS, 2019).

Chronic toxicity values for the effects of boric acid on sediment-dwelling invertebrates have been obtained for a freshwater midge (*Chironomus riparius*, harlequin fly), a freshwater bivalve (*Lampsilis siliquoidea*, fatmucket clam) and the aquatic worm (*Lumbriculus variegatus,* California blackworm). The respective toxicity values for these species are as follows: 28-day NOEC = 37.8 mg B/kg; 21-day LC_{25} (survival) = 363.1 mg B/kg; and 28-day NOEC = 100.8 mg B/kg (NICNAS, 2019).

Due to the high water solubility of boron and its low partitioning to sediment, sediment toxicity testing for boron is particularly challenging as it is difficult to ensure that exposure is through the solid phase (i.e., sediment) and not from the aqueous boric acid in the overlying water (NICNAS, 2019).

D. Terrestrial Toxicity

Ecotoxicological tests with plants and soil invertebrates have recorded modest chronic toxicity values (NOECs/ECs) in the range of 15.3 to 84.0 and 5.2 to 315 mg total B/kg, respectively (ECHA, 2008). However, to predict the potential toxicity of boron to plants and soil organisms, measuring the total boron concentration may be unsuitable. Instead, potential toxicity is better predicted using boron concentrations in the soil solution (extractable boron) (Mertens et al., 2011). In Australia, it is generally accepted that boron toxicity will pose a risk to terrestrial plants when soil concentrations exceed 15 mg/kg of extractable boron (NICNAS, 2019).

E. Calculation of PNEC

PNEC water

The ANZG water quality guideline (2021) derived a very high reliability DGV for (dissolved) boron in freshwater. The DGVs for 99, 95, 90 and 80% species protection are 340 µg/L, 940 µg/L, 1,500 µg/L and 2,500 µg/L, respectively. The 95% species protection level for boron in freshwater (940 µg/L) is recommended for adoption in the assessment of slightly-to-moderately disturbed ecosystems (ANZG, 2021).

PNEC sediment

Limited sediment toxicity data are available for boric acid and boron containing compounds in general (NICNAS, 2019). Due to the high water solubility of boron and its low partitioning to sediment, sediment toxicity testing for boron is particularly challenging as it is difficult to ensure that exposure is through the solid phase (i.e., sediment) and not from the aqueous boric acid in the overlying water (NICNAS, 2019). K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as boric acid and borax. Therefore, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. As a result, the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

In the ECHA REACH database (ECHA), a $PNEC_{soil}$ was derived for boron using the species sensitivity distribution method and an assessment factor of 2. The $PNEC_{soil}$ was determined to be 5.7 mg/kg soil dry weight.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Borax is an inorganic compound that dissociates completely to boric acid and the borate anion in aqueous media. Biodegradation is not applicable to these inorganic compounds; both boric acid and borate are also ubiquitous and are present in most water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable.

A BCF of < 0.1-10.5 L/kg has been reported for borates in fish and oysters. This data suggests that boric acid does not bioaccumulate in the aquatic environment. Thus, boric acid and borax do not meet the criteria for bioaccumulation.

The chronic toxicity data on boric acid has a NOEC > 0.1 mg/L. Acute E(L)C_{50} values are > 1 mg/L. Thus, borax and boric acid do not meet the criteria for toxicity.

The overall conclusion is that borax and boric acid are not PBT substances.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity Category 4 [Inhalation]

Eye Damage Category 1

Reproductive Toxicant Category 1B

STOT SE Category 3 [Respiratory irritation]

In addition to the hazard statements corresponding the GHS classifications, the following non-GHS hazard statement is to be added to the SDS: AUH071: Corrosive to the Respiratory Tract.

B. Labelling

Danger

According to the classification provided by companies to ECHA in CLP notifications this substance may damage fertility or the unborn child, causes serious eye damage, is harmful if swallowed, is harmful if inhaled, is suspected of damaging fertility or the unborn child, may cause respiratory irritation and causes skin irritation.

C. Pictogram

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water. Do not induce vomiting. Get medical attention. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

None identified.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use personal protective clothing. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust. Wear respiratory protection if ventilation is inadequate. Avoid contact with skin, eyes and clothing.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove.

D. Storage and Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place. Do not store with alkalis, acids or reducing agents.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for sodium perborate tetrahydrate.

Engineering Controls

Ensure adequate ventilation. Localised ventilation should be used to control dust levels below permissible exposure limits.

Personal Protection Equipment

Respiratory Protection: Use respiratory protection when airborne concentrations are expected to be high.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Sodium tetraborate decahydrate is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

ANZG. (2021). Toxicant default guideline values for aquatic ecosystem protection: Boron in freshwater. Australian and New Zealand Guidelines for Fresh and Marine Water Quality. CC BY 4.0. Australian and New Zealand Governments and Australian state and territory governments, Canberra, ACT, Australia.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Fail, P.A., George, J.D., Seely, J.C., Grizzle, T.B., and Heindel, J.J. (1991). Reproductive toxicity of boric acid in Swiss (CD-1) mice: assessment using the continuous breeding protocol. Fundam. Appl. Toxicol. 17: 225-239.

Hamilton, S.J., and Wiedmeyer, R.H. (1990). Concentrations of boron, molybdenum and selenium in chinook salmon. Trans. Amer. Fisheries Soc. 119: 500-510.

Heindel, J.J., Price, C.J., Field, E.A., Marr, M.C., Myers, C.B., Morrissey, R.E., and Schwetz, B.A. (1992). Developmental toxicity of boric acid in mice and rats. Fundam. Appl. Toxicol. 18: 266-272.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Mertens, J., Van Laer, L. and Salaets, P. (2011). Phytotoxic doses of boron in contrasting soils depend on soil water content. Plant Soil. 342:73-82.

National Toxicology Program [NTP]. (1987). Toxicology and Carcinogenesis Studies of Boric Acid (CAS No. [redacted] in $B6C3F_1$ Mice. NTP TR 324, NIH Publication No. 88-2580. National Toxicology Program, U.S. Department of Health and Human Services, National Institute of Health.

NICNAS. (2019). Boric acid and precursors to boric acid: Environment tier II assessment. Available on-line: https://www.industrialchemicals.gov.au/sites/default/files/Boric%20acid%20and%20precursors%20to%20boric%20acid_%20Environment%20tier%20II%20assessment.pdf

Price, C.J., Strong, P.L., Marr, M.C., Myers, C.B., and Murray, F.J. (1996a). Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fundam. Appl. Toxicol. 32: 179-193.

Price, C.J., Marr, M.C., Myers, C.B., Seely, J.C., Heindel, J.J., and Schwetz, B.A. (1996b). The developmental toxicity of boric acid in rabbits. Fundam. Appl. Toxicol. 34: 176-187.

Thompson, J.A., David, J.C. and Drew, R.E.(1976). Toxicity, uptake and survey studies of boron in the marine environment. Water Research. 10(10): 869-875.

USEPA. (2004). U.S. EPA (United States Environmental Protection Agency). Integrated Risk Information System (IRIS) – Boron and Compounds; CASRN [redacted] Available at: http://www.epa.gov/iris.

Warner et al. (2018). Revised Method for Deriving Australian and New Zealand Water Quality Guideline Values for Toxicants – update of 2015 version. Prepared for the revision of the Australian and New Zealand Guidelines for Fresh and Marine Water Quality. Australian and New Zealand Governments and Australian state and territory governments, Canberra, 48 pp.

Weir, R.J., Jr., and Fisher, R.S. (1972). Toxicologic studies on borax and boric acid. Toxicol. Appl. Pharmacol. 23: 351-364.

WHO. (1998). Environmental Health Criteria 204, Boron, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

2-PROPENAMID (IMPURITY)

This dossier on 2-Propenamid (impurity) (2PA) (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): prop-2-enamide

CAS RN: [redacted]

Molecular formula: C_3H_5NO

Molecular weight: 71.08 g/mol

Synonyms: 2-Propenamide; Acrylamide; Acrylamide solution 50%; EUROAMD

SMILES: C=CC(=O)N

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of 2PA

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Crystalline White solid	1	ECHA
Melting Point	84.5°C at 101.3 kPa	1	ECHA
Boiling Point	Not applicable as substance is solid	1	ECHA
Density	1130 kg/m³ at 30°C	2	ECHA
Vapour Pressure	Not applicable as substance is solid	1	ECHA
Partition Coefficient (log K_{ow})	-0.9 at 20°C	1	ECHA
Water Solubility	2,155 g/L at 30°C	1	ECHA
Flash Point	Not applicable as substance is solid	1	ECHA
Auto flammability	Not applicable as substance is solid	1	ECHA
Viscosity	Not applicable as substance is solid	1	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

2-Propenamid is expected to biodegrade and is not expected to sorb substantially to soils or sediments based on the low log K_{ow} and K_{oc} values. In addition, 2-propenamid is not expected to bioaccumulate.

B. Biodegradation

2PA was found to degrade approximately 100% in 28 days in the OECD Closed Bottle Test (301D) (ECHA) [KI Score = 1].

C. Environmental Distribution

No data available (ECHA). However, K_{oc} values of 3.554 L/kg (K_{ow} method) and 5.694 L/kg (MCI method) were estimated using USEPA EPI Suite™ KOCWIN v2.00 module. The estimated log K_{oc} values equal 0.551 and 0.755 for the K_{ow} and MCI methods, respectively [KI Score = 2]. Based on these estimated values, the substance is not expected to sorb substantially to soils or sediments.

D. Bioaccumulation

No experimental data were available for bioaccumulation or bioconcentration of 2PA. However, the log bioaccumulation factor (BAF) determined from regression-based calculations were performed using EPI Suite BCFBAF v3.01. Based on a log K_{ow} of -0.67, the log BAF according to the Arnot-Gobas method for assessing bioaccumulation at the upper trophic level was determined to be -0.047 [KI Score = 2]. The relatively low log BAF suggests 2PA will not bioaccumulate to any substantial degree.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of 2PA is low by the oral, inhalation and dermal routes. It is not irritating to the eyes or skin and is not a skin sensitiser. Repeated exposures of 2PA to rats in a chronic drinking water study exhibited neurotoxicity and carcinogenicity. *In vitro* and *in vivo* studies provide strong evidence that 2PA does not react directly with DNA. It has no reported reproductive or developmental effects.

B. Acute Toxicity

<u>Oral</u>

An EU Method B.1 (Acute Toxicity Oral) study was performed on Sprague-Dawley rats exposed to 2PA. Under the experimental conditions, the oral LD_{50} in rats of acrylamide in aqueous solution at 50% was 354 mg/kg in female rats with 95% confidence interval limits of 305-458 mg/kg. Toxicity was comparable in males. In accordance with the ethic and scientific recommendations concerning the LD_{50} a more precise determination was not conducted. Based on the results of this study, it can be concluded that the acute oral LD_{50} of acrylamide in rats is 177 mg/kg (ECHA) [KI score =1].

Inhalation

An OECD Guideline 433 draft (Acute Inhalation Toxicity: Fixed Concentration Procedure) was employed to estimate the acute inhalation toxicity of 2PA to an unspecified strain of male rat. The results of this test indicate that the 50.7% solution of acrylamide is practically non-toxic by the inhalation route with a LC_0 (60 mins) of 12 mg/L (ECHA) [KI score =2].

Dermal

An OECD Guideline 402 – Acute Dermal Toxicity was employed to estimate the acute dermal toxicity of 2PA to a non-specified strain of rabbit. Rabbits were occlusively dosed at 200, 795, 1,580 and 3,160 mg/kg of 50.7% aqueous acrylamide solution. Solution was applied to unabraided skin. The acute dermal LD_{50} for acrylamide was determined to be 1,141 mg acrylamide/kg bw (ECHA) [KI Score=1].

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was conducted to determine the skin irritation potential of 2PA using New Zealand White rabbits. Shaved areas of three male animals were treated with 0.5 g per animal of the test article prepared as a paste with 0.086 g of water. A semi-occlusive patch was overwrapped with a gauze binder and secured with tape for an exposure period of 4 hours. Post dosing, excess test article which had not penetrated was wiped away with a gauze pad moistened with water. Animals were observed for 1, 24, 48 and 72 hours after the removal of the bandage. Scoring was conducted according to the scale published in the OECD Guideline (No. 404 – 1992).

Neither erythema nor oedema was observed at any time. It can be concluded from the results obtained under the experimental conditions employed that acrylamide is not irritating to skin (ECHA) [KI score = 1].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) primary eye irritation study was performed using 2PA. Three male New Zealand White rabbits received 0.1 mL of undiluted solution in one eye. The other eye remained untreated. The exposure period was 24 hours. Reactions were scored at 1, 24, 48 and 72 hours and at 7, 14 and 21 days post-application to evaluate reversibility of the lesions.

Maximum conjunctivae, chemosis, iris and corneal opacity scores were 2, 2, 1 and 2.3, respectively, which were found to be fully reversible up to 21 days post exposure.

There were no deaths or remarkable body weight changes during the study period. Under the study conditions, 2PA is considered to cause irritation to the eye (ECHA) [KI score = 1].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) study (i.e., Buehler test) was performed on Pirbright-Hartley guinea pigs. Systemic toxic symptoms after application were not observed at any time during the study. Body weight development was positive and within normal ranges. No erythema nor oedema was observed at any point after the challenge application

in the control group. There were apparently no skin reactions in control animals but 85% of test animals gave a positive response. On the basis of these results, acrylamide should be considered a skin sensitiser in animals (ECHA) [Kl score = 1].

E. Repeated Dose Toxicity

Oral

An OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) was performed using Fischer 344 rats. 2PA was administered orally in drinking water for a period of two years. Dosing levels were given at 0.0, 0.01, 0.1, 0.5 and 2.0 mg/kg/day.

The rats were generally observed twice daily during the work week for overt signs of toxicity or changes in demeanour. These observations included the animals' movement within the cage, the availability of food and water, wastage of feed and the response to the opening and closing of the cage. Routine monitoring on weekends and holidays was limited to the removal of dead animals and animal husbandry procedures required to ensure the availability of food and water.

Parameters monitored during the study included mortality, body weight, food consumption, water consumption, clinical observations, haematology, clinical chemistry, urinalysis, organ weights, gross and histopathology. All rats were examined approximately monthly after the first month for palpable masses. Individual body weights were recorded monthly from all rats.

Overall, ingestion of 2PA induced neurotoxicity in F344 rats at doses ranging from 0.01-2.0 mg/kg/day. Testicular atrophy was observed in rats at elevated doses. The No Observed Adverse Effect Level (NOAEL) was determined to be 0.5 mg/kg in both sexes of rats (ECHA) [Kl Score = 1].

Inhalation

No data were available.

Dermal

No data were available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on 2PA based are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on 2PA

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) (Bacterial Reverse Mutation Assay)	-	-	2	ECHA

*+, positive; -, negative.

In Vivo Studies

Acrylamide has been extensively tested in a wide variety of *in vitro* and *in vivo* assays for detection of genetic effects. There is no compelling evidence that acrylamide induces point mutations or interacts with DNA *in vivo* to form DNA adducts. In contrast to point mutation and DNA damage assays, acrylamide induces a variety of chromosomal effects in bone marrow, but studies in spermatogonia are conflicting. Dominant lethal assays have generally produced positive results with acrylamide, which could be explained by chromosomal effects such as deletions. These studies, taken together, provide very strong evidence that acrylamide does not react directly with DNA (ECHA) [KI Score = 4].

G. Carcinogenicity

Oral

An OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) was performed using Fischer 344 rats. 2PA was administered orally in drinking water for a period of two years. Dosing levels were given at 0.0, 0.01, 0.1, 0.5 and 2.0 mg/kg/day.

Overall, ingestion of 2PA induced benign thyroid, mammary gland and tunica vaginalis tumours. The NOAEL was determined to be 0.5 mg/kg in both sexes of rats (ECHA) [KI Score = 1].

Despite National Toxicology Program conclusions that long-term dosing studies using 2PA provide clear evidence of carcinogenicity in rats, the cited study results provided in this dossier are equivocal relative to cancer responses. When evaluating a human relevance table, none of these tumors appear relevant to humans. Humans have substantially different mammary gland physiology from rodents and the tunica vaginalis tumors appear specific for the F344 rat. Only the thyroid may have significance (ECHA).

It should be noted that according to National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2002) acrylamide meets the National Occupational Health and Safety Commission (NOHSC) Approved Criteria (NOHSC, 1999) for classification as a Category 2 carcinogen (Risk Phrase R45 – May cause cancer).

Inhalation

No studies are available.

Dermal

No studies are available.

H. Reproductive Toxicity

Oral

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed on male and female Fischer 344 rats. 2PA was administered orally in drinking water at 0, 0.5, 2.0 or 5.0 mg/kg/day.

Long-term exposure to 2PA in the drinking water, over two generations in Fischer 344 rats, resulted in parental toxicity (reduced bodyweight, clinical signs of toxicity, histologic evidence of axonal swelling and/or degeneration in peripheral nerves) at 5.0 mg/kg/day, accompanied by prenatal lethality. Exposure to 2.0 mg/kg/day resulted in similar but lesser adult toxicity but no prenatal lethality. Exposure to 2.0 mg/kg/day resulted in no change to reproductive parameters in either generation except for reduced body weights and weight gain in F0 males in the pre-breed exposure period and reduced body weight and weight gain in F0 females late in the pre-breed exposure period. The only significant reproductive event induced by 2PA was decreased litter size as a result of dominant lethal mutations.

The NOAEL for all generations was determined to be 2 mg/kg/day (ECHA) [Kl Score = 1].

I. Developmental Toxicity

An OECD Guideline 414 (Prenatal Developmental Toxicity Study) was performed on Sprague-Dawley rats. Animals were dosed daily via oral gavage at 0, 2.5, 7.5 and 15 mg/kg.

Maternal Effects

There were no maternal mortalities and no clear clinical signs of toxicity. When corrected for gravid uterine weight, maternal body weight gain was decreased amongst animals receiving 7.5 and 15 mg/kg/day. The NOAEL for maternal toxicity was determined to be 2.5 mg/kg bw/day.

Developmental Effects

There were no apparent effects on embryo/foetal viability, growth or malformations. There was a slight, but not statistically significant, increase in the incidence of skeletal variations. The most frequently observed variation was the presence of a rudimentary extra lumbar rib. This finding is considered likely to be an indirect consequence of maternal toxicity or stress and is of limited toxicological importance. The NOAEL for developmental effects was determined to be 15 mg/kg bw/day (ECHA) [Kl score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for 2PA follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

Based on health considerations, the concentration of acrylamide in drinking water should not exceed 0.0002 mg/L according to Australian Drinking Water Guidelines Version 3.4. The guideline value for acrylamide of 0.0002 mg/L is based on a consideration of health effects in relation to the limit of determination for analysis using commonly available techniques.

Based on strict health related factors, a health-based derivation was determined as 0.0007 mg/L according to Australian Drinking Water Guidelines Version 3.4. A safety factor of 1,000 is used for the results of an animal study as a basis for human exposure (10 for interspecies variations, 10 for intraspecies variations and 10 for a less than lifetime study). An additional factor of 10 for carcinogenicity was not applied as tumours occur at doses above those that cause neurotoxic effects. The use of this safety factor was recommended by the NHMRC Standing Committee on Toxicity.

B. Cancer

An oral cancer slope factor for 2PA of 5×10^{-1} per mg/kg/day has been developed by USEPA and presented in the Integrated Risk Information System (IRIS) based on thyroid tumours and tunica vaginalis mesotheliomas (USEPA). Health based values will not be derived based on the noted slope factor since NICNAS has determined that the above noted drinking water guidance value is protective of both non-cancer and cancer effects.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

2PA does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

2PA has low acute and chronic aquatic toxicity.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on 2PA.

Table 3: Acute Aquatic Toxicity Studies on 2PA[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Onchorhyncus mykiss	96-hour LC_{50}	180	1	ECHA
Daphnia magna	48-hour EC_{50}	60	1	ECHA

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pseudokirchneriella subcapitata	72-hour EC_{50}	33 (growth inhibition) 50 (growth rate inhibition)	2	ECHA

Chronic Studies

Fish: A 28-day study was conducted to determine the toxicity of acrylamide monomer to carp (*Cyprinus carpio*). Fish were exposed to 2PA at concentrations of 0, 0.05, 0.5 and 5 mg/L. The NOEC was determined to be 5 mg/L (ECHA) [KI Score = 2].

Invertebrates: No freshwater invertebrate chronic toxicity data were available (ECHA) [KI Score = 1].

C. Terrestrial Toxicity

No data were available.

D. Calculation of PNEC

The PNEC calculations for 2PA follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (180mg/L), Daphnia (60 mg/L), and algae (33 mg/L). NOEC values from long-term studies are available for fish (5 mg/L). On the basis that the data consists of short-term studies for three trophic levels and long-term studies from one trophic level, an assessment factor of 100 has been applied to the lowest reported NOEC value of 5 mg/L. Therefore, the $PNEC_{water}$ is 0.05 mg/L.

PNEC sediment

2PA is expected to degrade rapidly in the environment. Moreover, based on the low K_{ow} and K_{oc} values, the substance is not expected to bind substantially to sediment. Therefore, a PNEC for sediment has not been calculated.

PNEC soil

2PA is expected to degrade rapidly in the environment. Moreover, based on the low K_{ow} and K_{oc} values, the substance is not expected to bind substantially to soil. Therefore, a PNEC for soil has not been calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

2PA is an organic substance that has been determined to be readily biodegradable. Thus, it does not meet the screening criteria for persistence.

The relatively low log BAF (-0.047) suggests 2PA will not bioaccumulate to any substantial degree. Therefore, 2PA does not meet the screening criterion for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on 2-PA are > 0.1 mg/L. The acute $E(L)C_{50}$ values from the acute aquatic toxicity studies on 2-PA are > 1 mg/L. Thus, 2-PA does not meet the criteria for toxicity.

Based on PBT assessment guidance cited above, 2PA is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Oral – Acute Tox. 3: H301: Toxic if swallowed.

Dermal – Acute Tox. 4: H312: Harmful in contact with skin.

Inhalation – Acute Tox. 4: H332: Harmful if inhaled.

Skin corrosion / irritation – Skin Irrit. 2: H315: Causes skin irritation.

Serious eye damage / eye irritation – Eye Irrit. 2: H319: Causes serious eye irritation.

Skin sensitisation – Skin Sens. 1: H317: May cause an allergic skin reaction.

Reproductive toxicity: H361: Suspected of damaging fertility or the unborn child.

Germ cell mutagenicity: H340: May cause genetic defects.

Carcinogenicity: H350: May cause cancer.

Specific target organ toxicity: STOT Rep. Exp. 1: H372: Causes damage to organs.

B. Signal word

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if

ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standards for 2-PA in Australia is 0.03 mg/m^3 as am 8-hour time weighted average (TWA). There is also a skin notation indicating that absorption through the skin may be significant source of exposure.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN number: 2074 (Solid)

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECETOC. (2000). European Centre for Ecotoxicology and Toxicology of Chemicals The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and the Related Food Web. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Technical Report No. 68, Brussels.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

NICNAS. (2002). Acrylamide Priority existing Chemical Assessment Report No. 23.

NOHSC (National Occupational Health and Safety Commission). (1999). List of Designated Hazardous Substances [NOHSC:10005(1999)]. Sydney, NOHSC.

USEPA. The Integrated Risk Information System (IRIS). www.epa.gov/iris.

2-PROPENOIC ACID, POLYMER WITH SODIUM PHOSPHINATE

This dossier on 2-propenoic acid, polymer with sodium phosphinate does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies pertinent to the risk assessment of 2-propenoic acid, polymer with sodium phosphinate in water treatment. Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

1 SUBSTANCE IDENTIFICATION

Chemical Name: 2-Propenoic acid, polymer with sodium phosphinate

CAS RN: [redacted]

Molecular formula: $(C_3H_4O_2.H_3O_2\text{-}P.Na)_x$-

Molecular weight: Variable

Synonyms: 2-propenoic acid, polymer with sodium phosphinate (1:1); 2-propenoic acid, polymer with sodium phosphinate; 2-propenoic acid-sodium phosphinate copolymer; acrylic acid sodium phosphinate polymer; acrylic acid, sodium hypophosphite polymer; acrylic acid-sodium hypophosphite copolymer; phosphinic acid, sodium salt, polymer with 2-propenoic acid; poly(acrylic acid-co-hypophosphite), sodium salt; poly(acrylic acid-co-sodium hypophosphite); sodium hypophosphite-acrylic acid copolymer

2 PHYSICO-CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of 2-Propenoic acid, Polymer with Sodium Phosphinate

Property	Value	Reference
Physical state at 20°C and 101.3 kPa	Colourless liquid	BioLab Water Additives, 1999
Melting Point	-1 to -3°C	BioLab Water Additives, 1999
Boiling Point	101 to 103°C	BioLab Water Additives, 1999
Specific Gravity	1.20 to 1.24	BioLab Water Additives, 1999
pH	3.5 to 4.5	BioLab Water Additives, 1999
Viscosity	90-150 centistokes (cSt) @ 25°C	BioLab Water Additives, 1999
Water Solubility	Miscible	BioLab Water Additives, 1999

3 ENVIRONMENTAL FATE PROPERTIES

In an OECD 301E test, 2-propenoic acid, polymer with sodium phosphinate degraded 20% in 28 days, indicating that it is not readily biodegradable (BioLab Water Additives, 1999).

As a polymer, 2-propenoic acid, polymer with sodium phosphinate is not expected to bioaccumulate, because its molecular weight will limit its bioavailability.

4 HUMAN HEALTH HAZARD ASSESSMENT

There is very limited information on 2-propenoic acid, polymer with sodium phosphinate.

A technical data sheet on Belsperse® 164 Dispersant (active ingredient: CAS No. [redacted] lists this product as having an acute oral LD_{50} value of >5,000 mg/kg in rats. The product is non-irritating to the skin and eyes (BioLab Water Additives, 1999).

In a letter to the U.S. EPA, male and female rats dosed by oral gavage with a 40% solution of this polymer showed treatment-related signs of osteomalacia associated with hyperphosphaturia and calciuria by week 8 of a 90-day study (U.S. EPA, 2016a).

THE U.S. EPA TSCATS database also has a brief summary of a 4-week rat oral gavage conducted on the product BELSPERSE 164 (CAS No. [redacted] At 5,000 mg/kg-day, there were adverse clinical signs, gross organ pathology and changes in blood biochemical parameters. The NOAEL was 2,000 mg/kg-day (U.S. EPA, 2016b).

5 DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicity information on 2-propenoic acid, polymer with sodium phosphinate is inadequate and/or unreliable for deriving toxicological reference and drinking water guidance values for this polymer.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

2-Propenoic acid, polymer with sodium phosphinate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

7 ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

2-Propenoic acid, polymer with sodium phosphinate exhibits low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies conducted on 2-propenoic acid, polymer with sodium phosphinate.

Table 2: Acute Aquatic Toxicity Studies on 2-Propenoic Acid, Polymer with Sodium Phosphinate

Test Species	Endpoint	Results (mg/L)	Reference
Rainbow trout	96-hr LC_{50}	>1,000	BioLab Water Additives, 1999
Zebra fish	96-hr LC_{50}	>1,000	BioLab Water Additives, 1999

Test Species	Endpoint	Results (mg/L)	Reference
Daphnia	24-hr EC_{50}	320	BioLab Water Additives, 1999
Algae	72-hr EC_{50}	130	BioLab Water Additives, 1999

Chronic Studies

No studies were located.

C. Terrestrial Toxicity

No studies were located.

D. Calculation of PNEC

The PNEC calculations for 2-propenoic acid, polymer with sodium phosphinate follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (>1,000 mg/L), *Daphnia* (>320 mg/L) and algae (>130 mg/L). No long-term studies on 2-propenoic acid, polymer with sodium phosphinate are available. On the basis of the short-term results from three trophic levels, an assessment factor of 1,000 has been applied to the lowest reported effect concentration of 130 mg/L for algae. The $PNEC_{water}$ is 0.13 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. The K_{ow} and K_{oc} have not been experimentally derived for 2-propenoic acid, polymer with sodium phosphinate; these values cannot estimate using QSAR models because of the high molecular weight of 2-propenoic acid, polymer with sodium phosphinate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$.

PNEC soil

There are no toxicity data for soil-dwelling organisms. The K_{ow} and K_{oc} have not been experimentally derived for 2-propenoic acid, polymer with sodium phosphinate; these values cannot be estimated using QSAR models because of the high molecular weight of 2-propenoic acid, polymer with sodium phosphinate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$.

8 PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

2-Propenoic acid, polymer with sodium phosphinate is not readily biodegradable. Thus, it meets the screening criteria for persistence.

2-Propenoic acid, polymer with sodium phosphinate is a high molecular weight polymer that is not expected to be bioavailable to aquatic or terrestrial organisms. Thus, it is not expected to bioaccumulate.

No chronic aquatic toxicity studies have been conducted on 2-propenoic acid, polymer with sodium phosphinate. The acute E(L)C_{50} values are >0.1 mg/L. Thus, it does not meet the screening criteria for toxicity.

The overall conclusion is that 2-propenoic acid, polymer with sodium phosphinate is not a PBT substance.

9 CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictogram

None.

10 SAFETY AND HANDLING

A. First Aid

Eye Contact

In the case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide, phosphorus oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for 2-propenoic acid, polymer with sodium phosphinate.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing closed work clothing is recommended.

F. Transport Information

2-Propenoic acid, polymer with sodium phosphinate is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

11 DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

12 REGULATORY INFORMATION

Australian AICS Inventory: Listed.

13 REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

BioLab Water Additives (1999). Belsperse® 164 Dispersant. General Product Information, http://lpq.com.mx/pdf/BELSPERSE%20164.PDF

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

U.S. EPA [EPA] (2016a). U.S. Environmental Protection Agency (EPA) Toxic Substance Control Act Test Submissions (TSCATS) database. DCN 88900000038; accessed October 2016.

U.S. EPA [EPA] (2016b). U.S. Environmental Protection Agency (EPA) Toxic Substance Control Act Test Submissions (TSCATS) database. DCN 88920001980; accessed October 2016.

AMMONIUM CHLORIDE

This dossier on ammonium chloride presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch *et al.*, 1997).

1 SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Ammonium chloride

CAS RN: [redacted]

Molecular formula: ClH_4N

Molecular weight: 53.49g/mol

Synonyms: Salmiac, Sal ammoniac, Ammonium muriate, Ammoniumchlorid, Ammonium chloride ((NH4)Cl), ammoniumchloride, Amchlor, Ammoneric, Darammon, Chlorammonic

SMILES: [NH4+].[Cl-]

2 PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of ammonium chloride.

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid	2	ECHA
Melting Point	338°C	2	ECHA
Boiling Point	Substance is a solid which melt above 300°C and decomposes before boiling.	2	ECHA
Relative Density	1.527	2	ECHA
Vapour Pressure	0	2	ECHA
Partition Coefficient (log K_{ow})	Not relevant - The substance is inorganic.	2	ECHA
Water Solubility	372 g/L at 20°C	2	ECHA
Flash Point	Not relevant - The substance is inorganic solid.	2	ECHA
Auto flammability	Not relevant - The substance is inorganic solid.	2	ECHA
Viscosity	Not relevant - The substance is inorganic solid.	2	ECHA

3 ENVIRONMENTAL FATE PROPERTIES

A. Summary

As an inorganic substance, ammonium chloride is not expected to biodegrade, adsorb to sediments or soil nor is it expected to bioaccumulate to any substantial extent.

B. Biodegradation

The inorganic nature of the material suggests that biodegradation is not applicable for this substance (ECHA).

C. Environmental Distribution

Adsorption/desorption

Ammonium chloride is highly soluble in water and soil moisture and is dissociated to the ammonium and chloride ions. Ammonium is bound in soil by the attraction of the positive charge on the ammonium ion to the negatively charged soil micelles. In soil, ammonium is adsorbed primarily by four mechanisms: chemical (exchangeable), fixation (non-exchangeable), reaction with organic matter and physical attractive forces. Since ammonium is so poorly mobile in soil, it is unlikely to leach to groundwater except under unusual circumstances, such as when the cation exchange capacity of the soil is exceeded.

D. Bioaccumulation

Based on the high water solubility and its ionic nature, ammonium chloride is not expected to adsorb or bioaccumulate to a significant extent. Ammonium (ammonia) is a naturally-occurring compound and a key intermediate in the nitrogen cycle. Since it is continually recycled, bioaccumulation, as it is usually considered, does not occur.

4 HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Ammonium chloride is of low toxicity concern.

B. Acute Toxicity

Oral

An OECD Guideline 401 (Acute Oral Toxicity) study was performed. The study was conducted according to a method whose principle is comparable to the OECD Guideline 401. A test group consisting of 10 animals/sex/dose (Sprague Dawley) was treated by single gavage with an aqueous solution of the test substance. Body weights were monitored during the 14 day observation period. The animals were observed for mortality and for clinical signs of toxicity for a period of 14 days. Decedents were subjected to necropsy. At the end of the observation period, the surviving animals were sacrificed (CO_2 asphyxiation) for the purpose of necropsy. The LD_{50} was determined to be 1, 410 mg/kg bw (ECHA) [KI Score = 1].

Inhalation

It is generally accepted that the principal toxic component of ammonium salts – such as ammonium chloride or -sulphate – is ammonia, rather than the corresponding anion. Therefore toxicity values for ammonium salts (such as: ammonium -sulphates, phosphates, carbonates, chlorides or nitrates), where the major toxic component is ammonia, can be considered as equivalent. Consequently, this hazard assessment comprises the total topic of ammonia toxicity.

Five studies were available for various ammonium compounds, the results based on ammonia are summarized in Table 2 below.

Table 2: Inhalation toxicity test data for ammonia

Test Summary	Species/Sex	Result (LC_{50})	Source
4 hr exposure duration	Rat/Male	> 3.6 mg/m³ air	ECHA [KI Score = 3]
1 hr exposure duration	Guinea pig/ not specified	> 0.81 mg/m³ air	ECHA [KI Score = 3]
8 hr exposure duration	Guinea pig/ not specified	> 800 mg/m³ air	ECHA [KI Score = 3]
4 hr exposure duration	Dog/not specified	> 9.5 mg/m³ air	ECHA [KI Score = 3]
1 hr exposure duration	Rabbit/not specified	> 2.2 mg/m³ air	ECHA [KI Score = 3]

Dermal

An EU Method B.3 (Acute Toxicity (Dermal)) study was available. A preliminary study was performed with Wistar rats (1 male and 1 female) dosed semi-occlusively at 2000 mg/kg body weight for 24 hrs. Slight irritation of treated skin in the female on days 2-4 after application. Duration of observation period following administration was 14 days. The frequency of observations occurred daily while body weights were determined before application and on days 8 and 15. The dermal LD_50 was determined to be > 2 000 mg/kg bw (ECHA) [KI Score = 3].

C. Irritation

Skin

In a dermal study provided in the SIDS Initial Assessment Report For SIAM 17 - Ammonium Chloride ([redacted] New Zealand white rabbits were occlusively exposed to 0.5 grams ammonium chloride in 1 mL of water.

For unabraded skin (12 test sites) 7 test sites were scored with a Draize score of 2 while 5 test sites had a Draize score of 3, 24 hours after removal of the test patch. These changes were not observed after 48, 72, 96 hours. No oedema or eschar was found at any observation time point. For abraded (12 test sites; 24 hour observation time point) an erythema score of 2 at 7 sites, and an erythema score of 3 was recorded at 5 sites. These

changes were not observed after 48, 72, 96 hours. No oedema or eschar was found at any observation time point (ECHA) [Kl. score = 2].

Eye

In a primary OECD Guideline 405 eye irritation study, the test substance is applied to the conjunctival sac of one eye in 2 Vienna White rabbits. The substance was tested as powder. The animals were observed after 10 min, 1 hour and 3 hours on the day of treatment and up to 8 days afterwards. The eyes were not washed out after 24 hours as specified in OECD Guideline 405.

The results of testing indicated that ammonium chloride can be classified as a Category 2 eye irritant based on GHS criteria (ECHA) [Kl. score = 2].

D. Sensitisation

A guinea pig maximisation test was performed. Dry powdered ammonium chloride was administered to Pirbright-White (Hoe: DHPK (SPFLac)) guinea pigs. Treated animals displayed no signs of intoxication throughout the entire study duration.

Intradermal injection with Freud's adjuvant (with and without the test substance) led to well defined erythema and slight oedema in control and the treated animals. Very slight to slight oedema appeared at the application sites injected with the test substance in physiological saline (0.9%). Scab formation was noted in all animals. The body weight gain of treated animals was not affected. Only 2 of 10 animals treated with the test substance formulation had a positive reaction. A barely noticeable erythema was seen at the application sites of these animals. The remaining animals showed no irritation effects. The substance was determined to be non-sensitizing (ECHA) [Kl. score = 2].

E. Repeated Dose Toxicity

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity Study in Rodents) was conducted using male and female Wistar rats. A NOAEL of 1,695.7 mg/kg bw/day was determined based on body weight reduction (ECHA) [Kl. Score = 2].

Inhalation

No adequately or reliable studies are available.

Dermal

No adequately or reliable studies are available.

F. Genotoxicity

In Vitro Studies

An OECD Guideline 471 (Bacterial Reverse Mutation Assay) study was performed. The results of the *in vitro* genotoxicity studies on ammonium chloride are presented in Table 3.

Table 3: *In Vitro* Genotoxicity Studies on ammonium chloride[1]

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay)	-	-	2	ECHA

*+, positive; -, negative

In Vivo Studies

An OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) was performed. No signs of general toxicity or bone marrow toxicity were observed in this study. Ammonium chloride did not induce micronuclei in the polychromatic erythrocytes (PCE) of the bone marrow of male rats treated up to 500 mg/kg/day (ECHA) [Kl. score = 2].

G. Carcinogenicity

Oral

An OECD Guideline 451 was conducted. In a 30-month feedings study, ammonium chloride (> 99.5% pure) was administered in diet continuously to 50 (5 week-old) Wistar rats/sex/dose at two doses: namely 1.0% and 2.1% for a duration of 30 months (ca. 131 weeks). The control group was presented non supplemented diets. No treatment-related abnormalities in condition or behaviour were observed in the rats of this study.

The clinical effects noted were of random nature and corresponded to the usual ageing symptoms seen in this strain of rats. There were also no adverse compound related effects on mortality, food consumption, haematology, clinical chemistry, urinalysis, or organ weights. The type and incidence of palpable masses noted during the chronic studies did not indicate any treatment-related effects. Body weights were significantly reduced at various periods over the 30-month study period in females of the low dose group and both sexes of the high dose group.

Histopathology examinations revealed dose-related increases in the incidence of zona glomerulosa hypertrophy in all treatment groups in both sexes at the end of the 30-month study. Early increases (after 4 and 13 weeks) in zona glomerulosa hypertrophy were also noted with the high (4%) level of NH4Cl. With 2.1% NH4Cl, the incidence of oncocytic tubules was significantly decreased after 30 months. The overall incidence of nephrosis was comparable among the groups throughout the studies, but after 30 months the incidence of severe nephrosis was decreased in males of the 2.1% NH4Cl group. While a NOAEL for toxicity is 2.1% NH4Cl (1104.6 mg/kg bw), the results of testing were determined to not be

treatment related (ECHA) [Kl. score = 2]. Thus, ammonium chloride is determined to not be carcinogenic.

Inhalation

No studies are available.

H. Reproductive Toxicity

An OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) was performed using Sprague-Dawley rats (ECHA) [Kl. score = 2]. Animals were divided between two subgroups (toxicity and reproductive subgroups). Males of both subgroups and females of the toxicity subgroup were treated until termination during week 6 of treatment. Doses (250, 750 and 1,500 mg/kg/day) were administered to the reproductive subgroup females for two weeks prior to pairing, and throughout pairing and gestation until Day 3 of lactation. Animals that were in parturition at the time of dosing were not dosed that day. Control animals received the vehicle over the same treatment period. Animals were not dosed on their scheduled day of necropsy. A NOAEL of 1500 mg/kg/day for reproduction/developmental toxicity was determined for parental and offspring generations (ECHA) [Kl Score = 1].

I. Developmental Toxicity

Oral

See reproductive toxicity discussion. A NOAEL of 1500 mg/kg/day for reproduction/ developmental toxicity was determined for parental and offspring generations (ECHA) [Kl Score = 1].

5 DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

A maximum of 0.5 milligrams ammonia per litre of water has been documented in the Australian Drinking Water Guidelines (ADWG, 2011) for aesthetic considerations. Thus, a drinking water guidance value will not be derived.

A. Cancer

Ammonium chloride was not carcinogenic to rats in chronic oral studies. Therefore, a cancer reference value was not derived.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

CMW does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

7 ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Ammonium chloride is of low acute and chronic toxicity concern to aquatic and terrestrial receptors. Details of relevant studies are provided below.

B. Aquatic Toxicity

Acute Studies

Species mean acute values (SMAV), were considered as relevant endpoints for the assessment of ammonium chloride toxicity. Table 4 lists the results of acute aquatic toxicity studies on ammonium chloride.

Table 4: Acute Aquatic Toxicity Studies on ammonium chloride.

Test Species	Endpoint	Results (mg/L)[1]	Klimisch score	Reference
Oncorhynchus mykiss	96 hr. LC_{50}	42.91	2	ECHA
Prosopium williamsoni	96 hr. LC_{50}	46.27	2	ECHA
Ceriodaphnia acanthina	SMAV[2]	98.5	2	ECHA
Daphnia magna	SMAV[2]	136.6	2	ECHA

1 – tests conducted at pH 8

2 – SMAV = species mean acute value

Chronic Studies

Fish:

Species mean chronic values (SMCV), were considered as relevant endpoints. The lowest species mean chronic value was calculated for *Lepomis macrochirus* (EC20 = 1.35 mg N/L and EC10 = 1.12 mg N/L = 4.28 mg/L ammonium chloride) (ECHA) [Kl. score = 2].

Invertebrates:

The lowest species mean chronic value (EC_{10}, adjusted to pH 8 and 25°C) was 0.66 mg N/L = 2.52 mg/L ammonium chloride for Hyalella Azteca (ECHA) [Kl. score = 2].

Aquatic Plants:

In an 18d-long, static test, growth of Chlorella vulgaris was inhibited by 50% at approximately 2700 mg/L ammonium sulphate (corresponding to 2186 mg/L ammonium chloride). An EC_{50} (5d) of 1300 mg/L was determined for Chlorella vulgaris (ECHA) [Kl Score = 2].

C. Terrestrial Toxicity

Acute toxicity to *Eisenia fetida* was tested in a study according to EPA/600/3-88/029 using ammonium chloride as the test substance (CAS: [redacted]). The 14d-LC_{50} value was 163 mg/kg soil (ECHA) [KI Score=2].

D. Calculation of PNEC

In aqueous solution, ammonium chloride is completely dissociated into the ammonium ion (NH4+) and the chloride anion (Cl-). Due to the inorganic nature of the substance standard biodegradation testing systems are not applicable. In unsterilized soil, ammonium chloride is mineralized fairly rapidly, and subsequently nitrified. Nitrification and de-nitrification processes also occur naturally in streams and rivers, as well as in many secondary sewage treatment processes. Based on the high water solubility and the ionic nature, ammonium chloride is not expected to adsorb or bioaccumulate to a significant extent (ECHA) [KI Score = 2].

Thus, only PNECwater will be derived.

PNEC Water

The PNEC water is derived based on invertebrate toxicity. The lowest species mean chronic value (EC_{10}, adjusted to pH 8 and 25°C) was 2.52 mg/L Ammonium chloride for *Hyalella Azteca.* Applying an assessment factor of 10 yields a PNECwater of 0.25 mg/L.

PNEC Sediment

Based on the dissociation characteristics of the substance, PNECsediment has not been determined.

PNEC Soil

Based on the dissociation characteristics of the substance, PNECsoil has not been determined.

8 PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Ammonium chloride is an inorganic substance for which biodegradability is not relevant. Thus it does not meet the screening criteria for persistence.

Ammonium chloride is an inorganic substance for which bioaccumulation is not relevant. Thus it does not meet the screening criteria for bioaccumulation.

Ammonium chloride is of low toxicity concern and therefore does not meet the screening criteria for toxicity.

Therefore, ammonium chloride is not a PBT substance.

9 CLASSIFICATION AND LABELLING

A. Classification

Harmful if swallowed, H302.

Causes serious eye irritation. H319.

B. Labelling

Warning

C. Pictogram

10 SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapor. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for ammonium chloride.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapor cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, as well as before eating, smoking and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Ammonium chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

11 DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

12 REGULATORY STATUS

Australian AICS Inventory: Listed.

13 REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

BUT-2-ENEDIOIC ACID (FUMARIC ACID)

This dossier on but-2-enedioic acid (fumaric acid) presents the most critical studies pertinent to the risk assessment of this substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): (2E)-but-2-enedioic acid

CAS RN: [redacted]

Molecular formula: $C_4H_4O_4$

Molecular weight: 116.07 g/mol

Synonyms: fumaric acid, 2-Butenedioic acid, trans-Butenedioic acid, Allomaleic acid, Boletic acid, (2E)-but-2-enedioic acid, Lichenic acid

SMILES: C(=CC(=O)O)C(=O)O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of But-2-enedioc Acid

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colourless crystalline solid	2	ECHA
Melting Point	287°C @ 101.3 kPa	2	ECHA
Boiling Point	Sublimes at 200°C; @ 0.23 kPa, fumaric acid sublimes at 165°C	2	ECHA
Density	1640 kg/m^3 at 20°C	2	ECHA
Vapour Pressure	0.02 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-4.02 @ 20°C (Experimental)	2	ECHA
Water Solubility	7 g/L @ 25°C	2	ECHA
Flash Point	Flash point is only relevant to liquids and low melting point solids	2	ECHA
Auto flammability	399°C	2	ECHA
Viscosity	Not applicable as substance is a solid	2	ECHA
Dissociation constant	K1 = 9.3 x 10^{-4} at 25°C K2 = 2.9 x 10^{-5} at 25°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Fumaric acid is readily biodegradable, is not expected to bioaccumulate, and has a low potential to adsorb to soil.

B. Partitioning

The pKa of fumaric acid is 3.03 and 4.54, indicating that this substance will exist partially in anion form in the environment and anions generally do not adsorb more strongly to soils containing organic carbon and clay than their neutral counterparts (PubChem).

Volatilisation of fumaric acid from moist soil surfaces is not expected to be an important fate process because the acid exists as an anion and anions do not volatilise (PubChem).

Hydrolysis is not expected to be an important environmental fate process since this substance lacks functional groups that hydrolyse under environmental conditions (PubChem).

C. Biodegradation

The ready biodegradability of fumaric acid was determined using the OECD 301B guideline in a GLP study.

Using a non-adapted sludge from a domestic source, the percentage of biodegradation observed comprised 60.1% after 11 days (i.e., within the 10-day window) and 67.5% after 28 days. The reference substance (sodium benzoate) incubated under the same conditions showed a percentage biodegradation of 60.1% after 11 days. Incubation of the test substance and the reference substance demonstrated that the test substance did not significantly inhibit the microbial activity of the activated sludge.

Accordingly, fumaric acid is considered readily biodegradable [KI score = 1]. If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

D. Environmental Distribution

No experimental data are available for fumaric acid. Using KOCWIN in EPI Suite™ (USEPA, 2017), the estimated K_{oc} values from the molecular connectivity index (MCI) is 0.865 L/kg. Thus, fumaric acid has a low potential for adsorption to soil and is expected to have very high mobility. Likewise, based on these values along with fumaric acid's high water solubility, if released to water, it will likely not adsorb to suspended solids or sediments.

E. Bioaccumulation

There are no bioaccumulation studies on fumaric acid. The substance has a low potential for bioaccumulation based on log $K_{ow} \leq 3$.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Fumaric acid is an organic dicarboxylic acid and is naturally found in plants and animals. Fumaric acid is approved for use as a food additive in Australia and use as a therapeutic agent in the treatment of psoriasis and other skin disorders, as wells as a feed additive for all animals without a maximum level. Dietary exposure results from the large volumes of fumaric acid used as a food acidulant in applications such as beverages, baking powders and fruit drinks. The Joint FAO/WHO Committee on Food Additives and Contaminants (JECFA, 1999) concluded that there is no safety concern at current levels of intake when used as a flavouring agent (ECHA).

Fumaric acid has low acute toxicity via oral, inhalation or dermal exposure and was practically nontoxic when tested in guideline-comparable studies of acute oral and acute dermal toxicity.

B. Acute Toxicity

Oral

An OECD Guideline 401 (Acute Oral Toxicity) was conducted using male and female Sprague Dawley rats. The substance was administered orally via gavage. The LD_{50} values for the oral administration of fumaric acid in rats range from 9,300 (female rats) to 10,700 mg/kg bw (male rats) (ECHA) [KI Score = 1].

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) was conducted using female New Zealand white rabbits. Single dose dermal toxicity of fumaric acid using female New Zealand albino rabbits was reported as 20,000 mg/kg (ECHA) [KI Score = 1].

Inhalation

An OECD Guideline 403 (Acute Inhalation Toxicity) was undertaken. An inhalation LD_{50} for rats is reported to be 1,306 mg/L (ECHA) [KI Score = 1].

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was conducted using small white Russian male and female rabbits. Dermal application of 0.5 g fumaric acid was mildly irritating to the skin of male and female rabbits. Fumaric acid did not elicit dermal reactions that would exceed the threshold for classification in accordance with EU criteria (ECHA) [KI Score = 1].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) was undertaken where test material was applied to the lower conjunctival sac of the right eye by pulling away the lower

eyelid. The left eye was treated in one animal. The contralateral eye served as a concurrent, inherent control.

Application of 0.1 g fumaric acid to the eyes of male and female rabbits was considered irritating to the eye and ocular mucous membrane. Fumaric acid is classified as an eye irritant (ECHA) [KI Score = 1].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) guinea pig maximisation test was conducted. Fumaric acid shows no sensitisation effect on the skin of female guinea pigs according to the Magnusson-Kligman maximisation test. Fumaric acid is not considered a skin sensitiser.

E. Repeat Dose Toxicity

A Peer-reviewed study comparable to OECD guideline 452 was conducted using male Osborne-Mendel rats over a two-year period.

In a two-year dietary study using male rats, a very slight increase in mortality rate and some testicular atrophy was observed after administration of 1.5% fumaric acid (approximately 750 mg/kg bw/day). Gross and microscopic examination of major organs revealed no abnormalities. The authors of this study concluded that inanition was partly responsible for testicular atrophy. A previous study conducted in a similar manner with female rats showed no adverse effects on reproductive organs after administration of up to 1.2% fumaric acid in the diet for 2 years. Based on the low incidence of mortality of male rats, 1.2% is very near a NOAEL for chronic exposure to fumaric acid (600 mg/kg bw/day). The 1.2% NOAEL (600 mg/kg bw/day) derived from the available long-term rat toxicity data was confirmed as the appropriate point of departure. No non-neoplastic or neoplastic effects were noted supporting the conclusion that the substance is not a carcinogen (ECHA) [KI Score = 2].

F. Genotoxicity

An OECD Guideline 476 (*In Vitro* Mammalian Cell Gene Mutation Test) was performed using mouse lymphoma L5178Y cells. Under the experimental conditions reported, fumaric acid did not induce mutations in the mouse lymphoma thymidine kinase locus assay using the cell line L5178Y in the absence and presence of metabolic activation. Thus, fumaric acid is not considered to be a mutagen.

G. Carcinogenicity

Fumaric acid is not considered to be a carcinogen and is not classified as such by the International Agency for Research on Cancer (IARC) or the United States Environment Protection Agency (USEPA). In agreement with the regulatory agency, the two-year repeated dose toxicity testing discussed above showed no carcinogenic effects.

H. Reproductive Toxicity

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed using male and female Charles River CD rats. Substance was administered orally via gavage in a corn oil vehicle at dosage levels of 20, 55 and 150 mg/kg/day.

In a multigeneration reproduction study (similar to OECD guideline 416) maleic anhydride (purity 99%) was administered to 10 male and 20 female rats/dose by gavage at dose levels of 0, 20, 55 and 150 mg/kg bw/day. The rats were mated to produce two generations, each with two litters. Groups of the same size from the second litter were used for subsequent generations and were given the same dose of maleic anhydride as were their parents. Since 100% mortality was observed among parental F1 female rats at 150 mg/kg bw/day, the high dose group was terminated in the F1 generation, and a parental systemic NOAEL of 55 mg/kg bw/day was the highest dose tested in the F1 generation. The study was reduced from a three-generation to a two-generation study.

Renal cortical necrosis occurred in high-dose P/F0 males and females. Increased kidney weights were observed in low- and mid-dose adult F1 females. Therefore, no NOAEL could be determined, and the LOAEL (systemic) was regarded as 20 mg/kg bw/day. With respect to fertility, neither a dose-related reduction nor a pattern (during the two consecutive matings) within the parental (P0) generation suggested a treatment-related effect. No adverse effects on fertility were observed. Based on these observations the NOAEL (fertility) was derived at 55 mg/kg bw/day (highest dose tested under the conditions of this study) (ECHA) [Kl Score = 1].

I. Developmental Toxicity

A peer reviewed dietary study was conducted on an unspecified strain of rat.

Rats were fed 1,000 or 10,000 ppm malic acid, a metabolite of fumaric acid, for 9 weeks prior to mating. One week after weaning of the last F1A litter, the P1 parents were remated to produce the F1B litter. Ten male and 20 female weanlings from each dose group were selected for the P2 generation and administered the appropriate diets. The animals were mated at 100 days of age to produce the F2A generation. One week after weaning of the F2A litter, the P2 parents were remated to produce the F2B litter.

Maternal Effects: Body weight gain of female animals was comparable to controls prior to mating. Body weight gains of male animals in test groups were slightly decreased compared to controls. Feed consumption, survival, appearance and behaviour were similar for P1 test and control rats. The P2 test and control animals were similar throughout the study and wheezing was observed in all groups during the F2B phase. A NOAEL for maternal systemic toxicity was determined to be > 10, 000 mg/kg/day.

Foetal Effects: The F2B generation showed no meaningful differences between test and control animals in the number and placement of implantation and resorption sites or in the number, weight or length of live neonates; none of the neonates died. The skeletal development of F2B neonates was similar between test and control animals. Slight differences in developmental indices were considered to be within the range of normal variations in foetal development and no trend toward lesser or greater skeletal development was observed (ECHA) [Kl Score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for fumaric acid follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021)

A. Non-Cancer

Oral

The repeated dose NOAEL for fumaric acid is 600 mg/kg/day and will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 50/(10 x 10 x 1 x 1 x 1) = 600/100 = 6 mg/kg/day.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (6 x 70 x 0.1)/2 = 21 mg/L

B. Cancer

The substance is not considered a carcinogen. Thus, a cancer reference value will not be calculated.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Fumaric acid does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Fumaric acid is of low acute toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 2 presents the results of acute aquatic toxicity studies on fumaric acid.

Table 2: Acute Aquatic Toxicity Studies on Fumaric Acid

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Danio rerio	96-hour LC_{50}	> 100	1	ECHA
Daphnia magna	48-hour EC_{50}	> 100	1	ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50}	> 100	1	ECHA

Chronic Studies

No data are available.

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

The PNEC calculations for the substance follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (> 100 mg/L), *Daphnia* (> 100 mg/L) and algae (> 100 mg/L). On the basis that the data consists of short-term results from three trophic levels, an assessment factor of 100 has been applied to the lowest reported NOEC of 100 mg/L for algae. The $PNEC_{water}$ is 1 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.637 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.8166/1280) \times 1000 \times 1$
$= 0.637$ mg/kg

Where:

$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 0.0346/1000 \times 2400]$
$= 0.8166\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= -0.865 \times 0.04$
$= 0.03460$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg) presented above as 0.865 L/kg.
f_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.0115 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.0173/1500) \times 1000 \times 1$
$= 0.0115$ mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 0.865 \times 0.02$
$= 0.0173\ m^3/m^3$

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg) presented above as 0.865 L/kg.
f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Fumaric acid is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Bioaccumulation of fumaric acid is not expected to occur based on it log K_{ow} value of -4.02 (Table 1). Thus, fumaric acid does not meet the screening criteria for bioaccumulation.

No chronic aquatic toxicity data exist on fumaric acid; however, the acute E(L)C_{50} values are > 1 mg/L in fish, invertebrates and algae. Therefore, fumaric acid does not meet the screening criteria for toxicity.

Therefore, fumaric acid is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H319: Causes serious eye irritation.

B. Labelling

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention if symptoms persist.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Get medical attention if symptoms persist.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray, powder or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours, or spray Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Pick up mechanically. If formation of dust cannot be avoided use respiratory filter device. Dispose of the material collected according to regulations.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for but-2-enedioic acid.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

But-2-enedioic acid is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DoEE. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1999. Fumaric acid. Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/Fumaric-acid#section=Computed-Descriptors. Accessed January 2022.

U.S. Environmental Protection Agency [EPA]. (2017). EPI Suite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

CALCIUM CHLORIDE

This dossier on calcium chloride presents the most critical studies pertinent to the risk assessment of calcium chloride in its use as use in coal seam gas extraction activities. It does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA) and the OECD-SIDS documents on calcium chloride (OECD, 2002). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Calcium dichloride

CAS RN: [redacted]

Molecular formula: $CaCl_2$

Molecular weight: 110.98 g/mol

Synonyms: Calcium chloride; calcium dichloride; calcium chloride anhydrous

SMILES: Cl(Ca)Cl

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Calcium Chloride

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White odourless solid; crystals; powder; or granules	2	ECHA
Melting Point	782°C @ 101.3 kPa	2	ECHA
Boiling Point	> 1,600°C @ 101.3 kPa	2	ECHA
Density	2150 kg/m^3 @ 25°C	2	ECHA
Vapour Pressure	-	-	-
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	745 g/L @ 20°C (very soluble)	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

Calcium chloride dissociates completely in aqueous solutions to calcium (Ca^{2+}) and chloride (Cl^-) ions. Calcium chloride and its dissociated ions are ubiquitous in the environment.

Because of its dissociation properties and high water solubility, calcium chloride is not expected to be adsorbed to soil. The calcium ion may bind to soil particulate or may form stable inorganic salts with sulfate and carbonate ions. The chloride ion is mobile in soil and eventually drains into the surface water because it is readily dissolved in water (OECD, 2002).

Calcium (Ca^{2+}) and chloride (Cl^-) ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated (Ganong, 1995). Neither calcium chloride nor its dissociated ions are expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Calcium chloride exhibits low acute toxicity by the oral and dermal routes. It is irritating to the eyes, but not to the skin. There was no toxicity or carcinogenic effects in rats given calcium chloride in the diet for 12 months. Calcium chloride is not genotoxic. No developmental toxicity was reported in pregnant female rats, mice or rabbits given oral doses of calcium chloride.

B. Acute Toxicity

The oral LD_{50} values in rats are 2,301, 4,179 and 3,798 mg/kg (ECHA) [KI score = 2]. The dermal LD_{50} in rabbits is > 5,000 mg/kg (ECHA) [KI score = 1].

C. Irritation

Application of 0.5 mL to the skin of rabbits for 4 hours under occlusive conditions was non-irritating. Erythema and edema scores at all time points were zero (ECHA) [KI score = 1].

Instillation of 100 mg of calcium chloride into the eyes of rabbits was moderately irritating. The mean of the 24, 48 and 72-hour scores were: 0.67 for conjunctival redness; 0.78 for chemosis; 1.0 for corneal opacity; and 0.0 for iridial lesions. There were no signs of irritation by Day 21 (ECHA) [KI score = 1].

Instillation of 100 mg of calcium chloride into the eyes of rabbits was highly irritating. The mean of the 24, 48 and 72-hour scores were: 1.9 for conjunctival redness; 2.2 for chemosis; 2.0 for corneal opacity; and 1.0 for iridial lesions. The effects were not fully reversible by Day 21 (ECHA) [KI score = 1].

Instillation of 100 mg of calcium chloride into the eyes of rabbits was irritating. The mean of the 24, 48 and 72-hour scores were: 1.54 for conjunctival redness; 1.65 for chemosis; 1.0 for corneal opacity; and 0.33 for iridial lesions. The effects were not fully reversible by Day 21 (ECHA) [KI score = 2].

D. Sensitisation

No reliable studies are available.

E. Repeated Dose Toxicity

<u>Oral</u>

Rats were fed a 20 mg calcium chloride/g body weight diet for 12 months. There were no differences in mortality, weight gain or feed consumption between treated and control groups. No neoplastic lesions were observed in the gastrointestinal tract, urinary tract, liver, heart, brain or spleen. The estimated daily intake of calcium chloride is 1,000 to 2,000 mg/kg/day (OECD, 2002) [KI score = 3].

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on calcium chloride are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Calcium Chloride

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium*)	-	-	2	ECHA
Bacterial reverse mutation (*S. typhimurium*)	-	-	2	ECHA
Chromosomal aberration (Chinese hamster lung cells)	-	NC	2	ECHA

*+, positive; -, negative; NC, not conducted.

In Vivo Studies

No studies are available.

G. Carcinogenicity

Rats were fed 20 mg calcium chloride/g diet for 12 months. There were no differences in mortality, weight gain or feed consumption between treated and control groups. No neoplastic lesions were observed in the gastrointestinal tract, urinary tract, liver, heart, brain or spleen. The estimated daily intake of calcium chloride is 1,000 to 2,000 mg/kg/day (OECD, 2002) [KI score = 3].

H. Reproductive Toxicity

No studies are available.

I. Developmental Toxicity

Pregnant female Wistar rats were dosed by oral gavage with 0, 1.76, 8.18, 38 or 176 mg/kg calcium chloride on GD 6-15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 176 mg/kg/day (ECHA) [KI score = 1].

Pregnant female CD-1 mice were dosed by oral gavage with 0, 1.89, 8.78, 40.8 or 189 mg/kg calcium chloride on GD 6-15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 189 mg/kg/day (ECHA) [KI score = 1].

Pregnant female Dutch rabbits were dosed by oral gavage with 0, 1.69, 7.85, 35.6 or 169 mg/kg calcium chloride on GD 6-18. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 169 mg/kg/day (ECHA) [KI score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Toxicological reference values were not derived from calcium chloride.

Calcium chloride dissociates in water to calcium and chloride ions. An Australian drinking water guidance value is not available for calcium (ADWG, 2021). The Australian drinking water guidance value for chloride is 250 mg/L based on aesthetics (ADWG, 2021).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Calcium chloride does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Calcium chloride is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on calcium chloride.

Table 3: Acute Aquatic Toxicity Studies on Calcium Chloride

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	4,630	2	OECD, 2002; ECHA
Lepomis macrochirus	96-hour LC_{50}	9,500-11,300	2	OECD, 2002; ECHA
Gambusia affinis	96-hour LC_{50}	13,400	2	OECD, 2002; ECHA
Lepomis macrochirus	96-hour LC_{50}	10,650	2	OECD 2002; ECHA
Daphnia magna	48-hour EC_{50}	2,400	1	OECD, 2002; ECHA
Daphnia magna	48-hour EC_{50}	2,770	2	OECD, 2002; ECHA
Ceriodaphnia dubia	48-hour EC_{50}	1,830	2	OECD, 2002; ECHA
Daphnia magna	48-hour EC_{50}	1,062	2	OECD, 2002; ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50}	2,900 (biomass)	1	OECD, 2002; ECHA

Chronic Studies

The 21-day EC_{50} and EC_{16} values for calcium chloride in a chronic *Daphnia* reproduction study were 610 and 320 mg/L, respectively (OECD, 2002).

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for calcium chloride follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (4,630 mg/L), invertebrates (1,062 mg/L) and algae (2,900 mg/L). Although a chronic *Daphnia* study is available, an NOEC or EC_{10} was not determined. On the basis that the data consist of short-term and long-term results from three trophic levels, an assessment factor of 100 has been applied to the lowest reported acute EC_{50} value of 1,062 mg/L from invertebrates. The $PNEC_{water}$ is 11 mg/L.

PNEC sediment

No experimental toxicity data on sediment organisms are available. Calcium chloride is highly soluble and dissociates completely in water. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as calcium chloride. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. Based on its properties, no adsorption of calcium chloride to sediment is to be expected, and the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No experimental toxicity data on soil organisms are available. Calcium chloride dissociates completely in water with its environmental distribution is dominated by its high water solubility. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as calcium chloride. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, no adsorption of calcium chloride to the soil is to be expected, and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Calcium chloride is an inorganic salt that dissociates completely to calcium and chloride ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both calcium and chloride ions are also ubiquitous and are present in most water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Calcium and chloride ions are essential to all living organisms, and their intracellular, and extracellular concentrations are actively regulated. Thus, calcium chloride is not expected to bioaccumulate.

A chronic toxicity has been conducted on calcium chloride, but an NOEC or EC_{10} was not determined. The acute E(L)C_{50} values for calcium chloride are > 1 mg/L in fish, invertebrates and algae. Thus, calcium chloride does not meet the screening criteria for toxicity.

The overall conclusion is that calcium chloride is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Eye Irritant Category 2

[Note: anhydrous calcium chloride requires the GHS classification Eye Irritant Category 1]

B. Labelling

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In the case of contact, immediately flush eyes with plenty of water for at least 15 minutes. If symptoms persist, seek medical advice.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on the conditions, decomposition products may include the following: hydrogen chloride gas, calcium oxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessarily provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for calcium chloride.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Calcium chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Ganong, W.F. (1995). Review of Medical Physiology, 17th Edition, Appleton & Lange, Norwalk, Connecticut, USA.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

OECD (2002). OECD-SIDS: Calcium chloride (CAS No. [redacted] UNEP Publications. Available at: https://hpvchemicals.oecd.org/UI/handler.axd?id=cb4247c6-7f28-4ca5-bf69-1f526956b6f9

CERAMIC MATERIALS & WARES, CHEMICALS

This dossier on Ceramic Materials & Wares, chemicals (CMW) presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch *et al.*, 1997).

1 SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Ceramic Materials & Wares, chemicals

CAS RN: [redacted]

Molecular formula: Not applicable (UVCB substance)

Molecular weight: Not applicable (UVCB substance)

Synonyms: Antimony oxide calcium titanate silicate ceramic opacifier, Barium calcium magnesium strontium aluminum silicate flux, Calcined bauxite, Calcined clay, Calcined clays, Calcined fireclay, Calcined kaolin

SMILES: Not applicable (UVCB substance)

2 PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of CMW

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid	2	ECHA
Melting Point	1320 °C	2	ECHA
Boiling Point	Not applicable for solids which melt above 300 °C	2	ECHA
Density	2.73 g/cm^3 @ 20°C	2	ECHA
Vapour Pressure	Not applicable for solids which melt above 300 °C	2	ECHA
Partition Coefficient (log K_{ow})	Not applicable as substance is inorganic	2	ECHA
Water Solubility	Measured at the maximum of conductivity at pH: 12.50. Calcium: 377- 390 mg/L Aluminium: 225-262 mg/L	2	ECHA

Property	Value	Klimisch score	Reference
Flash Point	Not applicable as substance is inorganic	2	ECHA
Auto flammability	Not applicable as substance is inorganic	1	ECHA
Viscosity	Not applicable as substance is inorganic	2	ECHA

3 ENVIRONMENTAL FATE PROPERTIES

A. Summary

As an inorganic substance, CMW is not expected to biodegrade, adsorb to sediments or soil nor is it expected to bioaccumulate to any substantial extent.

B. Biodegradation

No data is available for CMW. However, the inorganic nature of the material suggests that biodegradation is not applicable for this substance (ECHA).

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for CMW. However, the substance is not expected to adsorb to sediments or soil.

D. Bioaccumulation

No experimental data are available for CMW. However, the substance is not expected to adsorb to sediments or soil.

4 HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

CMW is of low acute and chronic toxicity concern to human receptors. Details from animal studies are provided below.

B. Acute Toxicity

Oral: An acute oral toxicity study (limit test) was performed with aluminium hydroxide (SH-20 Muster) in female CRL (WI)BR rats. This study has been performed in accordance with the OECD 423 (17 December 2001), Commission Regulation (EC) No 440/2008, B.1 tris (L 142, 30 May 2008), OPPTS 870.1100 (EPA 712-C-98-190, August 1998) and the Principles of Good Laboratory Practice (Hungarian GLP Regulations: 9/2001. (III. 30) (ECHA) [Kl. score 2].

Inhalation: A study was conducted according to EPA Guidelines for Test Procedures Subdivision F, Series 81-3 and TSCA 40 CFR 798.1150. Five healthy male and five healthy female Wistar Albino rats were exposed to fumed alumina in an inhalation chamber for 4 hours. The number of animals used and the exposure duration were adequate according to the guidelines. Based on the results of this study, the LC_{50} is greater than 2.3 mg/L (ECHA) [Kl. score = 2].

Dermal: An OECD Guideline 402 (Acute Dermal Toxicity) using New Zealand White rabbits. The test item "Weisskalkteig" is most appropriately translated as "white lime paste". As such it is an aqeous paste-like preparation and does not require further moistening in order to ensure good skin contact. 2500 mg/kg was applied to skin of the rabbits over a 24-hr period.

There were no indications of toxic effects from the test sample after dermal application. The dermal LD50 was determined to be > 2500 mg/kg (ECHA) [Kl. Score = 2].

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) study was performed using an unspecified strain of rabbit. Semi-occlusive dressings held the test item in place for 3 minutes, 1 hour and 4 hours on the skin of the first animal and for 4 hours for the two other animals.

In the primary dermal irritation study, the skin irritation/corrosion potential of LDSF® RG (Batch No.90121) was tested. 0.5 g of the test substance was applied on the skin of 3 rabbits under semi-occlusive conditions for 3 minutes, 1 hour and 4 hours on the skin of the first animal and for 4 hours for the two other animals.

The application of the test item did not induce colouring of the application site and did not interfere with grading of any skin lesion. Any cutaneous lesion was evaluated at approximately 1 hour, 24 hours, 48 hours, and 72 hours. No other cutaneous lesion was observed. Under the experimental conditions adopted, the test item was found to be a non skin irritant (ECHA) [Kl. score = 2].

Eye

In a primary irritation study, the eye irritation potential of LDSF® LT (Batch No.90122) was tested. 0.1 g of the test substance was introduced into the conjunctival sac of the left eye of each of the four animals. The untreated right eye served as a control. Only one animal was used for the study because LSDF® LT caused local pain and was probably severely irritating or corrosive. Therefore, exposure of two additional animals was not done.

The application of the test item did not induce colouring of the application site and did not interfere with grading of any eye lesion. Any conjunctival, iris and corneal lesion was evaluated at approximately 1 hour, 24 hours, 48 hours and 72 hours for two animals and 8 days, 15 days and 16 days after instillation of LDSF® LT (monitoring was stopped before the end of reversibility period).

Mean indices were calculated from results obtained for each rabbit at 24, 48 and 72 hours. Because ocular lesions and animal pain increased during the reversibility period and under the experimental conditions adopted, LSDF®LT (Batch No. 90122) CMW was determined to be an eye irritant (ECHA) [Kl. score = 2].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) study was performed in Guinea pigs (Dunkin Hartley (LAL/HA/BR) using the Magnusson and Kligman method. Methylcellulose (1%), selected based on results from a Preliminary Compatibility Test, was used as the vehicle in this study. Based on the preliminary dose range finding study, 1% (w/v) was used for a first induction stage by intradermal administration. This consisted of three injections to both left and right flanks: an injection with 0.10 mL of Freund's Complete Adjuvant mixed with physiological saline (1:1 v/v); an injection with 0.10 mL of the test item in 1% methylcellulose at the selected concentration; and an injection with 0.10 mL of test item at the appropriate concentration in a 1:1 (v/v) mixture of Freund's Adjuvant and physiological saline. The animals in the control group received three similar injections to each side with the omission of the test item. Again, based on the results of a dose range finding study, 100% (w/v) was used for a second induction stage by dermal application. 0.5 mL of the suspension was applied with occlusion for 48 hours. Two weeks after the last induction exposure, two concentrations were used for the occlusive epicutaneous challenge exposure: 0.5 mL of 75% (w/v) suspension was applied to the left flank of the animals and 0.5 mL of 37.5% (w/v) suspension was applied to the right flank. The test item was applied to the flanks of the test and control animals using a 5x5 cm sterile gauze patch saturated with the test item. The patches remained in place, occluded, for 24 hours. After patch removal, residual test item was removed with a swab and observations were made at 24 and 48 hours. No irritation effects were observed during the dose-range finding study or the induction exposures. In the test group, no positive responses were observed in the treated animal (n=10) with either the 75% (w/v) or 37.5% (w/v) formulations. No positive responses were observed on challenge exposure in the control animals (n=5). In summary, the Guinea-Pig Maximisation test was used to determine the skin sensitisation potential of the test item, aluminium hydroxide. Challenge with the test item produced no positive responses in the previously sensitised test animals or in the control animals. The incidence rate was 0% and the net score 0.00.

Thus, under the conditions of this test, aluminium hydroxide had no detectable sensitisation potential and does not meet EU criteria for classification for sensitisation (ECHA) [Kl. score = 2].

E. Repeated Dose Toxicity

<u>Oral</u>

An OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) GLP study was performed. No mortality or clinical signs of intoxication were observed in male and female Wistar rats due to treatment with Al chloride basic at dose levels of 40, 200 and 1000 mg/kg bw/day.

Treatment with Al chloride basic by oral gavage revealed paternal toxicity (irritation effect on glandular stomach mucosa, local effect) at 1000 mg/kg bw/day in both the male and

female Wistar rats. Based on findings observed macroscopically (red foci or thickening of the glandular mucosa of the stomach) and supported by microscopic examination, the maternal/parental NOAEL for local toxic effects on stomach was established at 200 mg/kg bw/day and LOAEL at the level of 1000 mg/kg bw/day, for both males and females.

No reproduction, breeding and early post-natal developmental toxicity was observed in rats at 1000 mg/kg bw/day for males and females. Based on the reported results, a NOAEL for reproduction, breeding and early post-natal developmental toxicity was suggested at a level of 1000 mg/kg bw/day (ECHA) [Kl. Score = 2].

Inhalation

An OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day Study) was performed on an unspecified rat strain. Intratracheal injection of aluminium powder (Al2O3 dust) caused nodular pulmonary fibrosis in the lungs of the rats only at the highest dose administered (100 mg). An NOAEC was determined to be 70 mg/m³ air (ECHA) [Kl. score = 3].

Dermal

No adequately or reliable studies are available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on CMW based on read-across from aluminium compounds are presented below in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on CMW[1]

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Mammalian cell gene mutation (OECD 476) (L5178Y mouse lymphoma cells)	-	-	2	ECHA

*+, positive; -, negative

1 – based on read across to aluminium compounds.

In Vivo Studies

An OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) was performed. No signs of general toxicity or bone marrow toxicity (based on the proportions of immature erythrocytes) were observed in this study. The authors concluded that aluminium hydroxide did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of male rats treated up to 2000 mg/kg/day (ECHA) [Kl. score = 2].

G. Carcinogenicity

Oral

No substance-specific data exist. Based on the weight of evidence approach for carcinogenicity resulting from animal exposure to surrogate substances (aluminium and

calcium dust) and epidemiological studies on cement workers, no classification for carcinogenicity is required (ECHA) (No Kl. score determined).

Inhalation

No studies are available.

H. Reproductive Toxicity

An OECD 426 was performed on Sprague Dawley rats. The ambiguity as to the critical period of exposure and the time-varying water consumption complicate the derivation of a point-of-departure from this study. A LOAEL of 1075 mg AlCitrate/kg bw/day (100 mg Al/kg bw/day) for aluminium toxicity is assigned. The critical effect was a deficit in fore- and hind-limb grip strength in the mid-dose group, supported by evidence of dose response and less consistently observed effects in the mid-dose animals: urinary tract lesions at necropsy (4 males, 1 female); body weight (mid-dose males weighed less than controls in the Day 120 cohort); defecation (more boluses produced by females in the mid-dose group compared with the controls); urination (mid-dose males produced more urine pools than controls); tail pinch (mid-dose females displayed more exaggerated responses); foot-splay (mid-dose females had significantly narrower foot-splay than the controls); and the albumin/globulin ratio (Day 64 mid-dose males had a greater mean ratio than the controls) (ECHA) [Kl. score = 2].

I. Developmental Toxicity

Oral

An OECD Guideline 414 (Prenatal Developmental Toxicity Study) was performed on Wistar rats.

The goal of study is to assess the developmental toxicity and embryotoxic/teratogenic potential of high doses of target compound - Al(OH)3 orally administered to rats during the period of active organogenesis. No significant general/maternal toxicity was observed in any Al treated groups that were orally exposed to Al hydroxide at doses 66.5, 133 and 266 mg Al/kg bw/day.

The results have contributed to the weight of evidence on the lack of pre-natal developmental toxicity of Al hydroxide administered orally to rats at high doses (66.6; 133 and 266 mg Al/kg bw/day (ECHA) [Kl. score = 2].

5 DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for CMW follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

Oral

The OECD Guideline 422 study was selected to determine guideline values. The NOAEL for reproduction, breeding and early post-natal developmental toxicity these studies is 1000 mg/kg-day. The NOAEL of 1000 mg/kg-day will be used for determining the oral Reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1

Oral RfD = 50/(10 x 10 x 1 x 1 x 1) = 1000/100 = 10 mg/kg-day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)
Drinking water guidance value = (10 x 70 x 0.1)/2 = 35 mg/L

B. Cancer

CMW was not carcinogenic to rats in chronic oral studies. Therefore, a cancer reference value was not derived.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

CMW does not exhibit the following physico-chemical properties:

- Explosivity

- Flammability
- Oxidising potential

7 ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

There are no studies available for “Reaction product of thermal process between 1000°C and 2000°C of mainly aluminium oxide and calcium oxide based raw materials with at least CaO+Al2O3 >80% , in which aluminium oxide and calcium oxide in varying amounts are combined in various proportions into a multiphase crystalline matrix”. As this substance is a UVCB substance with aluminium oxide (AL2O3) and calcium oxide (CaO) as the main constituents, data based on both main components were taken into account by read across following a structural analogue approach. Details from studies on surrogate substances are provided below.

B. Aquatic Toxicity

Acute Studies

Fish:

Thirteen acute toxicity studies for aluminium compounds to fish were found. All the studies are for informational purposes with a total of seven fish species, and are presented for demonstrating the completeness of the literature review. The available 96-h LC_{50}s varied from 0.078 to > 218.6 mg Al/L, and 16-d LC_{50}s ranged from 0.43 to 3.91 mg Al/L. The NOECs (96 h) varied from > 0.07 to > 50 mg Al/L (ECHA) [Kl. Score = 2].

Two short-term studies for calcium dihydroxide with fish were available. The findings for tests on rainbow trout (LC_{50} = 50.6 mg/L) were closely related to the initial pH of the test solutions. Therefore, the initial high pH is considered to be the main reason for the effects of the test item on the fish. The other short-term toxicity study for calcium dihydroxide with the marine species Gasterosteus aculeatus Linnaeus (threespine stickleback) was well described and a dose-response relationship was established (LC_{50} = 457 mg/L) (ECHA) [Kl. Score = 2].

Invertebrates:

Twelve short-term toxicity studies to six aquatic invertebrate species were identified for aluminium compounds. The available 48-h EC/LC_{50} values varied from 0.071 to > 99.6 mg Al/L. The acute NOECs (48 h) varied from > 0.005 to > 0.135 mg Al/L. Most of the variation in results can be explained by differences in hardness and DOC in the test media (ECHA) [Kl. Score = 2].

Two short-term toxicity studies with aquatic invertebrates are available for calcium dihydroxide. One study was conducted with Daphnia magna and the other one with a marine species. The short-term toxicity test with Daphnia magna was carried out according to the OECD 202 guidance taking into account GLP and thus resulting in a Klimish 1 score. The biological findings for Daphnia magna (immobility) were closely related to the initial pH

of the test solutions, which ranged from 7.7 in the controls to 9.5, 9.7, 10.1, 10.7 and 11.1 at 14.8, 22.2, 33.3, 50 and 75 mg Ca(OH)2 /L, respectively. Therefore the initial pH is considered to be the main reason for the effects of calcium dihydroxide on Daphnia magna.

Algae:

Six chronic toxicity studies to a freshwater microalga (Pseudokirchneriella subcapitata) were identified in the literature as Klimisch 1 or 2 studies. ECr10s and ECr50s ranged from 0.051 to 3.15 mg Al/L and 0.024 to 4.93 mg Al/L, respectively. Water quality data for these studies suggest a direct relationship between toxicity and pH, hardness and DOC.

Chronic Studies

Fish:

Four long-term reliable chronic toxicity studies for aluminium compounds to two species of fish (Pimephales promelas and Salveninus fontinalis) were identified as acceptable from the published literature. NOECs and EC_{10}s ranged from 0.088 to 2.3 mg Al/L and 0.078 to 5.19 mg Al/L, respectively (ECHA) [Kl. score = 2].

Invertebrates:

Six long-term chronic toxicity studies to two species of aquatic invertebrates (Ceriodaphnia dubia and Daphnia magna) were identified as acceptable studies. ECr_0 values were calculated using raw data provided from each study using the statistical program Toxicity Relationship Analysis Program (TRAP) version 1.10 from the US EPA National Health and Environmental Effects Research Laboratory (NHEERL). All other endpoints were as reported in each study. NOECs and EC_{10}s ranged from 0.076 to 4.9 mg Al/L and 0.021 to 0.997 mg Al/L, respectively. Water quality data for these studies suggest a direct relationship between toxicity and pH, hardness and DOC. For studies that experimentally manipulated water quality toxicity decreased with increasing pH, hardness and DOC (ECHA) [Kl. score = 2].

C. Terrestrial Toxicity

One short-term and one long-term study with Eisenia andrei are reported using soluble aluminium salts (ECHA). The studies are presented for completeness, but are not considered relevant for assessing the aluminium compounds being assessed in the dossier. In the short-term study, three aluminum salts were tested with an exposure period of 14 days. Three pH (KCl) levels were assessed, namely 3.3, 4.4 and 6.7. Aluminum chloride was most toxic and showed higher toxicity with lower pH levels. At pH (KCl) 4.4, the LC_{50} was 316 mg/kg dw (Al). Al2O3 did not affect survival at concentrations of 5000 mg/kg dw Al at pH levels of 2.4 and 7.1.

D. Calculation of PNEC

The above testing data is based on assumed release of aluminum and calcium from the CMW matrix. However, the substance "Reaction product of thermal process between 1000°C and 2000°C of mainly aluminium oxide and calcium oxide based raw materials with at least CaO+Al2O3 >80% , in which aluminium oxide and calcium oxide in varying amounts

are combined in various proportions into a multiphase crystalline matrix" is a UVCB substance.

In accordance with REACH Annex XI (1907/2006), it is scientifically not possible to determine the dissociation constant for such UVCB substances. Likewise, it is impossible to determine the pKa values of the single constituents in the UVCB by any mathematical calculation.

Based on the above noted information, PNECs are not applicable and will not be determined.

8 PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

CMW is an inorganic substance for which biodegradability is not relevant. Thus it does not meet the screening criteria for persistence.

CMW is an inorganic substance for which bioaccumulation is not relevant. Thus it does not meet the screening criteria for bioaccumulation.

There is data to suggest that aluminium and calcium may potentially exert toxic effects on aquatic receptors. However, there is no data to indicate the extent to which CMW might release aluminium and calcium. Moreover, the extent of aluminium or calcium toxicity appears to be highly related to receiving water chemistry. Therefore, specific toxicity of CMW is uncertain. Thus, CMW does not meet the screening criteria for toxicity.

Therefore, CMW is not a PBT substance.

9 CLASSIFICATION AND LABELLING

A. Classification

Causes serious eye damage H318.

B. Labelling

Danger

C. Pictogram

10 SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapor. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage
Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for CMW.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapor cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron, or full body suit will depend on the task.

Eye protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, as well as before eating, smoking and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

CMW is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

11 DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

12 REGULATORY STATUS

Australian AICS Inventory: Listed.

13 REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA] (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

DIAMMONIUM PEROXODISULPHATE

This dossier on diammonium peroxodisulphate presents the most critical studies pertinent to the risk assessment of diammonium peroxodisulphate in its use in drilling muds. It does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained primarily from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Diammonium peroxodisulphate

CAS RN: [redacted]

Molecular formula: $H_8N_2O_8S_2$

Molecular weight: 228.21 g/mol

Synonyms: Diammonium peroxydisulfate; Diammonium peroxydisulphate; Diammonium persulfate; Peroxydisulfuric acid (((HO)S(O)2)2O2), ammonium salt (1:2); Peroxydisulfuric acid (((HO)S(O)2)2O2), diammonium salt; Peroxydisulfuric acid, diammonium salt; ammonium persulphate

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Diammonium Peroxodisulphate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, odourless, crystalline solid	1	ECHA
Melting Point	ND. Decomposes at ca. 393 K (= 120°C) at 100.66 kPa	1	ECHA
Boiling Point	ND. Decomposes at ca. 393 K (= 120°C) at 100.79 kPa	1	ECHA
Density	1260 kg/m³ at 20°C	1	ECHA
Vapour Pressure	0 Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})	Not applicable as substance is inorganic	-	ECHA
Water Solubility	850 g/L @ 25°C	2	ECHA
Viscosity	ND. Substance is a solid at room temperature	-	ECHA
Dissociation constant (pKa)	Diammonium persulfate dissociates completely to ammonium cation and persulfate anion when it is dissolved in water.	-	ECHA
Flammability	Non-flammable	1	ECHA

ND – not determined

Diammonium peroxidisulphate is widely used in cosmetics and personal care products, perfumes and fragrances, adhesives and sealants, anti-freeze products, coating products, fillers, putties, plasters, modelling clay, non-metal-surface treatment products, inks and toners, leather treatment products, lubricants and greases, polishes and waxes and textile treatment products and dyes.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Diammonium peroxodisulphate dissociates in aqueous media to the ammonium cation and persulfate anion. Biodegradation is not applicable to inorganic compounds. Diammonium peroxodisulphate is not expected to bioaccumulate; it will dissociate to ions that are ubiquitous in the environment. Diammonium peroxodisulphate is not expected to adsorb to soil or sediment because of its dissociation properties and high water solubility.

B. Partitioning

Persulfates dissociate in water to the corresponding cation and persulfate anion. Hydrolysis is temperature and pH dependent. The persulfate anion, independent from the cation, undergoes decomposition in normal water or acid conditions, readily oxidising water to oxygen, producing acid conditions. All degradation products are ubiquitous to the environment (ECHA).

Diammonium peroxodisulphate was shown to be hydrolytically stable at 10°C and pH 4, 7 and 9, a minor hydrolysis was observed at 25°C, whereas a very strong hydrolysis at 60°C was observed within four days. The DT50 at pH 4 and 60°C was determined to be 27.2 h, at pH 7 and 9 and 60°C the DT50 was determined to be 36.5 h. The DT50 at environmentally relevant temperature (12°C) and pH 7 was extrapolated to be 1698.18 h (70.76 d) (ECHA) [Kl. Score = 1].

C. Biodegradation

Biodegradation is not applicable to inorganic compounds.

D. Environmental Distribution

No experimental data are available for diammonium peroxodisulphate. Persulfates are soluble in water and their vapour pressures are negligible. Thus, persulfates released into the environment are distributed into the water compartment in ionic form of the cation and persulfate ion. Persulfates are not expected to sorb to soil due to their dissociation properties, instability (hydrolysis) and high water solubility. They behave as free ions and decompose into sulfate and bisulfate ions. All decomposition products are ubiquitous in the environment (ECHA).

E. Bioaccumulation

There are no bioaccumulation studies on diammonium peroxodisulphate. Substances of the persulfate category are inorganic salts sharing the same anionic persulfate moiety. Persulfates are very soluble in water and are not expected to bioaccumulate in soil or aqueous solutions. They will decompose into organic sulfate or bisulfate (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Diammonium peroxodisulphate is irritating to the eyes, skin and respiratory tract. Inhalation of dust may cause asthma-like reactions. Repeated or prolonged contact may cause skin sensitisation. In a 90-day oral toxicity study in rats, systemic effects (intestinal changes) were observed at the highest dose (200 mg/kg bw/day). It is not carcinogenic or genotoxic, nor does the substance show evidence of reproductive or developmental toxicity.

B. Toxicokinetics/Metabolism

Persulphates are inorganic salts that decompose on heating without a definite melting point at temperatures above 100°C. Due to their properties as inorganic salts and considering their low vapour pressures, an exposure via inhalation is not very likely. Absorption by the skin is also not very likely. Generally, salts largely do not penetrate the skin. Persulphate salts rapidly hydrolyse upon contact with water or water vapour. As a result, persulphates will rapidly degrade and will eventually form the corresponding cations (ammonium, potassium, sodium) and persulphate anions. The persulphate anion, independent of the cation, undergoes further decomposition upon contact with water to form sulphate species. Based on these fundamental properties of persulphates, they are not likely to become bioavailable by inhalation, ingestion or contact by skin.

C. Acute Toxicity

Diammonium persulfate was tested for acute toxicity via the oral, dermal and inhalation routes in rats. In an acute oral toxicity study LD_{50} and LD_0 values of 742 mg/kg bw and 300 mg/kg bw, respectively, in the male rat and LD_{50} value of 700 mg/kg bw in the female rat were determined. In an acute dermal toxicity study LD_{50} and LD_0 values of greater than 2000 mg/kg bw and 2,000 mg/kg bw were determined, respectively. In an acute inhalation toxicity study (whole body exposure) LC_{50} and LC_0 values of greater than 2.95 mg/L and 2.95 mg/L, respectively, were determined.

D. Irritation

Diammonium peroxodisulphate is slightly irritating to the eye and skin of rabbits. Studies in humans indicate that aqueous solutions of 5% persulphate or higher can cause skin irritation.

E. Sensitisation

Results of animal skin sensitisation tests were negative when persulphate was applied topically but were positive when persulphate was injected intradermally. Repeated or prolonged contact may cause skin sensitisation.

F. Repeat Dose Toxicity

In a repeated dose 90-day oral toxicity study in rats (OECD Guideline 408), rats were fed three levels of test material, sodium persulphate (0, 300, 1000 and 3,000 ppm). On day 48 of the study, the concentration of the group receiving 1,000 ppm was increased to 5,000 ppm for the remainder of the study. The body weight of the rats in the two highest dose groups decreased during the last six weeks of treatment. There were no significant differences seen among the groups in urine analytical parameters, haematological blood parameters or both organ weight and body weight ratios. All rats survived the study. Intestinal changes were noted in rats which received 3,000 ppm of sodium persulfate for 13 weeks. These changes were seen more frequently among females than males. The

former received 50 percent more test material than the latter on a dose per body weight basis. No significant changes were seen among the controls or the groups which received 300 ppm, or 1,000 ppm in the diet for eight weeks, followed by 5,000 ppm in the diet for the remainder of the study. No other microscopic changes were noted on comparison among these three groups. LOAEL and NOAEL values of 200 and 91 mg/kg bw/day (3,000 and 1,000 ppm), respectively were determined.

G. Genotoxicity

Diammonium persulphate did not show any mutagenic effects in a bacterial reverse mutation assay.

H. Carcinogenicity

Diammonium persulphate of the persulphate category was tested for its skin carcinogenic potential in a 51-week dermal study with mice following a guideline similar to OECD Guideline 451. Based on the data obtained, diammonium persulphate was not considered carcinogenic. Diammonium peroxidisulphate is not listed in the Chemical Carcinogenesis Research Information System (CCRIS) or International Agency for Research on Cancer (IARC) databases or documented by USEPA as carcinogenic.

I. Reproductive/Developmental Toxicity

Diammonium persulphate was tested for oral reproductive/developmental toxicity in a screening test with rats according to OECD Guideline 421. No test substance-related effects were observed in P and F1 generations. A NOAEL value of 250 mg/kg/day for parental toxicity, reproduction parameters and developmental toxicity was determined. Dose levels were chosen based on the acute lethality studies for the ammonium salt and on a 90-day repeat-dose study in rats with the sodium salt (high dose: 225 mg/kg/day). In the developmental/reproduction study, animals were dosed prior to and during mating through gestation until lactation day 4. There was a transient depression in pup body weight at the 250 mg/kg dose level on lactation day 0 which resolved by lactation day 4. This effect was not considered adverse. Based on the available data, the persulphates do not show evidence of reproductive or developmental toxicity. The NOAEL is 250 mg/kg/day.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for diammonium peroxidisulphate follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021). There are no existing drinking water guideline values for ammonium ions.

A. Non-cancer

The substance will readily disassociate to its respective cations and anions. As noted above, there are no drinking water guidelines for ammonium ions as there is insufficient data to set a guideline value based on health considerations. The Australian Drinking Water Guideline value for sulphate may apply to sulphate ions (500 mg/L for health and 250 mg/L for taste aesthetic threshold). An ammonia guideline based on aesthetics is however 0.5 mg/L and will be used as drinking water guideline for this dossier.

B. Cancer

A cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Diammonium peroxidisulphate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Diammonium peroxodisulphate is of low toxicity concern to aquatic and terrestrial organisms.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies conducted on diammonium peroxodisulphate.

Table 2: Acute Aquatic Toxicity Studies on Diammonium Peroxodisulphate

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-hour LC_{50}	76.3 mg/L	1	ECHA
Daphnia magna	48-hour EC_{50}	120 mg/L	1	ECHA
Phaeodactylum tricornutum	72-hour EC_{10}	320 mg/L	1	ECHA

Chronic Studies

Long-term toxicity testing to fish was considered scientifically unjustified, due to the results obtained in the short-term toxicity to fish studies, the substance's physical-chemical properties and hydrolysis behaviour (ECHA).

An OECD Guideline 211 (Daphnia magna reproduction test) was performed and yielded a 21-day NOEC of 20.8 mg/L based on reproduction (ECHA) [KI Score = 1].

C. Terrestrial Toxicity

No terrestrial toxicity studies are available.

Persulfates are not expected to be distributed into the terrestrial compartment and consequently not expected to cause toxicity to terrestrial organisms and plants (ECHA).

D. Calculation of PNEC

$PNEC_{water}$

Experimental results are available for three trophic levels. Acute EC_{50} values are available for fish (76 mg/L), Daphnia (120 mg/L) and algae (84 mg/L). On the basis that the data consists of short-term

results from three trophic levels, an assessment factor of 1,000 has been applied to the lowest reported effect concentration of 76 mg/L for fish. $PNEC_{water}$ is 0.076 mg/L.

$PNEC_{sediment}$

No experimental toxicity data on sediment organisms are available. Diammonium peroxydisulphate dissociates completely in water with its environmental distribution is dominated by its high water solubility. K_{ow} and K_{oc} do not readily apply to inorganics, such as diammonium peroxidisulphate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sediment}$. Based on these properties, no adsorption of diammonium peroxydisulphate to sediment is to be expected.

$PNEC_{soil}$

No experimental toxicity data on terrestrial organisms are available. The environmental distribution of diammonium peroxydisulphate is dominated by its water solubility. Sorption of diammonium peroxydisulphate should probably be regarded as a reversible situation, i.e., the substance is not tightly nor permanently bound. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as diammonium peroxidisulphate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, diammonium peroxydisulphate is not expected to significantly adsorb to soil, and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Diammonium peroxodisulphate is an inorganic salt that dissociates to respective cations and anions. Biodegradation is not applicable to these inorganic ions. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Diammonium peroxodisulphate is not expected to bioaccumulate; it will dissociate to ions that are ubiquitous in the environment. Thus, the substance does not meet the screening criteria for bioaccumulation.

Chronic aquatic toxicity data is > 0.1 mg/L and acute aquatic toxicity data is >1 mg/L. Thus, diammonium peroxodisulphate does not meet the screening criteria for toxicity.

The overall conclusion is that diammonium peroxodisulphate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H272: May intensify fire; oxidiser.

H302: Harmful if swallowed.

H315: Causes skin irritation.

H317: May cause an allergic skin reaction.

H319: Causes serious eye irritation.

H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.

H335: May cause respiratory irritation.

B. Labelling

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Separate eyelids with fingers. Get medical attention.

Skin Contact

Remove contaminated clothing and shoes. Wash skin thoroughly with soap and water. Get medical attention.

Inhalation

If inhaled, remove from area to fresh air. Lay down quietly in recovery position. If breathing is difficult, give artificial respiration with breathing bag. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: sulphur oxides, nitrogen oxides, toxic pyrolysis products.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use personal protective clothing. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust. Wear respiratory protection if ventilation is inadequate. Avoid contact with skin, eyes and clothing.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove. Avoid dust formation. Store in closed containers and dispose of in accordance with federal, state and local regulations. Clean up spill area and treat as special waste.

D. Storage and Handling

General Handling

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust. Take off contaminated clothing and shoes. Wash thoroughly after handling. Do not eat, drink or smoke during work.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place. Do not store with alkalis, acids, or reducing agents.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for ammonium persulphate in Australia is 0.01 mg/m^3 as a peak exposure. A peak limitation is defined by Safe Work Australia as a maximum or peak airborne concentration of a substance determined over the shortest analytically practicable period of time which does not exceed 15 minutes.

Engineering Controls

Ensure adequate ventilation. Localised ventilation should be used to control dust levels below permissible exposure limits.

Personal Protection Equipment

Respiratory Protection: Use respiratory protection when airborne concentrations are expected to be high.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Wear suitable protective goggles (tightly fitting). Also wear face protection if there is a splash hazard. Ensure that eyewash stations and safety showers are close to the workstation location.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible. Remove and wash contaminated clothing before re-use. Contaminated work clothing should not be allowed out of the workplace.

F. Transport Information

UN1444 AMMONIUM PERISULPHATE

Class: 5.1

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol, Pharmacol. 25:1-5.

DICOCO DIMETHYL QUATERNARY AMMONIUM CHLORIDE

This dossier on dicoco dimethyl quaternary ammonium chloride (DQAC) (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. For the purposes of this dossier, a surrogate substance of like composition (Quaternary ammonium compounds, coco alkyltrimethyl, chlorides) (CAS RN [redacted] will be evaluated. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

1 SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Quaternary ammonium compounds, cocoalkyl trimethyl, chloride

CAS RN: [redacted]

Molecular formula: Not applicable (UVCB substance)

Molecular weight: Not applicable (UVCB substance)

Synonyms: Coco alkyltrimethyl ammonium chlorides, Quaternary ammonium compounds, coco alkyltrimethyl, chlorides

SMILES: Not applicable (UVCB substance)

2 PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of DQAC[1]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Amorphous wax-like oyster white solid	1	ECHA
Melting Point	No melting point could be determined, as the test substance undergoes decomposition before melting at a temperature >160°C	1	ECHA
Boiling Point	No boiling point could be determined as the test substance undergoes decomposition before boiling at >160°C.	1	ECHA
Density	0.935 g/cm^3 at 20°C	1	ECHA
Vapour Pressure	0.002 Pa at 25°C	1	ECHA
Partition Coefficient (log K_{ow})	2.39 at 20°C	1	ECHA

Property	Value	Klimisch score	Reference
Water Solubility	1,000 mg/L at 20°C	1	ECHA
Flash Point	Flash point is only relevant to liquids and low melting point solids	1	ECHA
Auto flammability	No self-ignition temperature was observed up to the maximum temperature of 405°C	1	ECHA
Viscosity	30.2mm²/s at 20°C	1	ECHA

1 – Data taken from testing on the surrogate quaternary ammonium compounds, coco alkyltrimethyl, chlorides (CAS RN [redacted]

3 ENVIRONMENTAL FATE PROPERTIES

A. Summary

DQAC is readily biodegradable, is unlikely to bioaccumulate, and has the potential to bind to soils and sediments. Details of supporting studies are provided below.

B. Biodegradation

An OECD Guideline 301 D (Ready Biodegradability: Closed Bottle Test) was performed on DQAC. The test substance at 3 mg/L was incubated with sludge from activated sludge plant treating predominantly domestic waste and O2 consumption was determined over a period of 28 days. The biodegradation was calculated as the ratio of the biochemical oxygen demand to the theoretical oxygen demand. The test substance reached a biodegradation of 75% at Day 28. Therefore, DQAC is considered readily degradable (ECHA) [KI Score = 2].

C. Environmental Distribution

Adsorption/desorption

An OECD Guideline 106 (Adsorption - Desorption Using a Batch Equilibrium Method) was performed on three soils and read across Quaternary ammonium salts (QAS) category. The experimentally determined mead Koc value of 1,640,329 L/kg is read across from QAS category substance. DQAC is expected to show a similar behaviour in soil (ECHA) [KI Score = 2].

D. Bioaccumulation

No data were available for bioaccumulation of DQAC. However, based on the low log Kow of 2.39, substantial bioaccumulation is not expected (ECHA) [KI Score = 2].

4 HUMAN HEALTH HAZARD ASSESSMENT

A Summary

DQAC is of low acute and chronic toxicity concern to human receptors. Details from animal studies are provided below.

B Acute Toxicity

Oral

An OECD Guideline 401 (Acute Oral Toxicity) was performed. The study was conducted to determine the acute oral toxicity of the test substance in Sprague-Dawley rats according to OECD 401 and EPA OPP 81-2 Guidelines, in compliance with GLP. Groups of 10 fasted animals (five males and five females per dose except for five males only at the highest dose) were administered 0, 512, 620, 750 or 908 mg/kg bw of the test substance via the oral route. The animals were observed for 14 days after dosing and then sacrificed and subjected to gross pathological examination. There was no mortality in the 512 mg/kg bw group while 3 out of 10 and 7 out of 10 rats died in the 620 and 750 mg/kg bw groups, respectively. All five animals in the highest dose group (908 mg/kg bw) died. Under the study conditions, the acute oral LD_{50} of the test substance in Sprague-Dawley rats was determined to be 684 mg/kg bw (i.e., equivalent to 226 mg a.i./kg bw) (ECHA) [Kl. score =1].

Inhalation

No acute inhalation data were found for DQAC.

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) was performed using New Zealand White rabbits. Under the conditions of the test, the acute dermal LD_{50} for male and female albino rabbits were determined to be 1,300 mg/kg bw (i.e., equivalent to 429 mg a.i./kg bw) and 1,900 mg/kg bw (i.e., equivalent to 627 mg a.i./kg bw) respectively, and the combined dermal LD_{50} was determined to be 1,600 mg/kg bw (i.e., equivalent to 528 mg a.i./kg bw) (ECHA) [Kl Score=1].

C Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was conducted to determine the skin irritation potential of a surrogate quaternary ammonium substance, Coco TMAC (active ingredient 33%), using New Zealand White rabbits. Six animals were treated with 0.5 mL undiluted test substance (33%) in a semi-occlusive patch (1" X 1" gauze) that was overwrapped with a gauze binder and secured with dermiform tape. Plastic restraint collars were applied and remained on the animals for the duration of the 4 h exposure period, after which the tape and test substance were removed. The Draize classification scoring criteria were used to evaluate the irritation potential. Application sites were observed for erythema and oedema at 4, 24, 48 and 72 h after exposure and then daily up to 14 d. The test substance induced moderate erythema and moderate to severe oedema on all sites.

Remission of irritation signs occurred as the study progressed; however, moderate irritation was still present in one rabbit after study Day 12 (erythema: 2 'slight'; edema:1 'barely perceptible'). In addition, desquamation was noted on all sites late in the study period and fissuring was present on two sites. The Primary Irritation Index was calculated to be 5.6

(indicative of moderate irritation). Under the study conditions, due to persistence of irritation reactions in one animal as well as desquamation on all sites and fissuring on 2 sites, the test substance is considered to be severely irritating to skin (ECHA) [Kl. score = 1].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) primary eye irritation study was performed using a surrogate substance, quaternary ammonium salt. Nine New Zealand White rabbits received 0.1 mL of undiluted solution in one eye. The other eye remained untreated. The eyelids were held closed for approximately 1 second after instillation. The eyes of three rabbits were washed for approximately 1 minute with 120 mL of lukewarm tap water commencing approximately 30 seconds after dosing. Both eyes were examined for ocular irritation in accordance with the method of Draize approximately 1, 24, 48 and 72 h after dosing and at 96 h and 7, 14 and 21 d. In addition, both eyes of all rabbits were further examined at 72 h and 7, 14 and 21 d with sodium fluorescein and ultraviolet light. Body weights were obtained and recorded on study day 0 (initiation) and at termination (Day 21). Based on the data obtained, the Maximum Average Scores (according to Kay and Calandra scoring system) for the test substance were calculated to be 96.8 (extremely irritating) at 14 d for the unwashed group and 69.7 (severely irritating) at both 72 and 96 h for the washed group. Purulent discharge, clear discharge, petite haemorrhage, blanching, corneal epithelial damage and peeling, corneal neovascularisation, sodium fluorescein stain retention, and vascularised granulation scar tissue was observed in all 6 animals. Same effects were observed in the washed group, except for vascularised granulation scar tissue. There were no deaths or remarkable body weight changes during the study period. Under the study conditions, the test substance is considered to cause irreversible effects on the eye (ECHA) [Kl. score = 1].

Sensitisation

An OECD Guideline 406 (Skin Sensitisation) study (i.e., Buehler test) was performed on Dunkin-Hartley guinea pigs.

The study was conducted to determine the sensitising potential of a read across substance, C12 -14 trimethyl ammonium chloride (TMAC). A pre-test was conducted to determine non-irritating concentrations to be used in the main study. For the main study the induction was carried out at: topical 0.1% w/v in aqueous ethanol for 6 h, repeated after 7 and 14 d. Challenge was done two weeks after the last induction treatment (Day 28): control and test animals received 0.1% w/v in acetone for 6 h on previously untreated site under closed patches. After 18 h the sites were treated with depilatory cream, rinsed and dried. After 3 h, challenge sites were evaluated for erythema on a scale of 0-3. Evaluation was repeated 24 h later. Results of the first grading were: 0/20 (3/20 showed a grade of 0.5; in control 2/10 showed a grade 0.5). Second grading: 0/20 (no erythema was observed in any of the animals); test substance was considered to be non-sensitising (ECHA) [Kl. score = 1].

D Repeated Dose Toxicity

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity Study in Rodents) was performed using Sprague Dawley rats. The 90-day study was conducted to determine the oral repeated dose toxicity of the test substance, Coco TMAC. Sprague-Dawley rats were administered the test substance at concentrations of 0, 100, 500 or 2000 ppm (i.e., corresponding to 0, 22, 113 and 273 mg/kg bw/day in males and 0, 25, 121, 297 mg/kg bw/day in females) in the diet for 90 d. The active ingredient dose equivalent was calculated to be 0, 7.9, 40.3 and 96.9 mg a.i./kg bw/day in males and 8.8, 42.9, 105.3 mg a.i./kg bw/day in females. The highest dose of 2000 ppm was reduced to 1000 ppm from Day 29 onwards due to deterioration in health of the test animals at 2000 ppm. At the highest dose, the treatment-related findings were clinical signs of toxicity, reduced body weight gain and food efficiency, organ weight changes and microscopic changes in the spleen and kidneys. At the mid dose, reduced body weight gain (males) and reduced food consumption, reduced absolute heart weight and higher incidence of haemosiderin accumulation in the kidneys of males was observed. No treatment-related effects were observed at the lowest dose. Based on the results of the study, dietary administration of the test substance to rats for a period of 90 d at levels up to 273 mg/kg bw/day resulted in toxicologically significant effects at the high dose and marginal effects at the next lower dose of 113 mg/kg bw/day (500 ppm). No such effects were demonstrated at the lowest dose of 22 mg/kg bw/day (100 ppm). The changes observed at the mid dose (500 ppm) were considered to be minor, isolated effects associated with the reduced palatability of the test substance and were considered not to represent an adverse health effect. Therefore, based on effects on body weight, food efficiency and clinical signs the study authors established the NOAEL at the mid dose level of 500 ppm (i.e., equivalent to 40.3 mg ai./kg bw/day) (ECHA) [Kl. Score = 1].

Inhalation

No data were available.

Dermal

An OECD Guideline 410 (Repeated Dose Dermal Toxicity: 21/28-Day Study) was performed on New Zealand White rabbits. The 28-day study was conducted to determine the repeated dose dermal toxicity of the read across substance, C16 TMAC, in New Zealand albino rabbits (both sexes).

The purity was not specified and the study included a lower than recommended number of animals (i.e., 10/group rather than 20/group as per guideline) and histopathology was performed only on limited organs. The test substance (0 and 10 mg test substance/kg bw/day) was applied to the shaved, intact skin of groups of 5 New Zealand albino rabbits/sex/group for 6.5 to 7 hours, 5 days/week for 4 weeks.

Dermal irritation readings were recorded daily. The animals were weighed weekly during the exposure period. Blood was collected for haematology measurements before initiation of dosing and prior to termination. Liver and kidneys weights were recorded at necropsy and

limited histopathology was conducted. There were no systemic treatment-related effects on body weights, haematology, organ weights, gross necropsy findings or histopathology. Treated areas of the skin showed mild to marked acanthosis with active mitosis, hyperkeratosis, and partial to extensive necrosis of the epidermis and hair follicles, partly with encrustation and exudate. Based on the results of the read across study, the NOAEL for systemic effects of DQAC (by read across to Coco TMAC therefore can be considered to be at 10 mg/kg bw/day (ECHA) [KI Score = 2].

E Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on DQAC based on read-across from aluminium compounds are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on DQAC[1]

Test System[1]	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) (Bacterial Reverse Mutation Assay)	-	[1]	2	ECHA

*+, positive; -, negative

1 – based on read across to Coco TMAC.

In Vivo Studies

An OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) was performed. The study was conducted to determine the clastogenic potential of a surrogate test substance, Coco TMAC (active ingredient 33%). Based on the results of a dose range finding assay, a dosage of 468 mg/kg bw (in1% methyl cellulose) was administered by oral gavage to male and female mice. Following dosing, the animals were examined regularly for any clinical signs of reaction.

Bone morrow smears were obtained at 3 sampling times: 24, 48 or 72 hours after dosing. One smear from each animal was examined for the presence of micronuclei in 1000 polychromatic erythrocytes. The ratio of polychromatic to normochromatic erythrocytes was assessed by examination of at least 1000 erythrocytes from each animal. A vehicle control (1% methylcellulose) and a positive control with mitomycin C by intraperitoneal injection were included. At all sampling times, mice treated with the test substance showed no significant increase in the frequency of micronucleated polychromatic erythrocytes. There was no significant decrease in the ratio of polychromatic to normochromatic erythrocytes at any of the three kill times after treatment. The positive control compound, mitomycin C, produced large, highly significant increases in the frequency of micronucleated polychromatic erythrocytes together with large decreases in the ratio of polychromatic to normochromatic erythrocytes and increases in the frequency of micronucleated normochromatic erythrocytes. Under the conditions of the study, the test substance, and by

association DQAC, was found to show no evidence of clastogenic potential in the bone marrow cells of mice (ECHA) [Kl. score = 1].

F Carcinogenicity

Oral

No substance specific data exist.

Inhalation

No studies are available.

Dermal

No studies are available.

G Reproductive Toxicity

Oral

See discussion on developmental toxicity below.

H Developmental Toxicity

Dermal

There are no oral developmental toxicity studies of DQAC. However, there is a dermal developmental toxicity study (OECD Guideline 414 - Prenatal Developmental Toxicity Study) of QAS category using C16 TMAC as a surrogate.

The study was conducted in New Zealand White rabbits. Twenty mated female rabbits per group were exposed topically (daily for 2 hours) from Days 7 to 18 of gestation at concentrations of 0, 0.5, 1.0, or 2.0% (equivalent to 0, 10, 20 and 40 mg a.i./kg bw/day, respectively). The control group was treated with deionised water only. Clinical condition and reactions to treatment were recorded at least once daily. Body weights were recorded on Days 0, 3, 6, 9, 12, 15, 18, 21, 24, 27 and 29 of gestation. All surviving females were sacrificed on Day 29 of gestation and the foetuses were removed by caesarean section. At necropsy the females were examined macroscopically. Live foetuses were weighed, sexed and were examined for visceral and skeletal abnormalities. Two control animals, one intermediate and one high dose died during the study. Two of the rabbits that died were aborted prior to death (one control and one intermediate dose). Two additional abortions occurred, one each in the intermediate and high dose groups. Deaths or abortions were not considered to be related to the test substance.

No treatment-related maternal body weight or food intake effects were noted. The incidence of foetal malformations, as well as genetic and developmental variations in the treated groups was comparable to that of the control group. No other treatment-related

effects were noted. Under the study conditions, the NOAEL of DQAC for maternal as well as developmental toxicity is considered to be 40 mg/kg bw/d in rabbits [Kl. score = 1].

5 DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for DQAC follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

Oral

The repeated dose NOAEL for DQAC has been determined to be 40.3 mg ai./kg bw/day. Thus, the NOAEL of 40.3 mg/kg-day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1

Oral RfD = 50/(10 x 10 x 1 x 1 x 1) = 40.3/100 = 0.4 mg/kg-day.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

where:

Human weight = 70 kg (ADWG, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (0.4 x 70 x 0.1)/2 = 1.4 mg/L

B. Cancer

No data on carcinogenicity was available. Therefore, a cancer reference value was not derived.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

DQAC does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

7 ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Details from studies on surrogate substances are provided below.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on DQAC.

Table 3: Acute Aquatic Toxicity Studies on DQAC[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Salmo gairdneri	96 h LC_{50}	3.2	2	ECHA
Daphnia magna	48 h EC_{50}	0.09	2	ECHA
Pseudokirchneriella subcapitata	72 h EC_{50}	0.062	2	ECHA

1 – data abstracted from quaternary ammonium compounds, Coco TMAC

Chronic Studies

Fish:

A study was conducted to determine the long-term toxicity to Fathead minnow (Pimephales promelas) of the read-across substance, C12-16 ADBAC (purity: 30%). Mortality, hatchability and growth were evaluated. Fish eggs (80 per concentration) were exposed for 34 d to mean measured concentrations of 0, 32.3, 75.9, 134.2, 186.8, 273.2 and 488.7 mg a.i./L of the radiolabelled test substance. Analytical determination was performed and the sample concentrations were verified by liquid scintillation counting. After 7 d, surviving fry from two replicates were thinned to 10 animals per replicate for each exposure group (total of 20 animals per concentration) and exposed to the same concentrations for a 28 d post-hatch static renewal toxicity test. Observations of symptoms and mortality were conducted daily. Under the conditions of the study, the 34 d NOEC for hatchability was 0.274 mg/L, the 34 d

NOEC and LC_{50} for survival were 0.032 and 0.094 mg a.i./L, respectively, and the 34 d NOEC for growth was
> 0.032 mg/L. Based on the results of the read across study, the 34 d NOEC of 0.032 mg/L is considered relevant for DQAC (ECHA) [KI Score = 2).

Invertebrates:

A study was conducted to determine the long-term toxicity to aquatic invertebrates of the read across substance, C16-18 and C18-unsaturated TMAC as a suitable surrogate for DQAC according to OECD Guideline 211.

Daphnia magna were exposed to six concentrations of the test substance in a 21-day static-daily renewal test in three different water types (i.e., laboratory blended water, well water and river water).

Analytical determination of the test substance was performed. Measured concentrations (µg/L; values represent the geometric mean of the 0- and 24-hour concentration analyses) were southwest well water at 1.6, 3.1, 6.8, 14.6, 30.6 and 60.8 µg a.i./L and river water at 35.7, 53.4, 68.3, 99.1, 122.3 and 309.3 µg a.i./L. The test in blended water was discontinued after 14 d due to inadequate reproduction by control organisms.

Mortality was monitored daily and the number of young produced in each beaker was recorded. Test substance concentrations were verified by analysis and represent the geometric mean of the 0 and 24 h concentration. Under the test conditions, the 21d NOEC of the test substance to *Daphnia magna* was equivalent to 0.0068 and 0.099 mg/L in southwest well and river water, respectively. The NOEC for DQAC was considered equal to 0.0068 mg/L (ECHA) [KI Score = 2].

C. Terrestrial Toxicity

No data were available.

D. Calculation of PNEC

The PNEC calculations for DQAC follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. The lowest acute EC_{50} value was 0.062 mg/L. On the basis that the data consists of short-term studies for three trophic levels, an assessment factor of 100 has been applied to the lowest reported EC_{50} value of 0.062 mg/L. Therefore, the PNECwater is 0.00062 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Moreover, the substance is expected to substantially disassociate to partition to sediments. Nonetheless, a PNECsed

was calculated using the equilibrium partitioning methodology. The PNECsed is 15.5 mg/kg sediment wet weight.

The calculations are as follows:

PNECsed = (Ksed-water/BDsed) x 1000 x PNECwater
= (3.2x10^4/1280) x 1000 x 0.00062
= 15.5

Where:

Ksed-water = suspended matter-water partition coefficient (m^3/m^3)
BDsed = bulk density of sediment (kg/m^3) = 1,280 [default]

Ksed-water = 0.8 + [(0.2 x Kpsed)/1000 x BDsolid]
= 0.8 + [(0.2 x 1.25x10^5/1000 x 1,280]
= 3.2x10^4

Where:
Kpsed = solid-water partition coefficient (L/kg)
BDsolid = bulk density of the solid phase (kg/m^3) = 2,400 [default]

Kpsed = Koc x foc
= 3.1x10^6 x 0.04
= 1.2x10^5

Where:

Koc = organic carbon normalised distribution coefficient (L/kg). The Koc was calculated as the midpoint of modelled Koc range and determined to be 3.1x10^6 L/kg.
foc = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the PNECsoil was calculated using the equilibrium partitioning method. The PNECsoil is 25.6 mg/kg soil dry weight.

The calculations are as follows:

PNECsoil = (Kpsoil/BDsoil) x 1000 x PNECwater
= (6x10^4/1500) x 1000 x 0.00062
= 25.6

Where:

Kpsoil = soil-water partition coefficient (m^3/m^3)
BDsoil = bulk density of soil (kg/m^3) = 1,500 [default]

Kpsoil = Koc x foc
= $3.1x10^6$ x 0.02
= $6.2x10^4$

Where:

Koc = organic carbon normalised distribution coefficient (L/kg). The Koc was calculated as the midpoint of modelled Koc range and determined to be $3.1x10^6$ L/kg.
Foc = fraction of organic carbon in soil = 0.02 [default].

8 PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

DQAC is an organic substance that has been determined to be readily biodegradable. Thus, it does not meet the screening criteria for persistence.

The estimated log Kow is equal to 2.39. Based on the log Kow, DQAC will not have a tendency to bioaccumulate (ECETOC, 2000). Therefore, DQAC does not meet the screening criterion for bioaccumulation.

DQAC is a high toxicity concern based on the results presented in Table 3. Thus, DQAC does meet the screening criteria for toxicity.

However, based on PBT assessment guidance cited above, DQAC is not a PBT substance.

9 CLASSIFICATION AND LABELLING

A. Classification

Acute toxicity - oral

Acute Tox. 3 H301: Toxic if swallowed.

Acute toxicity - dermal

Acute Tox. H311: Toxic in contact with skin.

Skin corrosion / irritation Skin Corr. 1C H314: Causes severe skin burns and eye damage.

Serious eye damage / eye irritation

Eye Damage 1 H318: Causes serious eye damage.

B. Labelling

Danger

C. Pictogram

10 SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapor. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for DQAC.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls

to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be an effective type of air-purifying respirator: organic vapor cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, before eating, smoking, and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

DQAC is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

11 DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

12 REGULATORY STATUS

Australian AICS Inventory: Listed.

13 REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECETOC. (2000). Persistent organic pollutants. Response to UNEC/INC/ CEG-1. Annex 1, Document No. 41. Brussels, Belgium.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA] (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

DISTILLATES (PETROLEUM), SOLVENT-DEWAXED HEAVY PARAFFINIC

This dossier on distillates (petroleum), solvent-dewaxed heavy paraffinic (DPHP) presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

1 SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Solvent-dewaxed heavy paraffinic distillate

CAS RN: [redacted]

Molecular formula: Not applicable (UVCB substance)

Molecular weight: ≥ 72 - ≤ 828 g/mol

Synonyms: None available

SMILES: Not applicable (UVCB substance)

2 PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of Distillates (petroleum), Solvent-dewaxed Heavy Paraffinic

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Liquid	1	ECHA
Melting Point	-60°C to 0°C	2	ECHA
Boiling Point	200°C to 800°C	2	ECHA
Density	0.81 to 0.97 g/cm^3 at 15°C	2	ECHA
Vapour Pressure	<0.1 hPa at 20°C	2	ECHA
Partition Coefficient (log K_{ow})	1.99 to 18.02 Midpoint of these values is log Kow = 8[1]	2	ECHA
Water Solubility	2.69E-12 to 2000 mg/L [1]	2	ECHA
Flash Point	>115 to 268°C	2	ECHA
Auto flammability	NA	2	ECHA
Viscosity	1.99 to 847 mm^2/s at 40°C	2	ECHA

1 - Standard tests for this endpoint are intended for single substances and are not appropriate for this complex substance.

3 ENVIRONMENTAL FATE PROPERTIES

A. Summary

DPHP is inherently biodegradable. There is a potential for bioaccumulation given the large range of Kow values for single constituents of the distillate mix. However, the inherent biodegradability of the substance suggests that bioaccumulation of the distillate mix would be mitigated. Similarly, binding to soils and sediment may occur but environmental degradation is expected to reduce the extent of sorption. Details of supporting studies are provided below.

B. Biodegradation

In a biodegradability study, Solvent Neutral 600 Base Oil (MRD-94 -981) was determined to be inherently biodegradable but not readily biodegradable with a mean degradation of 31.13% by day 28 (ECHA)[KI Score = 2].

C. Environmental Distribution

Adsorption/desorption

The substance is a hydrocarbon UVCB. Standard tests for this endpoint are intended for single substances and are not appropriate for this complex substance. Calculated log K_{oc} for constituents of this substance range between 1.71 and 14.70. A midpoint for these data is 6.495 resulting in a K_{oc} value of $3x10^6$. Note that this is the full range of predicted values and that this may be misleading or unrepresentative of the properties of the UVCB substance as a whole (ECHA) [KI Score = 3].

D. Bioaccumulation

The substance is a hydrocarbon UVCB. Standard tests for this endpoint are intended for single substances and are not appropriate for this complex substance. Calculated BCF for constituents of this substance range between 0.4 and 71,100 L/kg. Note that this is the full range of predicted values and that this may be misleading or unrepresentative of the properties of the UVCB substance as a whole (ECHA) [KI Score = 3].

4 HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

DPHP is of low acute and chronic toxicity concern to human receptors. Details from animal studies are provided below.

B. Acute Toxicity

Oral

An OECD Guideline 401 (Acute Oral Toxicity) was performed. Paraffinic oil sample API 78-9 (CAS No. [redacted] was administered via oral gavage to five Sprague-Dawley rats per sex at a single dose of 5,000 mg/kg (5 g/kg).

The rats were observed for clinical signs of toxicity, changes in body weight, and other gross abnormalities over a 14-day post-exposure observation period. All rats were killed and necropsied on day 14.

No mortalities or any sign of clinical sign of toxicity were observed in either male or female rats dosed at 5,000 mg/kg. Body weight gain was observed to be normal in all animals. One animal did exhibit hydronephrosis in the right kidney but this was not considered to be treatment-related. Necroscopy did not reveal any gross abnormalities in either male or female rats.

The acute oral LD_{50} was determined to be >5,000 mg/kg (ECHA) [Kl. score =1].

Inhalation

An OECD Guideline 403 (Acute Inhalation Toxicity) study was performed.

A group of five male and five female rats were exposed for 4 hours to an aerosol of the test material at a target concentration of 5 mg/L. Four additional groups of rats were then exposed for 4 hours to target aerosol concentrations of 1, 1.5, 2.5 and 3.5 mg/L. A control group exposed, in the chamber, to air only was also included. Animals were observed continuously during the first hour of exposure, hourly for the remainder of the exposure and once daily for the 14-day post exposure period. Mortalities were recorded and body weights were measured prior to exposure and again 7 and 14 days after exposure. On the 14th day post-exposure, necropsies were performed on all surviving animals. For all animals, including animals found dead, the lungs and any other abnormal tissues were removed and fixed for subsequent histopathological examination.

The LC_{50} for males and females was 2.18 mg/L with 95% confidence limits at 1.80 to 2.55 mg/L for insufficiently refined lubricant base oil (ECHA) [Kl. score = 1].

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) was performed using New Zealand White rabbits. API 78-9 was administered to four New Zealand White rabbits/sex at a dose of 5000 mg/kg for 24 hours. Prior to application of the test material, the exposure sites of four rabbits were abraded by making epidermal incisions. The remaining four rabbits were left unbraded. Another group of eight (four/sex) rabbits were used as control animals.

Behavioural reactions were monitored through the 24-hour contact period. Mortality, clinical signs of toxicity and behavioural abnormalities were observed twice daily through the 14-day post-exposure observation period. Body weight was recorded for all animals on Day 0, 7 and 14 of the study period. On Day 14 all animals were necropsied and observed for gross pathological changes.

Dermal administration of residual oils (petroleum), catalytic dewaxed (API 78-9)at 5000 mg/kg did not result in any dermal irritation or signs of clinical toxicity. Gross necroscopy did not reveal any signs of systemic toxicity at the 5000 mg/kg dose level.

The acute dermal LD_{50} for API 78-9 is greater than 5000 mg/kg (ECHA) [Kl Score=1].

C. Irritation

Skin

In a primary dermal irritation study, six New Zealand White rabbits (three male/three female) were dermally administered 0.5 mL solvent dewaxed light paraffinic oil (API 78-9, CAS [redacted] under occlusive wrap for 24 hours. After the exposure period, the bandages were removed and test sites were wiped with gauze sponges. The animals were observed thereafter and dermal irritation was scored using the Draize method at 24 hours, 72 hours and on Day 7 post-exposure.

Oedema was not apparent in male or female rabbits at any observation point. Very slight erythema was evident in all male and female rabbits at the 24-hour observation point. Very slight erythema was observed in only one male rabbit by the 72-hour observation point and no irritation was visible in any test animal by the end of the 7-day observation period. No differences in irritation were observed between intact and abraded skin sites.

Solvent dewaxed light paraffinic oil is not considered to be irritating to the skin of rabbits (ECHA) [Kl. score = 2].

Eye

In a primary eye irritation study, six New Zealand White rabbits (three male, three female) had 0.1 mL of dewaxed light paraffinic oil instilled into the conjunctival sac of their right eye. The left eyes of these rabbits served as treatment controls. Additionally, three rabbits (two male, one female) were administered the test material in the right eye and the eyes were rinsed with warm water 30 seconds following exposure.

Ocular lesions were observed for at 24, 48 and 72 hours post-exposure and fluorescein dye evaluations employed for each reading. Grading and scoring of ocular irritation was performed according to the Draize method.

Rabbits with washed eyes exhibited no irritation through the 72-hour observation period. A single male rabbit in the unwashed group exhibited conjunctival chemosis at the 48-hour observation period. The remaining rabbits showed no signs of irritation through the study period.

Solvent dewaxed light paraffinic oil is not considered to be an ocular irritant (ECHA) [Kl. score = 1].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) was performed . This study was performed in Hartley Guinea pigs.

In the induction phase of a skin sensitisation study, 0.4 mL of a 50% mixture of test material and paraffin oil was applied under an occlusive dressing to the shorn skin of 10 male and 10 female animals. Six hours after application, the dressings were removed and the skin wiped to remove residues of test material. The animals received one application each week for three weeks. The same application site was used each time. Two weeks following the third

application, a challenge dose (0.4 mL of a 1% mixture in paraffin oil) was applied in the same manner as the sensitising doses. A previously untreated site was used for the challenge application. The application sites for induction and challenge doses were read for erythema and oedema 24 and 48 hours after patch removal. To assist in the reading of the response to the final challenge dose, the test site was depilated three hours prior to reading by using a commercially available depilatory cream. 2,4-dinitrochlorobenzene at 0.3% in 80% aqueous ethanol was used as the positive control in the induction phase and 2,4-dinitrochlorobenzene in acetone was used as the positive control in the challenge phase. Vehicle control and naive control groups were included in this study and the procedure for these was the same as for the test groups.

In the challenge phase, one animal in the treatment group exhibited a very slight erythema reaction. No animals exhibited reaction in the naive or vehicle control group. In the positive control group, 20 animals exhibited a very slight to severe irritation reaction. The reactions of 18 animals exceeded the highest reaction observed in the naive positive control animals. In the naive positive control group, three animals exhibited very slight erythema reactions. Based on these results, the test material is not considered to be a skin sensitiser under the conditions of this study (ECHA) [Kl. score = 1].

E. Repeated Dose Toxicity

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity Study in Rodents) was performed. Heavy paraffinic distillate aromatic extract was administered to 10 male Sprague-Dawley rats/dose at dose levels 0, 125 or 500 mg/kg bw/day 5 days a week for 13 weeks. Four of 10 mice in the 500 mg/kg/day group were sacrificed prior to scheduled termination. All animals in the 125 mg/kg/day survived to date of sacrifice. No details on clinical signs were provided. Body weight was significantly reduced in the 500-mg/kg/day group. A significant decrease ($p<0.05$) was shown in red blood cell (RBC) parameters (including RBC count, haemoglobin and haematocrit) and platelet in males dosed orally at 500 mg/kg/day. Males orally dosed at 125 mg/kg/day showed a significant decrease in RBC parameters; platelet counts were slightly decreased in these rats but did not achieve statistical significance. There were no significant differences in the RBC morphology or white blood cell (WBC) differential data. The only statistically significant difference between the serum data from control and orally dosed rats was observed for SDH (0 mg/kg/day = 5±2 IU/l, 150 mg/kg/day = 8±2 IU/l, 500 mg/kg/day = 9±7 IU/l). Treatment-related dose-dependent changes in relative organ weights included increased liver weight in both groups, decreased prostate weight in both groups, decreased seminal vesicle weight in the high-dose group, and decreased thymus weight in both groups. Focal areas of red discoloration and/or generalized reddening were also observed in the brain, spinal cord, stomach and testes of many of the rats dosed orally at 500 mg/kg/day. Treatment-related histopathology was generally dose-dependent and occurred in the following tissues: adrenals, bone marrow, liver, stomach and thymus. Atrophy occurred in the male sex organs (testes, seminal vesicle and prostate). Sperm evaluations showed a significant increase in the frequency of sperm with abnormal heads in the rats dosed orally at 500 mg/kg/day (1.9% in controls and 3.2% in treated rats).

A NOAEL for heavy paraffinic distillate aromatic extract could not be identified and is less than 125 mg/kg/day when administered orally (ECHA) [Kl. Score = 1].

Inhalation

An OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day Study) was performed on Sprague-Dawley rats. One of two lubricant base oils [solvent-refined oil (SRO) and severely hydrotreated, hydrocracked oil (HBO)] was administered to Sprague-Dawley rats (10/sex/dose) by dynamic inhalation exposure at nominal concentrations of 0, 50, 220 or 1000 mg/m^3 for 6 hours per day, 5 days per week for approximately 4 weeks (, 17 days for SRO, and 20 days for HBO). The mass median aerodynamic diameter was approximately 1µm.

Foamy macrophages accumulated in the lungs of exposed animals with each material in a concentration-related manner, especially in alveoli close to alveolar ducts. Mild infiltration of polymorphonuclear leukocytes (PMNs) into alveoli was noted also with high aerosol concentrations. Increased numbers of alveolar macrophages are expected following deposition of a significant number of particles in the alveoli. The alveolar macrophages and the associated increase in neutrophilic leukocytes are part of the normal mechanism for removal of an increased particle load. The presence of neutrophils, therefore, is not necessarily a pathological occurrence.

Therefore, the NOEL is 220 mg/m^3 based on accumulation of alveolar macrophages in lung and the NOAEL is >980 mg/m^3 based on lack of systemic toxicity in males and females (ECHA) [Kl. score = 2].

Dermal

An OECD Guideline 410 (Repeated Dose Dermal Toxicity: 21/28-Day Study) was performed on New Zealand White rabbits. Five New Zealand White rabbits/sex/dose were topically administered hydrotreated light naphthenic oil six hours/day, three times a week for a period of 28 days at concentrations of 0, 200, 1000 or 2000 mg/kg body weight.

All animals were observed twice daily for mortality and signs of clinical toxicity and dermal irritation was scored daily (according to the Draize system). Body weights were measured and recorded for each rabbit at the end of the quarantine period, at weekly intervals during the study and prior to termination.

No mortality was observed in control animals or at any dose level tested. Soft feces was observed in some male and female rabbits in the control, mid-dose (1000 mg/kg) and high-dose (2000 mg/kg) dose groups. All female rabbits dosed at 2000 mg/kg hydrotreated light naphthenic oil appeared thin during the study period. Control males and females did not exhibit any dermal irritation while minimal irritation was observed in males and females dosed at 200 mg/kg hydrotreated light naphthenic oil. Slight to moderate irritation accompanied by very slight oedema and well-defined erythema was observed in males and females dosed at 1000 mg/kg. Moderate irritation with consistent erythema and oedema was seen in males and females dosed at 2000 mg/kg hydrotreated light naphthenic oil. A couple of females in the high-dose (2000 mg/kg) group also exhibited maximal erythema on day 20 of the study period. Body weight and body weight gain appeared to be normal in males in the control, low-dose (200 mg/kg), and mid-dose (1000 mg/kg) dose group. Mean body weights and body weight gain were lower (statistically significant) than control in the high-dose males and in the mid-dose (1000 mg/kg) and high-dose (2000 mg/kg) females. Most of the hematology parameters were found to be normal for males and females in all

dose groups. WBC counts in the low-dose (200 mg/kg) females were lower than those observed in control animals but were considered incidental and not treatment-related. Clinical chemistry parameters appeared to be normal in males and females in all dose groups. One female in the mid-dose (1000 mg/kg) dose group exhibited abnormally high Serum glutamic pyruvic transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT) levels but this was considered incidental, and not treatment-related. Mean terminal body weights of mid-dose (1000 mg/kg) females and high-dose (2000 mg/kg) males and females were observed to be lower (statistically significant) than the corresponding control animals. Absolute left and right testis weights and relative right testis weights for the high-dose (2000 mg/kg) dose males were also found to be lower (statistically significant) than the corresponding controls. All other statistically significant differences in organ weights in both males and females were considered to be incidental and not treatment-related. Post-termination gross morphology examinations revealed dry, scaly, rough, fissured, crusted and/or thickened skin in animals in the high-dose (2000 mg/kg) group. Two high-dose (2000 mg/kg) males were also observed to have bilaterally small testes. Histopathological examinations revealed slight to moderate proliferative changes of the skin accompanied by increased granulopoeisis of the bone marrow in all male and female rabbits dosed with 2000 mg/kg API 83-12. Testes of 3 of 5 high-dose (2000 mg/kg) males were observed to have bilateral diffuse tubular hypoplasia (atrophy) accompanied by aspermatogenesis and atrophy of accessory sex organs. Systemic effects may be a secondary effect due to effects at primary site of application.

The systemic toxicity NOAEL for this 28-day dermal toxicity study in the rabbit is 1000 mg/kg, based on the lack of adverse systemic effects observed at this dose level (ECHA) [KI Score = 1].

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on CMW based on read-across from aluminium compounds are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on DPHP[1]

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Petroleum industry modified OECD Guideline 471 (Bacterial Reverse Mutation Assay)	-	+	1	ECHA

*+, positive; -, negative
1 – based on read across to aluminium compounds.

In Vivo Studies

An OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) was performed. Male and female mice (Strain CD-1) were given a single intraperitoneal injection of five different paraffin oils in corn oil vehicle at doses of 0, 1.0, 2.5 or 5.0 g/kg. Bone marrow cells were harvested at 24, 48 and 72 hours post-dosing. One animal did not survive to scheduled

sacrifice, but there were no gross signs of toxicity. The micronucleus frequency was significantly greater than the concurrent negative control in bone marrow cells of male mice given 5.0 g/kg at 48 hours post-dosing, but the negative control was unusually low in this instance, and therefore the positive result at 5 g/kg (5000 mg/kg) is not considered significant. The substance is not considered mutagenic (ECHA) [Kl. score = 1].

G. Carcinogenicity

Oral

No substance specific data exist (ECHA) (Kl score = 3).

Inhalation

No studies are available.

Dermal

Numerous lifetime dermal carcinogenicity studies have been carried out on lubricant base oils. A comprehensive review of these studies is not provided however, the results are summarized below.

Overall, these studies have shown that lubricant base oils that have been refined to a sufficient degree of severity, i.e., solvent-extraction and/or severe hydrotreatment do not normally induce skin cancer in mice. However, lubricant base oils that have not been sufficiently refined may be carcinogenic to the skin. The IP 346 test is used to determine whether the lubricant base oils have been sufficiently refined to avoid dermal carcinogenic hazard. The method measures the quantity of dimethyl sulfoxide (DMSO) extract which has been proved to correlate to the carcinogenic properties of the other lubricant base oils. Other lubricant base oils are classified for dermal carcinogenic hazard unless they have been shown to contain less than 3 wt% DMSO extractable material according to the IP 346 method.

In order to understand the effects of various types of refining processes (i.e., hydrotreatment, solvent extraction, combined solvent extraction and hydrotreatment) on carcinogenic potential, 94 lubricant base oils and related materials were evaluated in the mouse epidermal cancer bioassay these studies, male C3H mice, ca. 6-10 weeks of age, were randomly distributed into test groups of 40 or 50 animals. In early studies, mice were housed five per cage in suspended wire-mesh cages. In later studies, they were housed singly, in the same type of cages. The hair in the interscapular area was clipped once weekly to facilitate test material application. The test materials were applied by automatic pipette in either 37.5 microlitres aliquots twice a week or 25 microlitres aliquots three times a week. In early studies, the treatment continued until the animals died spontaneously or were sacrificed in a moribund state. In later studies, surviving mice were sacrificed after either 24 months of treatment or at the time at which grossly diagnosed squamous cell carcinomas were recorded. Animals were examined twice weekly for the appearance of dermal tumours. Each tumour in the treatment area was examined carefully and classified grossly. All grossly diagnosed tumours were examined microscopically after study termination.

Of the 94 samples tested for carcinogenic activity, 57 produced no tumour-bearing animals and the remaining 37 produced one or more. Among the groups containing tumour-bearing animals, seven had one, six had two, two had four and the remaining 22 had five or more. At least five tumour-bearing animals are required to differentiate statistically one of the treatment group responses from that of an equally sized negative control group (containing no tumour-bearing animals), Thus, responses were statistically significant in 22 of the 37 groups containing tumour-bearing animals. Overall, based on the refinement status of DPHP, the substance is considered carcinogenic via the dermal route (ECHA) [KI Score = 3].

H. Reproductive Toxicity

Oral

An OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) was performed on Sprague Dawley rats.

A lubricant base oil (IP 346 < 3 wt%) was administered by gavage at a dose of 1000 mg/kg (bw) to a group of 12 male and 12 female Sprague-Dawley rats. Rats designated F0 animals were dosed for a minimum of 14 days prior to mating. Dosing was continued after mating until a total dosing period of 30 days had elapsed for males and until day 4 of lactation for females (39 days). The animals were observed twice daily for appearance, behaviour, morbidity and mortality. Males and females were also observed during dosing and for one hour thereafter. Male F0 body weights were recorded weekly. Female F0 body weights were also recorded weekly until evidence of mating was observed and then on gestation days 0, 7, 14 and 20 and on lactation days 1 and 4. Food consumption was also recorded for F0 (both sexes). Animals were paired on a 1:1 basis. Positive evidence of mating was confirmed either by the presence of sperm in a vaginal smear or a vaginal plug. The day when evidence of mating was identified was termed Day 0 of gestation.

The following fertility indices were calculated: Female mating index; Male mating index; Female fertility index; and Male fertility index. All females were allowed to deliver their young naturally and rear them to post-natal day 4. Females were observed twice daily during the period of expected parturition for initiation and completion of parturition and for signs of dystocia. After parturition, litters were sexed and examined for evidence of gross malformations, numbers of stillborn and live pups. Litters were examined daily, and each pup received a detailed physical examination on days 1 and 4 of lactation. All abnormalities were recorded. The live litter size and viability index were calculated. All surviving pups were necropsied on post-natal day 4. A complete gross examination was made on all animals at necropsy. Selected organs of parental animals were weighed, and a wide range of tissues were fixed for subsequent histopathological examination.

There were no clinical findings and growth rates and food consumption values were normal. Fertility indices and mating indices for males and females were both 100%. At necropsy, there were no consistent findings, and the animals were considered to be normal. Organ weights and histopathology were considered normal. The NOAEL for this study was ≥1000 mg/kg/day (ECHA) [KI Score = 1].

I. Developmental Toxicity

Dermal

There are no oral developmental toxicity studies of lubricant base oils with IP 346 > 3%. However, there is a dermal developmental toxicity study (OECD Guideline 414 - Prenatal Developmental Toxicity Study) of a distillate aromatic extract (DAE) from a heavy paraffinic vacuum distillate which can be used as a worst case basis to assess the developmental toxicity of lubricant base oils with IP 346 > 3 wt%.

In this study heavy paraffinic DAE (CAS No. [redacted] 318 Isthmus Furfural Extract, was tested in a dermal study during gestation days 0 to 19 for developmental effects and maternal toxicity in the Sprague-Dawley rat.

Heavy paraffinic distillate furfural extract produced maternal, reproductive and foetal toxicity. Maternal toxicity was exhibited as vaginal discharge (dose-related), body weight decrease, reduction in thymus weight and increase in liver weight (125 mg/kg/day and higher) and aberrant haematology and serum chemistry (125 and/or 500 mg/kg/day). Evidence of potential reproductive effects was shown by an increased number of dams with resorptions and intrauterine death. DAE was developmentally toxic regardless of exposure duration as indicated by increased resorptions and decreased foetal body weights. Furthermore, when exposures were increased to 1000 mg/kg/day and given only during gestation days 10 through 12, cleft palate and ossification delays were observed. Cleft palate was considered to indicate a potential teratogenic effect of DAE (ECHA) [Kl. score = 1].

5 DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for DPHP follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

Oral

The repeated dose NOAEL for heavy paraffinic distillate aromatic extract could not be identified but is less than 125 mg/kg/day when administered orally. 125 mg/kg/day is considered the NOAEL for purposes of developing a drinking water guideline. For reproduction, breeding and early post-natal developmental toxicity, the NOAEL is 1000 mg/kg-day. The NOAEL of 1000 mg/kg-day will be used for determining the oral Reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10

UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 10

Oral RfD = 50/(10 x 10 x 1 x 1 x 1) = 125/1000 = 0.10 mg/kg-day.

It should be noted that the oral RfD of 0.1 mg/kg/day is in good agreement with an RfD of 0.1 mg/kg/day for EC9–EC10, >EC10–EC12 and >EC12–EC16 aliphatic fractions developed by the World Health Organization (WHO, 2008).

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

where:

Human weight = 70 kg (ADWG, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (0.1 x 70 x 0.1)/2 = 0.3 mg/L

B. Cancer

DPHP was not carcinogenic to rats in chronic oral studies. Therefore, a cancer reference value was not derived.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

DPHP does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

7 ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Details from studies on surrogate substances are provided below.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on DPHP.

Table 3: Acute Aquatic Toxicity Studies on DPHP

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-h LC_{50}	>100	2	ECHA
Daphnia magna	48-h EC_{50}	>10,000	2	ECHA
Pseudokirchneriella subcapitata	72-h NOEL	>100	2	ECHA

Chronic Studies

Fish:

Results of computer modelling to estimate aquatic chronic toxicity of other lubricant base oils in a 28-day freshwater fish study show no chronic toxicity to freshwater fish at or below its maximum attainable water solubility (ECHA) [KI Score = 3).

Invertebrates:

In a key semi-static 21-day long-term Daphnia magna toxicity test, 10 animals/loading were exposed to the Water Accommodated Fraction (WAF) of other lubricant base oil LVIN 38 (CAS #[redacted] at nominal concentrations of 1, 10, 100 and 1000 mg/L. A NOEL was 10 mg/L based on reproduction but was attributed to a non-treatment related effect, the cause of which was unknown. Further testing would be required to clarify the consequences of exposure to a 100 mg/L WAF of the base oil (ECHA) [KI Score = 2].

In a supporting semi-static 21-day long-term Daphnia magna reproduction test, 10 animals/loading were exposed to the WAF of solvent-refined heavy paraffinic distillate (PSG 1860; CAS #[redacted] at nominal concentrations of 0, 10 and 1000 mg/L. The EL_{50} was > 1000 mg/L and the NOEL was ≥ 1000 mg/L based on the lack of mortality or reproduction impairment (ECHA) [KI Score = 2].

In supporting semi-static 21-day long-term Daphnia magna reproduction test (OECD 211; KS = 2), 10 animals/loading were exposed to the WAFs of other lubricant base oils HVI 60, XHVI 4.0, HVI 65 and LVIN 38 (CAS #[redacted] at nominal concentrations of 1 and 1000 mg/L. The NOELs for other lubricant base oils HVI 60, XHVI 4.0 and HVI 65 were ≥ 1000 mg/L based on reproduction. The NOEL for LVIN 38 was ≥1 mg/L based on reproduction this substance was retested across a wider range of nominal concentrations and a NOEL of 10 mg/L was determined (ECHA) [KI Score = 1].

C. Terrestrial Toxicity

No data were available.

D. Calculation of PNEC

The PNEC calculations for DPHP follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. The lowest acute EC_{50} value was >100 mg/L. On the basis that the data consists of short-term studies for three trophic levels, an assessment factor of 100 has been applied to the lowest reported EC_{50} value of 100 mg/L. Therefore, the PNECwater is 1 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Moreover, the substance is not expected to substantially partition to sediments. Nonetheless, a PNECsed was calculated using the equilibrium partitioning methodology. The PNECsed is 469 mg/kg sediment wet weight.

The calculations are as follows:

PNECsed = (Ksed-water/BDsed) x 1000 x PNECwater
= 3.2×10^4/1280 x 1000 x 1
= 2.5×10^4

Where:

Ksed-water = suspended matter-water partition coefficient (m3/m3)
BDsed = bulk density of sediment (kg/m3) = 1,280 [default]

Ksed-water = 0.8 + [(0.2 x Kpsed)/1000 x BDsolid]
= 0.8 + [(0.2 x 1.25×10^5/1000 x 1,280]
= 3.2×10^4

Where:
Kpsed = solid-water partition coefficient (L/kg).
BDsolid = bulk density of the solid phase (kg/m^3) = 2,400 [default]

Kpsed = Koc x foc
= 3.1×10^6 x 0.04
= 1.2×10^4

Where:

Koc = organic carbon normalized distribution coefficient (L/kg). The Koc was calculated as the midpoint of modelled Koc range and determined to be 3.1×10^6 L/kg.

foc = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the PNECsoil was calculated using the equilibrium partitioning method. The PNECsoil is $4x10^4$ mg/kg soil dry weight.

The calculations are as follows:

PNECsoil = (Kpsoil/BDsoil) x 1000 x PNECwater
= (0.06/1500) x 1000 x 0.3
= $4x10^4$

Where:

Kpsoil = soil-water partition coefficient (m3/m3)
BDsoil = bulk density of soil (kg/m3) = 1,500 [default]

Kpsoil = Koc x foc
= $3.1x10^6$ x 0.02
= $6.2x10^4$

Where:

Koc = organic carbon normalised distribution coefficient (L/kg). The Koc was calculated as the midpoint of modelled Koc range and determined to be $3.1x10^6$ L/kg.

Foc = fraction of organic carbon in soil = 0.02 [default].

8 PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REAC Criteria methodology (DEWHA, 2009; ECHA, 2008).

DPHP is an organic substance that has been determined to be inherently biodegradable. Thus, it does not meet the screening criteria for persistence.

The estimated log Kow is equal to 8. There is clear experimental evidence that super-lipophilic substances (log Kow > 7.2) will not have a significant tendency to bioaccumulate (ECETOC, 2000).

Therefore, DPHP is considered to not meet the screening criterion for bioaccumulation.

DPHP is a low toxicity concern based on the results presented in Table 3. Thus, DPHP does not meet the screening criteria for toxicity.

Therefore, DPHP is not a PBT substance.

9 CLASSIFICATION AND LABELLING

A. Classification

May cause cancer via dermal exposure. H350

B. Labelling

Danger

C. Pictogram

10 SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eye and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapor. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for DPHP.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapor cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, before eating, smoking, and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

DPHP is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

11 DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

12 REGULATORY STATUS

Australian AICS Inventory: Listed.

13 REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECETOC. (2000). Persistent organic pollutants. Response to UNEC/INC/ CEG-1. Annex 1, Document No. 41. Brussels, Belgium.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA] (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

WHO. (2008). Petroleum Products in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality. WHO/SDE/WSH/05.08/123.

DIUTAN (CAS NO. [redacted]
DIUTAN GUM (CAS NO. [redacted]

This dossier on diutan and diutan gum presents the most critical studies pertinent to the risk assessment of these substances in its use in coal seam gas extraction activities. Diutan (CAS No. [redacted] can also be referred to as diutan gum (CAS No. [redacted] This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained for diutan gum from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): (2R,3R,4S,5S)-2,3,4,5-tetrahydroxyhexanal (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanal (2S,3S,4S,5R)-2,3,4,5-tetrahydroxy-6-oxohexanoic acid acetic acid calcium dihydride hydrate magnesium dihydride potassium hydride sodium hydride

CAS RN: [redacted]

Molecular formula: $C_{20}H_{46}CaKMgNaO_{21}$

Molecular weight: Not applicable as substance is a UVCB.

Synonyms: Diutan gum; S 657; S-657 Gum; GEOVIS XT; GEOVIS XTL; KELCO-CRETE DG

Chemical Name (IUPAC): D-glucuronic acid, polymer with 6-deoxy L-mannose and D-glucose, acetate, Ca Mg K Na salt

SMILES: Not applicable

CAS RN: [redacted]

Molecular formula: $(C_6H_{12}O_6.\ C_6H_{12}O_5.\ C_6H_{10}O_7)x.C_2H_4O_2.\ xCa.xK.xMg.xNa$

Molecular weight: Not applicable as substance is a UVCB.

Synonyms: Diutan; D-Glucurono-D-gluco-6-deoxy-L-mannan, acetate, calcium magnesium potassium sodium salt.

SMILES: Not applicable

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1:Overview of the Physico-chemical Properties of Diutan Gum (CAS No. [redacted]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Off-white solid powder	1	ECHA
Melting Point	No melting point was determined. Test substance decomposed at >175°C.	2	ECHA

Property	Value	Klimisch score	Reference
Boiling Point	No data	-	-
Density	1430 Kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	~0.1 kPa @ 25°C	-	NICNAS, 2010
Partition Coefficient (log K_{ow})	-3.56 @ 20°C	2	ECHA
Water Solubility	40 g/L @ 20°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Diutan/diutan gum is readily biodegradable, is not expected to bioaccumulate, and has a low potential to adsorb to soil.

B. Biodegradation

A GLP-compliant study conducted in accordance with the OECD guideline was available. The test material (diutan gum) attained 95% degradation after 28 days and satisfied the 10-day window validation criterion, whereby 60% degradation must be attained within 10 days of the degradation rate exceeding 10%. The test material can therefore be considered to be readily biodegradable under strict terms and conditions of the OECD guideline 301B [KI Score = 1] (ECHA).

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

No experimental data are available for diutan/diutan gum. Based on the low experimentally determined log K_{ow} (-3.56) value, the substance has a low potential to adsorb to soil and will be highly mobile in soil.

D. Bioaccumulation

No experimental data are available for diutan/diutan gum. Based on the low log K_{ow} (-3.56), the potential for bioaccumulation is low.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Diutan has low acute toxicity by the oral and inhalation routes. It is not irritating to the skin and eyes and is not a skin sensitiser. No systemic effects were seen in repeated dose oral toxicity studies in rodents. The substance is not carcinogenic or genotoxic. No reproductive or developmental toxic effects were identified.

B. Toxicokinetics

A screening level toxicokinetic study was performed using male and female Sprague-Dawley rats. Radio labeled Gellan Gum mixed with corn oil was administered via gavage. Specific activity of formulated dose was checked by sample combustion and scintillation counting.

The study was performed in three stages. Stage 1 involved CO_2 collection from 1 male, 1 female. Stage 2 consisted of faeces collection and tissue distribution analysis from 4 males, 4 females. One female was excluded from the study due to abnormal findings at necropsy suggestive of maldosing. Stage 3 involved collection of blood levels from 4 males, 4 females.

Stage 1 results showed less than 0.55% of dosed radioactivity was expired in the form of $^{14}CO_2$. Stage 2 results indicated that females excreted 1.85 +/- 0.55% of dosed ^{14}C in urine, 86.79 +/- 3.08% in faeces. The Stage 3 results recorded low levels of radioactivity in the blood: mean peak blood radioactivity in both sexes was close to 3,000 DPM/mL blood, occurring around 5.5 hours post-dosing in males, 5.25 hours post-dosing in females.

The low levels of radioactivity recorded in tissues and blood samples and the high levels of radioactivity excretion in faeces suggest very little absorption from the gastrointestinal tract occurred following oral dosing. No potential for bioaccumulation was indicated by the study findings. Based on the close chemical similarity between gellan gum and diutan, it is reasonable to predict that a comparable pattern of non-absorption would be seen if diutan were to be similarly tested (ECHA) [Kl. score = 2].

C. Acute Toxicity

Oral

An acute Limit Test, in accord with USEPA test guideline USEPA 40 CFR 163.81-1 was performed. Six male and six female Sprague Dawley rats were administered 5,000 mg/kg in corn oil via gavage. Rats were weighed prior to dosing, then 7 and 14 days later and were observed 1, 2 and 4 hours post-dose, then daily up to 14 days after dosing. Gross pathology observations were made at necropsy. No evidence of toxicity was seen. A no observed effect level (NOEL) of 5,000 mg/kg was determined (ECHA) [Kl Score = 2].

Inhalation

A standard acute inhalation study was performed according to method USEPA 40 CFR 163.81-3. Five male and five female Sprague-Dawley rats were exposed whole body to substance dust for 4 hours in air at a measured test atmosphere of 0.316 mg/L (mean across sampling times). Particle size distribution (measured using Andersen plate sampler during the final 15 minutes of exposure): 100% < 10 microns, 28.9% ≤ 1.1 microns.

After 14 days post-exposure observation, all rats were terminated. Following gross pathology observations at necropsy, lungs and tracheal structures were collected into buffered formalin. Lungs and tracheal samples were also collected from a sample of rats taken at the time of animal delivery (pre-study) and from a supplementary non-exposed control group (additional to the air-exposed controls) at study termination.

No evidence of toxicity was seen after 4-hour exposure of rats to the test substance in a dust atmosphere (nominally 4.9 mg/L and measured at 0.316 mg/L). The difference between nominal and

measured concentrations may indicate that close to a maximum practicable concentration was achieved (ECHA) [KI Score = 2].

Dermal

No studies were available.

D. Irritation

Skin

A non-guideline dermal irritation study was performed on Dunkin-Hartley guinea pigs. The substance was applied in arachis oil at four different concentrations at separate sites on the clipped flanks: 5, 10, 25, 50%. Application sites were occluded for 24 hours and observed 1, 24 and 48 hours after dressing removal. Erythema and oedema scores at 50% concentration did not indicate test substance was irritating (ECHA) [KI Score = 2].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) was performed on albino rabbits. 100 mg substance was applied to one eye while the contralateral eye served as a control. Ocular reactions were observed at 24, 48 and 72 hours post-treatment. Cornea opacity, iris and conjunctivae scores were not indicative of irritation. Therefore, diutan is considered not irritating (ECHA) [KI Score = 2].

E. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) was performed on male Dunkin-Hartley guinea pigs. Intradermal induction was performed with 5% w/w in dried arachis oil. Topical (epicutaneous) induction was performed with 50% w/w in dried arachis oil. Topical challenge was performed with 25% and 10%, w/w in dried arachis oil. The test material produced a 0% (0/10) sensitisation rate and was determined as a non-sensitiser to guinea pig skin under the conditions of the test (ECHA) [KI score = 1].

F. Repeated Dose Toxicity

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) was performed using the structural analogue K9A50: gellan gum (EC 275-117-5). Male and female Sprague-Dawley rats (20 each) were dosed at 3%, 4.5% and 6% nominally in the diet.

Mortality was checked twice daily; clinical signs were recorded once daily. Bodyweights and food consumption recorded pre-treatment and weekly during treatment. Opthalmoscopy checks (control and high-dose groups) were performed pre-treatment and prior to termination.

Haematology, blood chemistry and urinalysis were checked pre-treatment (health screen satellite group) and (together with faecal moisture content) in weeks 6 and 12 of treatment period (10 or 12 rats/sex/group).

Rats fed 6% gellan gum in diet for 13 weeks (corresponding to daily intakes ranging from 2.95 to 7.26 g/kg/day) showed no evidence of treatment related toxicity. It is reasonable to predict that a similar

pattern of low subchronic toxicity would be seen if diutan were to be tested in the same way (ECHA) [KI score = 2].

Inhalation

No adequate studies for human health risk assessment are available.

Dermal

No adequate studies for human health risk assessment are available.

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on diutan are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Diutan[1]

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-*	-*	2	ECHA

1 – Surrogate substance (Biozon - EC 476-190-8) evaluated
*+, positive; -, negative.

Diutan is not expected to induce mutations in the mouse lymphoma thymidine kinase locus assay using the cell line L5178Y in the absence and presence of metabolic activation.

In Vivo Studies

An OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) was performed using the surrogate, Gellan gum (EC 275-117-5). Oral administration of gellan gum at up to 2 x 450 mg/kg produced no detectable increase in the frequency of micronucleated bone marrow cells in treated mice. It is predictable that diutan would give a similarly negative result if tested in the same manner.

H. Carcinogenicity

A mouse carcinogenicity study of the close chemical analogue gellan gum found that inclusion in diet at up to 3% had no significant toxic effect and did not increase the incidence of neoplastic (malignant or benign) or non-neoplastic lesions. The overall mean achieved intake of gellan gum at the highest tested level was calculated to be 4.9 g/kg/day (males) or 6.2 g/kg/day (females).

The open literature also includes a short summary of a rat carcinogenicity study which supports the conclusion that gellan gum is non-carcinogenic. The Joint FAO/WHO Expert Committee on Food Additives(1990) cites a carcinogenicity study in which rats first exposed to gellan gum in utero were then fed gellan gum at up to 5% in the diet for approximately 104 weeks.

No neoplastic or non-neoplastic changes were associated with gellan gum exposure.

The close chemical analogue gellan gum showed no evidence of carcinogenicity in rodent carcinogenicity studies. It is predictable that diutan would give a similarly negative result if tested in the same manner (ECHA) [KI Score = 2].

I. Reproductive Toxicity

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed. Male and female Sprague Dawley rats were dosed with the diutan surrogate Gellan gum (EC 275-117-5) at 2.5, 3.8 and 5% in the diet per study guidelines.

Details on results (P0): No toxicologically significant effects were noted for general toxicity or reproductive function. No evidence of parental toxicity and no effect on reproductive performance seen at highest treatment level (5%).

Details on results (F1 and F2): No evidence of toxicity, no effect on reproductive performance and no effect on development of F1 rats seen at the highest treatment level (5%). No effects on F2 development seen at the highest treatment level (5%).

Administration of gellan gum to P and F1 rats at levels up to 5% in diet resulted in achieved adult intakes within the range 2.8-6.5 g/kg (males), 3.0-4.2 g/kg (females). No evidence of toxicity or adverse effects on reproductive performance or development was seen. Given the close similarity between gellan gum and diutan, it is reasonable to predict that diutan would show a similar lack of toxicity to reproduction (ECHA) [KI Score = 2].

J. Developmental Toxicity

An OECD Guideline 414 (Prenatal Developmental Toxicity Study) was performed with the diutan surrogate gellan gum (EC 275-117-5). The substance was administered via diet and restricted to the period of organogenesis (gestation dates 6-15). Females mated with one male of proven fertility; mating confirmed by presence of spermatozoa in vaginal lavage (designated gestation day 0).

Maternal Toxicity

No evidence of maternal toxicity was seen. Minor gross pathology findings at termination were considered unrelated to treatment. Pregnancy rate was at least 88% in all groups.

Embryotoxic / Teratogenic effects

The incidence of major malformations in test groups was no different from that among controls. Subcutaneous oedema and accompanying skin changes in 7 foetuses from one litter made the occurrence of minor external/visceral anomalies significantly raised at 3.8%. Cases of reduced ossification at 2.5% (mainly ribs) and 3.8% (mainly parietal bones) made group values significantly different from controls. Common skeletal (sternebrae 1-4) variants were significantly increased at 3.8%. None of the above minor anomalies/variants were seen in rats of the highest treatment group (5% in diet); it was concluded that they were not related to gellan gum exposure. It is reasonable to predict that diutan would show a similar lack of toxicity to development (ECHA) [KI score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for diutan follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) was performed using the structural analogue K9A50: gellan gum (EC 275-117-5). The lowest NOAEL of 2.95 g/kg/day (i.e., 2,950 mg/kg bw/day) from this study was used to determine the oral RfD and drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 2950/(10 x 10 x 1 x 1 x 1) = 2950/100 = 29.5 mg/kg bw/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (29.5 x 70 x 0.1)/2 = 103.25 mg/L

B. Cancer

The single carcinogenicity study by the oral route indicates diutan is not a carcinogen. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Diutan does not exhibit the following physico-chemical properties:

- Flammability
- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Diutan is of low acute toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 presents the results of acute aquatic toxicity studies on diutan/diutan gum.

Table 3: Acute Aquatic Toxicity Studies on Diutan Gum

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss (Rainbow Trout)	96-hour LC_{50}	100	1	ECHA
Daphnia magna	48-hour LC_{50}	> 100	1	ECHA
*Desmodesmus subspicatus (*previous name*: Scenedesmus subspicatus)*	72-hour EC_{50}	> 100 (growth rate and biomass)	1	ECHA

Chronic Studies

No data is available.

C. Terrestrial Toxicity

No data is available.

D. Calculation of PNEC

PNEC calculations for diutan acid follow the methodology discussed in DEWHA (2009).

PNEC water

Acute experimental results are available for three trophic levels (Table 3). Acute E(L)C50 values are available for fish (100 mg/L), invertebrates (> 100 mg/L) and algae (>100 mg/L). On the basis that the data consists of short-term results from three trophic levels, an assessment factor of 100 has been applied to the lowest reported value. The $PNEC_{water}$ for diutan is 1.0 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Moreover, the low K_{ow} indicates that diutan is not expected to partition to sediments. Therefore, a the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.63 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
= (0.809/1280) x 1000 x 1.0
= 0.63 mg/kg sediment wet wt.

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
= 0.8 + [(0.2 x 0.035/1000 x 2400]
= 0.82 m^3/m^3

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
= 0.865 x 0.04
= 0.035 L/Kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for calculated from EPI Suite™ using the MCI is 0.865 L/kg .
F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Moreover, diutan is biodegradable and due to its low K_{ow}, is not expected to partition to soil. Therefore, a $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.01 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
= (0.02/1500) x 1000 x 1.0
= 0.01 mg/kg soil dry weight

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
= 0.865 x 0.02
= 0.017 m^3/m^3

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for calculated from EPI Suite™ using the MCI is 0.865 L/kg.
F_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Diutan/diutan gum is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Bioaccumulation of diutan/diutan gam is not expected to occur based on it log K_{ow} value of -3.56. Thus, diutan/diutan gum does not meet the screening criteria for bioaccumulation.

No chronic toxicity data is available. The E(L)C_{50} values from the acute aquatic toxicity studies on diutan/diutan gum are > 1 mg/L. Thus, diutan/diutan gum does not meet the criteria for toxicity.

Therefore, diutan/diutan gum is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not Classified

B. Labelling

Not Classified

C. Pictogram

Not Classified

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. If eye irritation persists, seek medical attention, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

No significant adverse health effects are expected to develop if only small amounts (less than a mouthful) are swallowed. Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas. Not expected to cause an environmental hazard as a result of its intended use, disposal or incineration.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage and Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid dust formation. Avoid conditions that generate airborne dust in handling, transfer and cleanup. Keep away from heat, flame sparks and other ignition sources. Static charge may cause flash fire. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Store in a roofed and well-ventilated area. Keep container tightly closed. Store away from heat and light.

E. Exposure Controls/Personal Protection

Occupational Exposure Standards

If handling generates dust levels which cause irritation, or results in personal exposure exceeding the Occupational Exposure Standard (OES) of 10 mg/m^3 (8 hr time-weighted average [TWA] reference period) for total inhalable dust, then suitable approved dust respirator should be used.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Although this product does not present a significant skin concern, minimise skin contamination by following good industrial practice. Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: This product does not cause significant eye irritation or eye toxicity requiring special protection. Where there is significant potential for eye contact, wear chemical goggles and have eye flushing equipment available.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, as well as before eating, smoking and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Diutan is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DoEE. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Joint FAO/WHO Expert Committee on Food Additives (1990). Toxicology Monograph 724 (Food Additive Series 28.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

NICNAS. (2010). National Industrial Chemicals Notification and Assessment Scheme. Full Public Report. Diutan Gum https://www.industrialchemicals.gov.au/sites/default/files/SN20%20Public%20Report%20PDF.pdf

ALCOHOLS, C12-14, ETHOXYLATED

This dossier on ethoxylated C12-C14 alcohol presents the most critical studies pertinent to the risk assessment of alcohols, ethoxylated C12-C14 alcohol in its use in coal seam gas extraction activities. As very little information exists upon which to assess ethoxylated C12-C14 alcohol, this dossier is based on an assessment of a surrogate substance C12-15, ethoxylated alcohols CAS [redacted] This approach is appropriate since the surrogate substance differs from the subject substance by only a single carbon molecule. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

1 SUBSTANCE IDENTIFICATION

Chemical Name: Alcohols, C12-14, ethoxylated

CAS RN: [redacted]

Molecular formula: (C2H4O)1-3(CH2)10-13C2H6O

Molecular weight: Not available

Synonyms: Alcohols, C12-14, ethoxylated

SMILES: Not available

2 PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of Alcohols, C12-15, Ethoxylated (1 to 2.5 moles ethoxylated)

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Clear liquid with a rancid odour*	2	ECHA
Melting Point	7.22°C	2	ECHA
Boiling Point	ca. 287°C	1	ECHA
Density	0.926 g/cm^3 @ 15.56°C	1	ECHA
Vapour Pressure	Negligible	-	ECHA
Partition coefficient (log K_{ow})	5.06* @ 25°C	2	ECHA
Water Solubility	7 – 63 mg/L @ 25°C	2	ECHA
Flash Point	165.56°C	2	ECHA
Auto flammability	235°C	2	ECHA
Viscosity	28.1 mPA s (dynamic) @ 20°C	2	ECHA

*Based on alcohols, C12-14, ethoxylated (1 to 2.5 EO) [CAS No. [redacted]

3 ENVIRONMENTAL FATE PROPERTIES

A. Summary

Alcohols, C12-15, ethoxylated is readily biodegradable. It has a low potential for bioaccumulation and a moderate potential for absorption to soil and sediment.

B. Biodegradation

Alcohols, C12-15, ethoxylated is readily biodegradable. In an OECD 301B test, degradation was 72% in 28 days, but failed the 10-day window (ECHA) [Kl. score = 1].

An alcohol, C12-15, ethoxylated (7 EO) degraded 80 to 88% in 28 days when tested using a shake-flask CO_2-evolution test method (ECHA) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for alcohols, C12-15, ethoxylated. Using KOCWIN in EPISUITE™ (U.S. EPA, 2018), the estimated K_{oc} values for surrogates of alcohols, C12-15, ethoxylated are:

C12 linear alcohol, ethoxylated (2 EO): 279.5 L/kg (MCI) and 464.2 L/kg (K_{ow})

C15 linear alcohol, ethoxylated (2 EO): 1,691 L/kg (MCI) and 3,018 L/kg (K_{ow})

D. Bioaccumulation

The bioconcentration factor (BCF) values for alcohol ethoxylates in fathead minnows have been reported to range from <5 to 387.5 (Toll et al., 2000). The uptake rates varied from 330 to 1660 (L x kg/d) and elimination rates varied from 3.3 to 59 per day (Toll et al., 2000). The high concentrations in fish is thought to be prevented by an efficient biotransformation of the alcohol ethoxylates, leading to a high elimination rate.

4 HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of alcohols, C12-15, ethoxylated is low by the oral and dermal routes. The skin irritation rabbit studies on alcohols, C12-15, ethoxylated have shown mixed results, but human patch studies on these alcohol ethoxylates do not support a skin irritant classification. Alcohols, C12-15, ethoxylated is expected to be irritating to the eyes of rabbits. Alcohols, C12-15, ethoxylated is not a skin sensitiser. Repeated dose toxicity studies on alcohol ethoxylates similar to alcohols, C12-15, ethoxylated in rats do not indicate any target organ effects. These alcohol ethoxylates are not genotoxic, carcinogenic, and have a low potential for reproductive and developmental toxicity.

B. Acute Toxicity

No acute toxicity studies are available on alcohols, C12-15, ethoxylated.

The oral LD_{50} in rats for $C_{12\text{-}15}AE_3$ is >5,000 mg/kg (ECHA) [Kl. score = 2]. The oral LD_{50} in rats for $C_{12\text{-}15}AE_7$ is 1,700 mg/kg (HERA, 2009) [Kl. score = 2]. The oral LD_{50} value in rats for $C_{12\text{-}}$

$_{13}AE_{6.5}$ is 2,100 mg/kg (HERA, 2009) [Kl. score = 2]. The oral LD_{50} value in rats for $C_{12\text{-}15}AE_{11}$ is >2,000 mg/kg in males and between 1,000 and 2,000 mg/kg in females (HERA, 2009) [Kl. score = 2]. The oral LD_{50} values in rats for $C_{14\text{-}15}AE_{13}$ in two separate studies are 1,100 and 1,000 mg/kg (HERA, 2009) [Kl. score = 2]. The relative number of EO units, but not the carbon chain length, appears to influence acute oral toxicity (HERA, 2009).

An acute dermal LD_{50} values of >2,000 mg/kg were determined for $C_{12\text{-}14}AE_3$ and $C_{12\text{-}14}AE_6$ in two separate studies (HERA, 2009) [Kl. score = 2]. The acute dermal LD_{50} of $C_{12\text{-}15}AE_7$ is >2,000 mg/kg (HERA, 2009) [Kl. score = 2].

C. Irritation

Skin

Application of 0.5 mL isotridecanol, ethoxylated (3 EO) to the skin of rabbits for 4 hours under occlusive conditions was considered irritating (ECHA) [Kl. score = 2].

Application of 0.5 mL isotridecanol, ethoxylated (3 EO) to the skin of rabbits for 4 hours under semi-occlusive conditions was not considered irritating (ECHA) [Kl. score = 2].

In a 24-hour human patch test, there was some short-lived redness in some individuals from the application of $C_{12\text{-}14}AE_3$, but there was no scaling or oedema in any subjects (HERA, 2009) [Kl. score = 2].

In a standard 4-hour human patch test, the irritation potential of $C_{12\text{-}15}AE_5$ and $C_{12\text{-}15}AE_5$ were compared to 20% sodium dodecyl sulfate (which is classified a skin irritant under GHS). The results showed that neither alcohol ethoxylate should be classified as a skin irritant (Basketter et al., 2004) [Kl. score = 2].

Eye

Most alcohol ethoxylates tested as the undiluted neat test material are moderately to severely irritating to the eyes of rabbits, with an eye irritation index (EII) ranging from >25 to 50 (HERA, 2009). The alcohol ethoxylates $C_{12\text{-}14}AE_3$, $C_{12\text{-}14}AE_6$, $C_{13}AE_6$, and $C_{12\text{-}14}AE_{10}$ were found to be moderately to severely irritating to the eyes of rabbits (HERA, 2009). In another study, $C_{12\text{-}15}AE_{11}$ was considered moderately to severely irritating to the eyes of rabbits (HERA, 2009).

Some alcohol ethoxylates were reported to be practically or minimally irritating to the eyes of rabbits with EII scores of 0.5 to 15. These alcohol ethoxylates include: $C_{12\text{-}15}AE_3$, $C_{14\text{-}15}AE_7$, $C_{12\text{-}14}AE_{15}$, $C_{14\text{-}15}AE_{18}$, and $C_{13}AE_{20}$ (HERA, 2009).

D. Sensitisation

No sensitisation studies are available on alcohols, C12-15, ethoxylated.

In a guinea pig maximisation test, $C_{12\text{-}13}AE_{<2.5}$ (CAS No. [redacted] was not considered a skin sensitiser (ECHA) [Kl. score = 2].

In a guinea pig maximisation tests, $C_{12\text{-}15}AE_3$, $C_{12\text{-}15}AE_7$, and $C_{14\text{-}15}AE_7$ were not considered skin sensitisers (HERA, 2009) [Kl. scores = 2].

E. Repeated Dose Toxicity

Oral

Rats were given in their diet 0%, 0.0313%, 0.0625%, 0.125, 0.25, 0.5 or 1.0% $C_{12\text{-}15}AE_7$ for 90 days. The animals in the ≥0.25% groups showed significantly reduced body weight gain, which was associated with marked decreases in food and water consumption. Relative liver weights were significantly increased in the ≥0.5% male rats and ≥0.25% females. Histopathologic examination showed hepatocytic enlargement in the ≥0.125% groups, suggesting increased liver metabolism on the basis of increased alkaline phosphatase activity at the higher dose levels. The NOAEL was established at 0.0625% in the diet or 102 mg/kg-day (HERA, 2009) [Kl. score = 2].

Rats were fed $C_{12\text{-}14}AE_7$ in the diet at concentrations of 0%, 0.0313%, 0.0625%, 0.125%, 0.25%, 0.5% and 1.0% for 90 days. The animals in the ≥0.25% groups showed significantly reduced body weight gain, which was associated with marked decreases in food and water consumption. Relative liver weights were significantly increased in the ≥0.5% male rats and ≥0.25% females. Histopathologic examination showed hepatocytic enlargement in the ≥0.125% groups, suggesting increased liver metabolism on the basis of increased alkaline phosphatase activity at the higher dose levels. The NOAEL was established at 0.0625% in the diet or 110 mg/kg-day (HERA, 2009) [Kl. score = 2].

Male and female Wistar rats were given in their diet 0, 300, 1,000, 3,000 and 10,000 ppm $C_{14\text{-}15}AE_7$ for 90 days. There were no deaths during the study. Mean body weights and feed were lower in 10,000 ppm males and the 3,000 ppm females. Feed consumption was lower in the 10,000 ppm animals and the 3,000 ppm females. Relative liver weights were increased in the ≥3,000 ppm animals, and relative spleen weights were increased in the 10,000 ppm males. Clinical chemistry changes were noted in the 10,000 ppm group and consisted of significantly higher urea, chloride and potassium levels in males; significantly higher urea, chloride and cholesterol in females. Increased total leucocytes and lymphocytes were seen in the 10,000 ppm animals and in the 3,000 ppm males. The 10,000 ppm females showed lower numbers of neutrophils; mean cell volume and mean cell haemoglobin were identified in one or both sexes fed in the ≥3,000 ppm dose groups. In the 1,000 ppm females, there were minor, but statistically significant changes in the liver and kidney weights and plasma urea concentration; these effects were considered to be of no toxicological significance. Histopathologic examination showed no treatment-related effects at any dose level. The NOAEL for this study is 1,000 ppm in the diet, which corresponded to 50 mg/kg-day (HERA, 2009) [Kl. score = 2].

Rats were given in their diet 0, 0.1, 0.5, or 1% $C_{14\text{-}15}AE_7$ for 90 days. Body weights, food intake, organ weights, and hematology and clinical chemistry parameters were similar across groups. The NOAEL for this study is 1% in the diet, which corresponded to 700 and 785 mg/kg-day for males and females, respectively (HERA, 2009) [Kl. score = 2].

Rats were given in their diet 0, 0.1, 0.5 or 1% $C_{12\text{-}13}AE_{6.5}$ or $C_{14\text{-}15}AE_7$ for two years. Body weight gain was reduced in the 1% males and ≥0.5% females, which was likely due to the reduced food consumption in these animals. At study termination, organ to body weight ratios were increased in the ≥0.5% females (liver, kidney and brain), 1% females (heart), and

1% males (liver). A dose-related focal myocarditis was observed in males. While focal myocarditis is commonly observed in non-treated aging rats, the incidences in the treated animals were higher than in the controls. The NOAEL was established at 0.1% or 50 mg/kg-day (HERA, 2009) [Kl. score = 2].

Male and female CR rats were given in their diet $C_{14\text{-}15}AE_7$ at 0.1, 0.5 and 1% for two years. A treatment-related body weight depression was observed in females at the two highest treatment levels and in males at the 1% dose level, probably due to the poor palatability of the diet. Relative liver, kidney, heart and thyroid/parathyroid gland weights were increased in the 1% dietary group at study termination. Histopathological examination showed a dose-related increase in the incidence of focal myocarditis at the 12-month time point, but not at the end of the study at two years. The NOAEL for this study was considered to be 0.5% in the diet, which corresponded to 162 and 190 mg/kg-day for males and females, respectively (HERA, 2009) [Kl. score = 2].

Inhalation

No studies are available.

Dermal

No adequate studies are available.

F. Genotoxicity

In *Vitro* Studies

The genotoxicity studies conducted on alcohol ethoxylates are reviewed in HERA (2009). The results of few of the *in vitro* studies on similar alcohol ethoxylates to alcohols, C12-15, ethoxylated are presented below in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Selected Alcohol Ethoxylates

Test Substance	Test System	Results*		Klimisch Score	References
		-S9	+S9		
$C_{14\text{-}15}AE_7$	Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	HERA, 2009
$C_{14}AE_{12}$	Chromosomal aberrations (CHO cells)	-	-	2	HERA, 2009

*+, positive; -, negative

In *Vivo* Studies

In two separate studies, CD-1 mice were given an intraperitoneal dose of 0, 50 or 100 mg/kg $C_{12\text{-}15}AE_3$ or $C_{12\text{-}14}AE_9$. There were no increases in the frequency of micronuclei in the bone marrow cells (Talmage, 1994) [Kl. score = 2].

Male and female Tunstall rats were given a single oral gavage dose of 0, 250, 500 or 1,000 mg/kg $C_{14\text{-}15}AE_7$. There were no increases in chromosomal aberrations in the bone marrow cells (HERA, 2009 [Kl. score = 2].

G. Carcinogenicity

No studies are available on alcohols, C12-15, ethoxylated.

Male and female Sprague-Dawley rats were given in their diet $C_{12\text{-}13}AE_{6.5}$ in the diet at doses up to 1% (500 mg/kg-day). Reduced food consumption was noted at the higher dose levels (*i.e.*, 0.5 and 1% for females and 1% for males), resulting in a lower body weight gain compared to the control group. No treatment-related histopathology was found and no increase in tumour incidence was observed (HERA, 2009) [Kl. score = 2].

Male and female Charles River rats were given in their diet 0, 0.1, 0.5 or 1% $C_{14\text{-}15}AE_7$ for two years. There were no treatment-related changes in general behaviour and appearance. The survival rate of the test animals was comparable if not better than the controls. Body weights of the 0.5% females and the 1% males and females had significantly lower weight gains than the control. There were no treatment-related effects on organ weights and tumour incidence (HERA, 2009) [Kl. score = 2].

Male and female Sprague-Dawley rats were given in their diet $C_{14\text{-}15}AE_7$ at 0.1, 0.5 and 1% for two years. A treatment-related body weight depression was observed in females at the two highest treatment levels and in males at the 1% dose level, probably due to the poor palatability of the diet. There was no evidence for any carcinogenic activity (HERA, 2009) [Kl. score = 2].

H. Reproductive Toxicity

No studies are available on alcohols, C12-15, ethoxylated.

CD rats were given in their diet 0, 0.05, 0.1 or 0.5% (approximately 0, 25, 50 or 250 mg/kg-day) $C_{12}AE_6$ in a two-generation reproductive toxicity study. There were no treatment related effects in the parents or pups on general behaviour, appearance or survival. At 0.5%, there was reduced weight gain in both the parental animals and the pups compared to the controls. Fertility was unaffected by treatment. The NOAEL for reproductive toxicity is 0.5% in the diet, which corresponds to 250 mg/kg-day (HERA, 2009) [Kl. score = 2].

In a two-generation developmental and teratogenicity study, CD rats were given in their diet 0, 0.05, 0.1 or 0.5% $C_{14\text{-}15}AE_7$ (approximately 0, 25, 50 or 250 mg/kg-day). Three of the treated groups were given the test substance continuously throughout the study; in the other three groups the females received the test substance on GD 6-15 and the males were untreated. None of the deaths of parental rats during the study was considered to be compound-related. There were no treatment-related changes in behaviour or appearance in the parental rats or pups. Slightly lower body weight gain was noted in the 0.5% continuously treated females. Food consumption was similar for control and treated rats. Fertility, gestation and viability indices were similar across groups. The average 21-day body weights for the 0.5% continuous treated pups were significantly lower than that of the control. Relative liver weights of the 0.5% continuously treated F_1 parental animals were increased at the 91-day sacrifice; relative liver weights of the 0.5% continuously treated males were also increased at the 60-day and caesarean section sacrifices. There were no treatment-related histopathological lesions in any of the tissues from the F_0 and F_1 generations. The NOAEL for reproductive toxicity is 0.5% in the diet or 250 mg/kg-day (HERA, 2009) [Kl. score = 2].

I. Developmental Toxicity

No studies are available on alcohols, C12-15, ethoxylated.

In a two-generation reproductive toxicity study, Charles River rats were given in their diet 0, 0.05, 0.1 or 0.5% (about 0, 25, 50 or 250 mg/kg-day) $C_{12}AE_6$. General behaviour, appearance and survival were unaffected by treatment. At the 0.5% dose level, adults and pups gained less weight than the control rats. In the 0.5% dose group, there was a statistical increase in embryo lethality and soft tissue anomalies and at the 0.1% there was a statistical decrease in mean foetal liver weight. Neither of these effects was considered to be treatment-related by the authors as they showed no dose response characteristics. The NOAEL for maternal toxicity is 50 mg/kg-day. The NOAEL for developmental and teratogenicity is 0.1% in the diet or 50 mg/kg-day (HERA, 2009) [Kl. score = 2].

Pregnant rabbits were given by oral gavage 0, 50, 100 or 200 mg/kg $C_{12}AE$ from gestational days 2 to 16. Nine control rabbits and 31 treated rabbits died during the study. Surviving rabbits at the 200 mg/kg dose group generally showed slight losses of body weight. At 100 and 200 mg/kg, ataxia and a slight decrease in body weight was observed in the pregnant animals. In seven treated and two control rabbits, early deliveries were recorded. There were no treatment-related effects on corpora lutea, implantations, number of live foetuses and spontaneous abortions. The NOAEL for maternal toxicity is 50 mg/kg-day; the NOAEL for developmental toxicity is 200 mg/kg-day (HERA, 2009) [Kl. score = 2].

5 DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for alcohols, C12-15, ethoxylated follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

<u>Oral</u>

Two-year dietary studies in rats have been conducted on alcohol ethoxylates $C_{12-13}AE_{6.5}$ and $C_{14-15}AE_7$ (HERA, 2009). The lowest NOAEL from these studies is 50 mg/kg-day based on increased organ weights. The NOAEL of 50 mg/kg-day will be used to derive an oral reference dose and drinking water guidance value for alcohols, C12-15, ethoxylated.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:
UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1

Oral RfD = 50/(10 x 10 x 1 x 1 x 1) = 50/100 = <u>0.5 mg/kg-day</u>

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

where:
Human weight = 70 kg (ADWG, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (0.5 x 70 x 0.1)/2 = 1.8 mg/L

B. Cancer

Several alcohol ethoxylates similar to alcohols, C12-16, ethoxylated were not carcinogenic to rats in a two-year dietary study. Thus, a cancer reference value was not derived.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Alcohols, C12-15, ethoxylated does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

7 ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Alcohol, C12-15, ethoxylated has moderate chronic toxicity concern to aquatic life.

B. Aquatic Toxicity

In developing a water quality guideline for alcohol ethoxylates (ANZECC & ARMCANZ, 2000), the toxicity data was normalised for a specific alkyl chain length or a specific number of ethoxylate (EO) groups. The NOECs listed below were normalised to an alkyl chain length of C13.3 and EO of 8.2.

Freshwater fish: 2 species, 720 to 1,500 mg/L.

Freshwater crustaceans: 2 species, 590 to 860 mg/L.

Freshwater rotifers: 1 species, *Brachionus calyciflorus*, 1,300 mg/L.

Freshwater algae, diatoms and blue-green algae: 6 species, 200 to 8,700 mg/L.

Freshwater mesocosms: 4 NOEC data for multiple species tests were 80, 80, 320 and 330 mg/L, although replication was insufficient to meet OECD (1992) requirements. Normalised data were 380, 380, 320 and 1,520 mg/L.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

PNEC water

The ANZECC water quality guideline (2000) for freshwater is: "A high reliability trigger value of 140 mg/L was derived for AE (normalised data) using the statistical distribution method with 95% protection."

For the purposes of calculating the PNEC values for sediment and soil, the $PNEC_{water}$ will be 0.14 mg/L.

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ values are 0.9 to 5.6 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (9.28/1500) \times 1000 \times 0.14$
$= 0.87$

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (60.36/1500) \times 1000 \times 0.14$
$= 5.63$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 464 \times 0.02$
$= 9.28$

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 3,018 \times 0.02$
$= 60.36$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} values for alcohols, C12-15, ethoxylated based on K_{ow} values range from 464 to 3,018 L/kg (see section 3 C.).
F_{oc} = fraction of organic carbon in soil = 0.02 [default].

8 PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Alcohols, C12-15, ethoxylated is readily biodegradable and thus does not meet the screening criteria for persistence.

The BCFs in fish for ethoxylated alcohols (which includes alcohols, C12-15, ethoxylated) have been reported to range from <5 to 387.5. Thus, alcohols, C12-15, ethoxylated does not meet the screening criteria for bioaccumulation.

The chronic NOEC values for alcohols ethoxylates are >0.1 mg/L. Thus, alcohols, C12-15, ethoxylated do not meet the criteria for toxicity.

Thus, alcohols, C12-15, ethoxylated is not a PBT substance.

9 CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity Category 4 [Oral]

Eye Irritant Category 2

Aquatic Chronic Toxicity Category 3

B. Labelling

Warning

C. Pictogram

10 SAFETY AND HANDLING

A. First Aid

<u>Eye Contact</u>

Rinse immediately with plenty of running water. If easy to do, remove contact lenses. Get medical attention.

Skin Contact

Wash with soap and water. Get medical attention if symptoms occur.

Inhalation

Treat symptomatically. Move to fresh air. Get medical attention.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. Seek medical attention.

B. Fire Fighting Information

Extinguishing Media

Water spray, dry chemical, foam. Do not use water jet.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon oxides.

Special Protective Equipment for Firefighters

Self-contained breathing apparatus and full protective clothing must be worn in case of fire.

C. Accidental Release Measures

Personal Precautions

Wear appropriate personal protective equipment. Do not breath mist or aerosol.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Absorb spill with inert absorbent material, then place in a container for chemical waste.

D. Storage And Handling

General Handling

Protect against moisture. Shut containers immediately after taking product because product takes up the humidity of air. No special precautions are necessary beyond normal good hygiene practices.

Other Handling Precautions

Wash hands thoroughly after handling. Avoid breathing mists or aerosols.

Storage

Keep container closed.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for the substance.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Wear respiratory protection if ventilation is inadequate.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Chemical safety goggles.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Isotridecanol, ethoxylated is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

11 DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

12 REGULATORY STATUS

Australian AICS Inventory: Listed.

13 REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

ANZECC & ARMCANZ (2000). Australian and New Zealand guidelines for fresh and marine water quality. National Water Quality Management Strategy Paper No 4, Australian and New Zealand Environment and Conservation Council & Agriculture and Resource Management Council of Australia and New Zealand, Canberra, Australia.

Basketter, D.A., York, M., McFadden, J.P., and Robinson, M.K. (2004). Determination of skin irritation potential in the human 4-h patch test. Contact Dermatitis 51: 1-4.

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA] (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Human and Environmental Risk Assessment (HERA) on Ingredients of Household Cleaning Products: Alcohol Ethoxylates (2009), http://www.heraproject.com.

OECD (1992). Report of the OECD workshop on extrapolation of laboratory aquatic toxicity data to the real environment. OECD Environment Monographs No. 59, Organisation for Economic Co-operation and Development, Paris.

Talmage, S.S. (1994). Environmental and Human Safety of Major Surfactants – Alcohol Ethoxylates and Alkylphenol Ethoxylates, pp. 35, The Soap and Detergent Association, Lewis Publishers, Boca Raton, Florida.

Toll, J., Haller, M., Labee, E., Verweij, M., and Sijm, D.T.H.M. (2000). Toxicology and Chemistry, 19 646–653.

U.S. Environmental Protection Agency [EPA] (2018). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of9Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

ETHOXYLATED OLEIC ACID

This dossier on ethoxylated oleic acid presents the most critical studies pertinent to the risk assessment of this substance in its use in drilling muds. As there is limited data on ethoxylated oleic acid, data from ethoxylated decanol (CAS RN [redacted] will be used to further assess ethoxylated oleic acid. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

1 SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-(decyloxy)ethan-1-ol

CAS RN: [redacted]

Molecular formula: not applicable, UVCB

Molecular weight: 130.23g/mol

Synonyms: 2-(Decyloxy)decanol, Deceth-4, Ethylene glycol monodecyl ether, Emulphogene DA 630, 2-(decyloxy)ethan-1-ol, Decyl alcohol, ethoxylated, Decanol, 2-(decyloxy)- , 2-(Decyloxy)decanol

2 PHYSICAL AND CHEMICAL PROPERTIES

Key physical and chemical properties for the substance are shown in Table 1.

Table 1 Overview of the Physico-chemical Properties of Ethoxylated Decanol

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Clear and colourless liquid	2	ECHA
Melting Point (101 kPa)	-27°C	1	ECHA
Boiling Point (101 kPa)	224°C	1	ECHA
Density (25°C)	0.88 g/cm^3	2	ECHA
Vapor Pressure (kPa @ 20°C)	0.08	2	ECHA
Partition Coefficient (log K_{ow})	4.9	2	ECHA
Water Solubility (µg/L at 25°C, pH = 6-7)	82	2	ECHA
Flash Point @ 101.3 kPa	118.7°C	2	ECHA
Auto flammability (101,325 Pa)	220°C	1	ECHA
Viscosity (mm^2/s @ 25°C)	13.911	2	ECHA

3 ENVIRONMENTAL FATE PROPERTIES

A. Summary

Ethoxylated decanol is readily biodegradable. It is not expected to bioaccumulate and decanol has a low tendency to bind to soil or sediment.

B. Biodegradation

An OECD Guideline 301 B (Ready Biodegradability: CO2 Evolution Test) was performed. Decanol, ethoxylated (6 EO) was tested for ready biodegradation according to OECD 301B. The degradation of the test item was 83% within 28 days (after acidification). The biodegradation of the test item reached the criterion for ready biodegradation (ECHA) [Kl. score = 1].

C. Environmental Distribution

Adsorption/desorption

Due to the specificity of the work carried out for alcohol ethoxylates, the lowest resulting Koc value based on modelling are used for further assessment is 1057 L/kg (at 20°C), indicating low mobility in soil (ECHA) [Kl Score = 2].

Bioaccumulation

A BCF of 237 L/kg was determined using the fathead minnow (ECHA) [Kl Score = 2].

4 HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Ethoxylated decanol has low acute toxicity by the oral route and limited acute toxicity by the dermal route. No data were available for the inhalation route. It is not a skin and eye irritant nor is it a skin sensitiser. Repeated exposure studies in rodents caused limited toxicity. No data were available to evaluate carcinogenic effects although the lack of mutagenic effects suggests the substance is not a carcinogen. Ethoxylated decanol is not expected to have an effect on reproduction based on findings in animals from similar compounds. No developmental toxicity was seen in animals exposed to ethoxylated decanol by the oral, dermal or inhalation routes.

B. Acute Toxicity

Oral

An OECD Guideline 401 (Acute Oral Toxicity) study was performed on male/female Sprague-Dawley rats. Substance was administered via oral: gavage at a dose of 5,050 mg/kg bw. The LD_{50} > 5,050 mg/kg bw (ECHA) [Kl Score = 1].

Inhalation

An OECD Guideline 403 (Acute Inhalation Toxicity) study was performed on male/female Sprague-Dawley rats. The LC_{50} was determined to be > 1,600 mg/m³ air (ECHA) [Kl Score = 2].

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) study was performed on male/female Wistar rats. The LD_{50} of > 2,000 mg/kg bw was determined (ECHA) [KI Score = 2].

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was performed on New Zealand White rabbits. Very slight erythema was present at each observation through 24 hours in three animals. Oedema was not observed at any time throughout the study. Reported skin irritation results for the test animals indicate the substance is not an dermal irritant (ECHA) [KI Score = 2].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) was conducted using New Zealand White rabbits. Cornea opacity scores, iris score, conjunctivae score, and chemosis scores indicated that the substance was not irritating to the eye (ECHA) [KI Score = 2].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) was performed on Dunkin-Hartley guinea pigs.

A study was performed to assess the contact sensitisation potential of the test material in the albino guinea pig. Ten test and five control animals were used for the main study. Based on the results of sighting test, the concentration of the test material for the induction and challenge phases were selected as follows:

- Intradermal Induction: 1% w/v in arachis oil
- Topical Induction: undiluted as supplied
- Topical Challenge: 50% and 25% v/v in arachis oil

The test material produced a 0% (0/10) sensitisation rate and was classified as a NON-SENSITISER to guinea pig skin (ECHA) [KI Score = 1].

E. Repeated Dose Toxicity

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity Study in Rodents) was performed on male and female Wistar rats. The oral repeated dose toxicity of the target substance was estimated based on an adequate and reliable subchronic oral toxicity key study performed with a structural analogue source substance. Daily oral exposure of male and female rats via the diet for 90 consecutive days to the test substance did not result in any toxicologically relevant effects. The NOAEL was determined to be > 500 mg/kg bw/day, corresponding to the highest dose tested. The result of the key study is further supported by additional (supporting) studies of various structural analogue source substances. Therefore, a systemic NOAEL after oral exposure for the target substance of > 500 mg/kg bw/day is established. The differences in molecular structure between the target and the source

substances are unlikely to lead to differences in oral repeated dose toxicity (ECHA) [Kl. score = 2].

Inhalation

No inhalation repeat dose data were available.

Dermal

No dermal repeat dose data were available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on ethoxylated decanol are presented in Table 3.

Table 3 *In Vitro* Genotoxicity Studies on Ethoxylated oleic acid[1]

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains) OECD Guideline 471 (Bacterial Reverse Mutation Assay)**	-	-	2	ECHA

*+, positive; -, negative

** Neither E.coli WP2 strains nor S. typhimurium TA102 were used

1 – Data from ethoxylated decanol used (CAS RN [redacted] as surrogate for ethoxylated oleic acid.

In Vivo Studies

An OECD Guideline 475 (Mammalian Bone Marrow Chromosome Aberration Test) was performed on male and female Sprague-Dawley rats. Rats were administered single doses of 450, 900 and 1500 mg/kg bw/day. Post euthanasia, femoral bone marrow smears were prepared. No chromosomal aberrations were noted. Therefore, the substance is considered to be non-mutagenic in vivo (ECHA) [Kl Score = 2].

G. Carcinogenicity

No studies are available.

H. Reproductive Toxicity

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed on male/female Fischer 344 rats. Animals were treated dermally with doses of 1, 10 and 25% (w/v) to shaved dorsal region. The reproductive toxicity of the target substance is estimated based on an adequate and reliable two-generation reproductive toxicity study of a structural analogue source substance with subsequent detailed examination of foetuses. Dermal treatment of pregnant rats with the test substance at doses of 10, 100 and 250 mg/kg bw/day resulted in no maternal toxicity and hence a dermal NOAEL for maternal systemic toxicity of >/= 250 mg/kg bw/day. The NOAEL for reproductive toxicity, based on

observations in the P0, F1 and F2 generations was determined to be 250 mg/kg/day [Kl. score = 2].

I. Developmental Toxicity

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed on male/female Fischer 344 rats. Animals were treated dermally with doses of 1, 10 and 25% (w/v) to shaved dorsal region. The developmental toxicity of the target substance is estimated based on an adequate and reliable two-generation reproductive toxicity study of a structural analogue source substance with subsequent detailed examination of foetuses. Dermal treatment of pregnant rats with the test substance at doses of 10, 100 and 250 mg/kg bw/day resulted in no maternal toxicity and hence a dermal NOAEL for maternal systemic toxicity of >/= 250 mg/kg bw/day. Foetal abnormalities observed include malformations of eyes and front as well as hind limbs. All developmental effects were due to spontaneous occurrence and were considered not to be treatment-related. The dermal developmental NOAEL was thus determined to be >/= 250 mg/kg bw/day. No developmental toxicity is therefore expected for the target substance. As explained in the category justification, the differences in molecular structure between the target and the source substances are unlikely to lead to differences in the developmental toxicity and teratogenicity.

5 DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for ethoxylated oleic acid follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

Non-Cancer

Oral

Two-year chronic studies have been conducted in rats given dermal doses of ethoxylated decanol. The lowest NOAEL from these studies is 50 mg/kg-day, based on reduced body weight and clinical signs in rats dosed with 150 and 500 mg/kg-day ethoxylated decanol. The NOAEL of 50 mg/kg-day will be used for determining the oral Reference Dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:
UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UFr (route to route variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1

Oral RfD = 50/(10 x 10 x 10 x 1 x 1 x 1) = 50/1000 = 0.05 mg/kg-day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:
Human weight = 70 kg (ADWG, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (0.25 x 70 x 0.1)/2 = 0.875 mg/L

Cancer

Ethoxylated decanol was not carcinogenic to rats in chronic oral studies. Therefore, a cancer reference value was not derived.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Ethoxylated decanol does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

7 ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Ethoxylated oleic acid is moderately toxic to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 4 lists the results of acute aquatic toxicity studies conducted on ethoxylated oleic acid.

Table 4 Acute Aquatic Toxicity Studies on Ethoxylated oleic acid

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Cyprinus carpio and Danio rerio	96-hour LC_{50}	1.2	1	ECHA
Daphnia magna	48-hour EC_{50}	0.39	2	ECHA
Desmodesmus subspicatus	72-hour EC_{50}	1.4 (biomass) 1.8 (growth rate)	2	ECHA

Chronic Studies

No chronic test data were sufficient to derive meaningful toxicity values.

C. Terrestrial Toxicity

In an acute toxicity test according to OECD 207 no effect on earth worm *Eisenia fetida* was observed up to the highest test item concentration of 1,000 mg/kg soil dw. Therefore, the NOEL is determined to be >1,000 mg/kg dw (ECHA) [KI Score = 2].

D. Calculation of PNEC

The PNEC calculations for ethoxylated oleic acid follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute EC_{50} values are available for fish, invertebrates and plants. On the basis that the data consists of short-term studies from three trophic levels, an assessment factor of 1,000 has been applied to the lowest reported EC_{50} value of 0.39 mg/L for invertebrates. The $PNEC_{water}$ is 0.39 µg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Moreover, the experimentally derived log Koc is 3. Given the relatively low log Koc value, a $PNEC_{sed}$ was not calculated.

PNEC soil

There is only a single acute toxicity study on terrestrial receptors (i.e., NOAEL >1000 mg/kg soil). Given the limited data for the soil compartment, an assessment factor of 1000 was applied to derive a $PNEC_{soil}$ of 1 mg/kg dw.

8 PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Ethoxylated oleic acid is readily biodegradable; thus it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of 4.93, ethoxylated oleic acid does not meet the screening criteria for bioaccumulation.

The aquatic toxicity studies indicate toxicity >0.1 mg/L. Thus, ethoxylated oleic acid does not meet the screening criteria for toxicity.

Therefore, ethoxylated oleic acid is not a PBT substance.

9 CLASSIFICATION AND LABELLING

A. Classification

Causes serious eye irritation. H319.

B. Labelling

Warning

C. Pictogram

10 SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapor. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for ammonium chloride.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapor cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, as well as before eating, smoking and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

The substance is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

11 DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

12 REGULATORY STATUS

Australian AICS Inventory: Listed.

13 REFERENCE

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

GELATINS

This dossier on gelatins presents the most critical studies pertinent to the risk assessment of gelatins in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Gelatins

CAS RN: [redacted]

Molecular formula: Not applicable as substance is a UVCB whose specific chemical composition is dependent on formulation processes.

Molecular weight: Depending on the specific commercial use, the molecular weight can range from 72 to 132 kDaltons (i.e., 72,000 to 132,000 g/mol) (Farrugia et. al., 1998)

Synonyms: None identified.

SMILES: Not applicable.

II. PHYSICAL AND CHEMICAL PROPERTIES

Gelatin is a white to yellow, translucent powder. It is hydrolysed and partially degraded collagen obtained by acid, alkaline or enzymatic hydrolysis. It is a polypeptide. Depending on the source of collagen and the method of its manufacturing process of recovery from collagen, gelatin contains an average of the following amino acids: glycine 21%, proline 12%, hypoproline 12%, glutamic acid 10%, alanine 9%, arginine 8%, aspartic acid 6%, lysine 4%, serine 4%, leucine 3%, valine 2, phenylalanine 2%, threonine 2%, isoleucine 1%, hydroxylysine 1%, histidine <1% and tyrosine <0.5% (Gorgieva and Kokol, 2011).

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Gelatins are readily biodegradable; they are not expected to bioaccumulate or adsorb to soil.

B. Biodegradation

As a natural polymer, gelatin is expected to be readily biodegradable by most proteases when environmental conditions are adequate. While high molecular weight polymer degradation rates are generally thought to be low, the biopolymeric nature of gelatin in a variety of cross-linked forms appears to result in rapid biodegradation (e.g., 3-10 days) in the environment (Patel et. al., 2000).

Gelatin, as a rapidly biodegradable protein, is a rich source of amino acids and other nutrients such as nitrogen and carbon for bacteria and fungi. The increased bioavailability of nutrients could lead to a significant increase in biological oxygen demand (BOD) as a result of degradation of gelatin and the stimulated growth of microorganisms. High BOD will deplete local dissolved oxygen concentrations

when gelatin or its breakdown products are released into the aquatic environment in sufficient quantities relative to the volume of the receiving water body. This depletion of oxygen has the potential to place significant stress on some organisms within the aquatic environment (DoEE, 2017).

C. Environmental Distribution

Given the hydrophilic nature of gelatin it is unlikely that this biopolymer would adsorb to the soil or sediment.

D. Bioaccumulation

The potential for bioaccumulation is low. Based on the biological properties and the environmental fate of gelatin, especially the rapid biodegradation, prolonged exposure of aquatic organisms to the biopolymer will be highly unlikely (DoEE, 2017).

IV. HUMAN HEALTH HAZARD ASSESSMENT

There is no data on the human health hazard for this substance. However, based on its biopolymeric nature and uses in foods and medicines, the human health toxicity concern is expected to be very low.

NICNAS has assessed gelatin in an IMAP Tier 1 assessment and it was concluded that it poses no unreasonable risk to the environment[1]. In addition, based on an assessment of human health and environmental hazards, NICNAS also identified gelatin as a chemical of low concern to the environment (NICNAS, 2017 and DoEE, 2017). Chemicals of low concern are unlikely to have adverse environmental effects or be a concern to human health if they are released to the environment from coal seam gas operations.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Toxicological reference and drinking water guidance values have not been derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Gelatin does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

There are no aquatic toxicity studies on gelatin. However, it is expected to have low concern for aquatic toxicity since any gelatin released into aquatic ecosystems will be rapidly degraded by microorganisms through enzymatic digestion to the individual amino acids or short peptides. If sufficient quantities of gelatin were abruptly released into a water body, this could cause temporary changes in water quality for local organisms, such as reduced dissolved oxygen concentrations (DoEE, 2017).

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]2C+

B. Aquatic Toxicity

No aquatic toxicity data was available.

C. Terrestrial Toxicity

No relevant studies were available.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Gelatins are readily biodegradable; thus, it does not meet the screening criteria for persistence.

The rapid degradation and expected lability to enzymatic degradation suggests gelatins will not meet the screening criteria for bioaccumulation.

There are no aquatic toxicity studies on gelatins. It is expected to have low concern for aquatic toxicity because of its bio-composition (e.g., various amino acids and crosslinked substituents) and rapid degradation rates in the environment. Thus, gelatin does not meet the screening criteria for toxicity.

The overall conclusion is that gelatin is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

Based on the low concern of this substance, and according to the majority of notifications provided by companies to ECHA under the Classification, Labelling and Packaging of Substances and Mixtures Regulation No 1272/2008, no hazards have been classified.

X. SAFETY AND HANDLING

Based on the low concern status of this substance, no specific safety or handling precautions are relevant.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy (DoEE). (2017). Environmental risks associated with surface handling of chemicals used in coal seam gas extraction in Australia, Project report Appendices A, B, C, D, F, and G prepared by the Chemicals and Biotechnology Assessments Section (CBAS) in the Department of the Environment and Energy as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Farrugia, C.A., Farrugia, I.V. and Groves, M.J. (1998). Comparison of the Molecular Weight Distribution of Gelatin Fractions by Size-exclusion Chromatography and Light Scattering. Pharm. Pharmacol. Commun. 1998, 4: 559-562

Gorgieva, S, and Kokol V. (2011). 'Collagen- vs. Gelatine-Based Biomaterials and Their Biocompatibility: Review and Perspectives', in: Pignatello R (ed) Biomaterials applications for nanomedicine, INTECH, retrieved from http://www.intechopen.com/books/biomaterials-applications-for-nanomedicine.

Klimisch, H. J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol Pharmacol. 25:1-5.

NICNAS. (2017). Chemicals of low concern for human health based on an initial assessment of hazards, Project report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra

Patel, Rajaram dattu, Dalev, P.G., and Mark, J.E. (2000). Biodegradation of chemically modified gelatin films in lake and river waters. Journal of Applied Polymer Science 76(1):29 – 37

ISOPROPANOL

This dossier on isopropanol presents the most critical studies pertinent to the risk assessment of isopropanol in its use in coal seam gas extraction activities. It does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Propan-2-ol

CAS RN: [redacted]

Molecular formula: C_3H_8O

Molecular weight: 60.1 g/mol

Synonyms: Isopropanol, isopropyl alcohol, 2-propanol, *sec*-propyl alcohol, dimethylcarbinol

SMILES: CC(C)O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Isopropanol

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colourless liquid	2	ECHA
Melting Point	-88.5°C; -89.5°C[1]	2	ECHA
Boiling Point	82.5°C; 82.3°C @ 101.3 kPa	2	ECHA
Density	800 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	4,400 Pa @ 20°C; 6,002 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	0.05 @ 25°C	2	ECHA
Water Solubility	Miscible	2	ECHA
Viscosity	2.038 mPa s @ 25°C	2	ECHA

[1] No information on the atmospheric pressure reported.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Isopropanol is readily biodegradable. It is not expected to bioaccumulate. Isopropanol has a low tendency to bind to soil or sediment.

B. Partitioning

Isopropanol is miscible in water. Volatilisation from water surfaces or moist soil surfaces is expected to be an important fate process based upon this compound's estimated Henry's Law constant of 0.821 Pa m^3/mole. It is also expected to volatilise from dry soil surfaces based upon its vapour pressure (Pub Chem).

C. Biodegradation

Aerobic biodegradation of isopropanol has been shown to occur rapidly under non-acclimated conditions, based on a result of 49% biodegradation from a 5-day BOD test (Bridie et al., 1979). Additional biodegradation data developed using standardised test methods show that isopropanol is readily biodegradable in both freshwater and saltwater media (72 to 78% biodegradation in 20 days) (Price et al., 1974).

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

D. Environmental Distribution

No experimental data are available for isopropanol. Using KOCWIN in EPI Suite™ (USEPA, 2017), the estimated K_{oc} value from log K_{ow} is 3.478 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 1.53 L/kg.

E. Bioaccumulation

Bioconcentration of isopropanol in aquatic organisms is not expected to occur based on a measured log K_{ow} of 0.05 (ECHA). Based on this estimated value, the substance is expected to have very high mobility in soil. If released to water, based on this value and its water solubility, it is also not expected to adsorb to suspended solids and sediment.

Volatilisation from water surfaces is expected with half-lives for a model river and model lake of 86 hours and 29 days, respectively (PubChem).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of isopropanol is low by the oral, dermal and inhalation routes. At high exposure levels, isopropanol is irritating to the eyes, nose and throat and may cause transient central nervous system depression. It is not a skin sensitiser, but in some individuals, there may be an allergic contact dermatitis due to cross-sensitisation to other alcohols, such as ethanol. Repeated high exposures cause reversible narcotic effects, consistent with other short-chain alcohols. Isopropanol is not genotoxic. Lifetime inhalation studies in rodents showed no carcinogenic effects. The weight-of-evidence indicates that

isopropanol is not a reproductive toxicant. In a two-generation reproductive toxicity study, the male mating index was affected by isopropanol exposure; the significance of this effect is, however, unclear. Developmental toxicity can occur at maternally toxic doses; but it is not a teratogen. Isopropanol also does not affect neurobehavioral development.

B. Acute Toxicity

The acute oral LD_{50} of isopropanol has been reported as 4,700 mg/kg, 5,300 mg/kg, 5,500 mg/kg and 5,400 mg/kg in rats; 4,500 mg/kg in mice; and 5,030 mg/kg, 7,800 mg/kg and 7,900 mg/kg in rabbits (ECHA) [KI Score = 2].

The acute dermal LD_{50} in rabbits has been reported to be 12,900 mg/kg (ECHA) [KI Score = 2].

The acute inhalation 8-hour LC_{50} in rats was 19,000 ppm in females and 22,500 ppm in males (ECHA) [KI Score = 2]. Exposure of rats to 16,000 ppm for 8 hours resulted in four deaths out of six animals (ECHA) [KI Score = 2].

In an acute neurotoxicity study, male and female F344 rats were exposed to 0, 500, 1,500, 5,000 or 10,000 ppm isopropanol for 6 hours. A spectrum of behavioural effects indicative of narcosis, defined as a generalised loss of neuromotor and reflex function, was observed in animals of the 10,000 ppm group and to a lesser extent in the 5,000 ppm animals. Recovery from these effects was observed by 24 hours for the 10,000 ppm animals and by 6 hours for the 5,000 ppm animals. A concentration-dependent decrease in motor activity was observed for the 1,500 ppm males and the 5,000 ppm females. The results show that exposure of rats to isopropanol vapour produces transient, concentration-related narcosis and/or central nervous system sedation. The NOAEL for acute neurotoxicity is 500 ppm (ECHA) [KI Score = 2].

C. Irritation

Isopropanol applied to the intact or abraded skin of rabbits and guinea pigs produced negligible irritation. Liquid isopropanol is moderately irritating to the eyes of rabbits. Isopropanol produced little irritation when tested on the skin of six human subjects (ECHA) [KI Score = 1].

D. Sensitisation

There have been reports of isolated cases of dermal irritation and/or skin sensitisation. Except for three case reports, the positive reactions were observed on patch testing patients with contact dermatitis due to ethanol. These patients also had a positive reaction to ethanol.

E. Repeat Dose Toxicity

<u>Oral</u>

In a drinking water study, rats ingested 0.5 to 10% of isopropanol for 27 weeks and showed decreased body weight gain but no gross or microscopic tissue abnormalities (ECHA) [KI score = 3]. Increased formation of hyaline droplets in the proximal tubules was reported in male rats given 1–4% isopropanol in drinking water for 12 weeks (ECHA) [KI Score = 3].

A two-generation reproductive toxicity study has been conducted in rats given isopropanol by oral gavage. Pre-mating exposures were for at least 10 weeks for both generations. The results from this study are presented in the Reproductive Toxicity section (ECHA) [KI Score = 2].

Inhalation

F344 rats and CD-1 mice (both sexes) were exposed to 0, 100, 500, 1,500 or 5,000 ppm isopropanol for 6 hours/day, 5 days/week for 13 weeks. There were no deaths during the study. During and immediately following exposure to 5,000 ppm, ataxia, narcosis, hypoactivity and a lack of startle reflex were observed in some rats and mice. Narcosis was not observed in rats during exposure following week 2, suggesting some adaptation to isopropanol. During exposures to 1,500 ppm, narcosis, ataxia, and hypoactivity were observed in some mice, whereas only hypoactivity was observed in rats. Immediately following exposures, ataxia and/or hypoactivity were observed in a few rats or mice exposed to 5,000 ppm. Overall, the 1,500 and 5,000 ppm rats and the 5,000 ppm female mice showed increased body weights and/or body weight gain during the study. Liver weights relative to body weight were observed in rats of both sexes and the 5,000 ppm female mice; however, no corresponding microscopic changes were noted in the liver. Histopathological evaluation showed a slight increase in the size and frequency of hyaline droplets in the kidneys of the isopropanol-exposed rats. Excluding the clinical signs of CNS depression, the NOAEL for this study is 5,000 ppm (ECHA) [KI Score = 1].

In a subchronic neurotoxicity study, male and F344 rats were exposed by inhalation to 0, 100, 500, 1,500 or 5,000 ppm for 13 weeks. Neurobehavioural evaluations included a functional observation battery (FOB), motor activity and neuropathology. Effects of narcosis were observed in the 5,000 ppm groups only. There were no changes in FOB, but increased motor activity was noted in 5,000 female rats at weeks 9 and 13. Neuropathological examination revealed no exposure-related lesions in the nervous system. The NOAEL for acute effects is 500 ppm, and the NOAEL for subchronic neurotoxicity is 1,500 ppm (ECHA) [KI Score = 1].

An additional subchronic neurotoxicity study was conducted to clarify the increased motor activity findings. Female F344 rats were exposed to 0 or 5,000 ppm of isopropanol vapour for 6 hours/day, 5 days/week. Half of the animals in each group were exposed for 9 consecutive weeks and the other half for 13 consecutive weeks. After 9 weeks of exposure, the motor activity effect was reversible within 2 days after the last exposure. Subtle differences in the shape of the motor activity versus test session time curve were noted in both the 9-week and the 13-week exposed animals, although it was unclear whether these changes were treatment-related. Complete reversibility of these changes did not occur until 1 and 6 weeks after the last exposure in the 9 and 13 week exposure groups, respectively (ECHA) [KI Score = 2].

Male and female CD-1 mice were exposed by inhalation to 0, 500, 2,500 or 5,000 ppm isopropanol vapour 6 hours/day, 5 days/week for 18 months. An additional group of mice (all exposure levels) were assigned to a recovery group which were exposed to isopropanol for 12 months and then retained until study termination at 18 months. Survival was similar across all groups. Clinical signs were noted in the 5,000 ppm animals and included hypoactivity, lack of a startle reflex, ataxia, prostration and narcosis. Some of the animals in the 2,500 ppm group also showed hypoactivity, lack of a startle reflex and narcosis. Ataxia was the only exposure-related clinical sign that was noted for the 5,000 ppm animals

following exposure. There was a concentration-related increase in body weights and body weight gain in both the 2,500 and 5,000 ppm animals (both sexes). There were no exposure-related changes in the hematological parameters at the 12- and 18-month time points. At study termination, there was a concentration-related increase in liver weights in the females, with the 5,000 ppm females being statistically significant. Nonneoplastic lesions were limited to the testes (males) and the kidney. In the testes, enlargement of the seminal vesicles occurred in the absence of associated inflammatory or degenerative changes. The kidney effects included tubular proteinosis and/or tubular dilatation. The incidence of testicular and kidney effects was not increased in the isopropanol-exposed recovery animals. The NOAEL is 500 ppm (ECHA) [KI Score = 2].

Male and female Fischer 344 rats were exposed to 0, 500, 2,500 or 5,000 ppm isopropanol vapour 6 hours/day, 5 days/week for 24 months. The mortality rates for all male rats were 82, 83, 91 and 100% for the 0, 500, 2,500 and 5,000 ppm groups, respectively. The corresponding values for the female rats were 54, 48, 55 and 69%. The main cause of death for the 5,000 ppm rats (both sexes), as well as for much of the mortality of the 2,500 ppm male rats, was chronic progressive nephropathy. Clinical signs were seen in the 5,000 ppm animals and included hypoactivity, lack of a startle reflex and narcosis. Some of the 2,500 ppm animals also showed a lack of a startle reflex. Body weight of the 5,000 ppm animals showed an initial decrease; from Weeks 6-72, body weights and body weight gain were increased. A similar pattern was seen in the 2,500 ppm males. Liver weights were increased in the ≥2,500 ppm male at 18 months, in the 2,500 ppm males at 24 months and in the 5,000 ppm females at 24 months. Kidney weights were increased in the 5,000 ppm males at 18 months and in the 5,000 ppm females at 24 months. Isopropanol exposure resulted in impaired kidney function, as indicated by various urine chemistry changes in male (2,500 and 5,000 ppm) and female (5,000 ppm) rats. Animals in these groups also exhibited histopathological effects in the kidneys which appeared to be an exacerbated form of chronic progressive nephropathy. The NOAEL is 500 ppm (ECHA) [KI Score = 1].

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on isopropanol are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Isopropanol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* TA98, TA100, TA1535, TA1537)	-	-	2	ECHA
Bacterial reverse mutation (*S. typhimurium* TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538)	-	-	2	ECHA
Sister Chromatid Exchange (V79 cells)	-	-	2	ECHA
Mammalian cell gene mutation (CHO/HGPRT)	-	-	1	ECHA

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Adenovirus (SA7) cell transformation (Syrian hamster embryo cells)	NA	-	2	ECHA

*+, positive; -, negative; NA, not applicable

In Vivo Studies

Male and female ICR mice were given a single intraperitoneal injection of 0, 350, 1,173 or 2,500 mg/kg isopropanol. There were no increases in micronuclei in the bone marrow polychromatic erythrocytes at the 24, 48 or 72-hour post-dosing time points at any dose level (ECHA) [KI Score = 1].

G. Carcinogenicity

Oral

No studies are available.

Inhalation

The carcinogenic potential of isopropanol was evaluated via inhalation using three strains of mice. Male mice were exposed to 7.5 ppm of isopropanol for 3 to 7 hours/day, 5 days/week for 5 to 8 months. Animals were killed at either 8 or 12 months. There was no significant increase in the number of lung tumours observed (ECHA) [KI Score = 3].

Male and female CD-1 mice were exposed by inhalation to 0, 500, 2,500 or 5,000 ppm isopropanol vapour for 6 hours/day, 5 days/week for 18 months. An additional group of mice (all exposure levels) were assigned to a recovery group which were exposed to isopropanol for 12 months and then retained until study termination at 18 months. There was no increased frequency of neoplastic lesions in any of the isopropanol-exposed animals (ECHA) [KI Score = 1].

Male and female Fischer 344 rats were exposed to 0, 500, 2,500 or 5,000 ppm of isopropanol vapour for 6 hours/day, 5 days/week for 24 months. The mortality rates for all male rats were 82, 83, 91 and 100% for the 0, 500, 2,500 and 5,000 ppm groups, respectively. The corresponding values for the female rats were 54, 48, 55 and 69%, respectively. The main cause of death for the 5,000 ppm rats (both sexes), as well as for much of the mortality of the 2,500 ppm male rats, was chronic progressive nephropathy. The only neoplastic lesion noted was increased interstitial (Leydig) cell adenomas in male rats. The frequency of these tumours, although elevated above the control animals, was within the historical control range of the testing facility and within the range reported for control animals from the National Toxicology Program carcinogenicity studies (ECHA) [KI Score = 1].

H. Reproductive Toxicity

In a two-generation reproductive toxicity study, Sprague–Dawley rats were dosed by oral gavage with 0, 100, 500 or 1,000 mg/kg isopropanol. There were seven parental deaths that were considered treatment-related: two high-dose F_0 females, two F_1 high-dose females,

one mid-dose F_0 female, and two low-dose F_1 males. Lactation body weight gain was increased in the 500 and 1,000 mg/kg females in both generations, and liver and kidney weights were increased in the 500 and 1,000 mg/kg groups in both sexes. Centrilobular hepatocyte hypertrophy was noted in some 1,000 mg/kg F_1 males. There were some kidney effects in the 500 and 1,000 mg/kg F_0 males and in all treated F_1 male rats. The kidney effects were characterised by an increased number of hyaline droplets in the convoluted proximal tubular cells, epithelial degeneration and hyperplasia, and proteinaceous casts. Increased mortality occurred in the high-dose F_1 offspring during the early postnatal period; no other clinical signs of toxicity were observed in the offspring from either generation. Offspring body weight, however, in the 1,000 mg/kg group was reduced during the early postnatal period. There was significant mortality in the F_1 weanlings (18/70) before the selection of the F_1 adults. A statistically significant reduction was observed in the F_1 male mating index of the 1,000 mg/kg group (73 versus 97% in the controls). There were no other treatment-related effects on reproduction, including fertility and gestational indices, or histopathology of the reproductive organs. A benchmark dose level of 420 mg/kg/day was calculated (lower bound on dose associated with a 5% response rate) for the decrease in the male mating index (ECHA) [KI Score = 1].

In a one-generation reproductive/embryotoxicity study, male and female Wistar rats were given 0, 0.5, 1.0 or 2.0% isopropanol in their drinking water. The calculated intakes for males were 383, 686 and 1,107 mg/kg/day (pre-mating) and 347, 625 and 1,030 mg/kg/day (18 weeks of treatment). The calculated intakes for females were 456, 835 and 1,206 mg/kg/day (premating); 668, 1,330 and 1,902 mg/kg/day (gestation); and 1,053, 1,948 and 2,768 mg/kg/day (postpartum). An immediate, statistically significant dose-dependent decrease occurred in water intake in the male rats. Intake was reduced ~5-14% (1% group; premating period) and ~30% (2% group; days 7-11 to end of study). Overall mean feed consumption was significantly lower in treated versus control animals. Male body weights (2% only) were reduced throughout the study. Water consumption was initially reduced in the 1% and 2% females, but the 2% group recovered to only ~70% of the control values (premating); it continued to be reduced during the gestation and lactation period. Mean maternal body weights were reduced (all treated groups) at the start of gestation, with partial recovery during the gestation period except for the 2% group. Overall weight gain during gestation in these groups were similar to the controls. Following parturition from PND 4 onward, the 2% dams had significantly lower body weights. There were no infertile males in any group, and no treatment-related effect on female fertility or on length of gestation. The number of pups/litter on GD 1 was reduced in the 2% group; because it was not replicated in the embryotoxicity portion, an increase in pup mortality during parturition or GD 0, followed by cannibalism of the dead pups by the dam was suggested. No macroscopic abnormalities were seen in females; nor was there any treatment-related histopathological changes seen in the reproductive tissue in the 2% parental animals. Absolute kidney weight and relative kidney, liver and spleen weights were increased in the 2% F_0 males; increased absolute liver and kidney weights and relative liver weights in the 2% F_0 females. In the embryotoxicity portion, there was a statistically significant increase in the total number of pre-implantation losses in the 2% animals. Whole body oedema was seen in 40% of the foetuses in 3/8 litters in the 2% group. No macroscopic abnormalities of the viscera of these foetuses were detected, and the incidence of oedema was not related to gender. In the one-generation portion, postnatal pup survival and in the average pup weight (by PND 7) were decreased in the 2% group. F_1 generation animals of both sexes showed increased relative liver weights at all dose levels, and the 2% males had higher relative kidney weights. A slight but significant decrease in absolute brain weight and increase in relative empty cecum weights in both sexes of the 2% F_1 generation group was observed. No treatment-related gross

abnormalities were observed in the F_1 generation animals at necropsy. The NOAEL for reproductive toxicity is 2% in drinking water, the highest dose tested (ECHA) [KI Score = 1]. The effects of isopropanol (2.5% in drinking water) on the reproduction and growth of rats were assessed in a multigenerational study. No reproductive toxicity was observed. The NOAEL for reproductive toxicity is 2.5% isopropanol in drinking water (ECHA) [KI Score = 4].

Isopropanol was administered as a 3% solution in drinking water to Wistar rats. Reduced parental body weight gain, food, and water consumption were observed in the treated animals compared with the controls. Fertility, litter size and pup weights at postnatal days 4 and 21 were reduced in treated animals compared with the controls. In the second generation, the isopropanol concentration was reduced to 2%, and there were essentially no effects (ECHA) [KI Score = 4].

I. Developmental Toxicity

Oral Studies

Isopropanol was given at concentrations of 0, 0.5, 1.25 or 2.5% in the drinking water to female Wistar rats on GD 6 to 16. The calculated intakes of isopropanol during GD 6-16 were 596, 1,242 and 1,605 mg/kg/day. There was an immediate reduction in water intake in the 2.5% dose group, and this was statistically significant throughout the treatment period when compared to controls. A smaller reduction in water intake was also seen in the 1.25% females (statistically significant during GD 6-9), with no change in the 0.5% females. Palatability of the drinking water may have been the problem since water intake significantly increased the first day following the end of the treatment period for all dose groups. Feed consumption patterns paralleled the water consumption during and after treatment in the mid- and high-dose groups. Overall, mean body weights of the 2.5% females were lower than the controls from GD 7 to termination. Effects on weight gain in the 0.5% and 1.25% females were limited to a failure to gain weight during the first (0.5%) and second (1.25%) day of treatment. There were no treatment-related effects in post-implantation loss, mean number of implantation sites or live foetuses. There was a slight dose-dependent decrease in mean litter weight and a significant decrease in mean foetal weight in the 1.25% and 2.5% groups. A statistically significant increase in variations was observed, indicative of a lower degree of ossification in the treated animals. There was a dose-dependent decrease in the number of foetuses with the 4th sacral arch and a dose-dependent increase in the number of foetuses with less than 2 caudal arches. The sternum also showed reduced ossification because there were increased numbers of foetuses with small, absent or incompletely ossified sternebrae. The NOAEL for maternal and developmental toxicity is 596 mg/kg/day (ECHA) [KI Score = 1].

In a rat developmental study, female Sprague–Dawley rats were dosed by oral gavage with either 0, 400, 800 or 1,200 mg/kg of isopropanol during gestational days 6 to 15. Two dams (8%) died at 1,200 mg/kg and one dam (4%) died at 800 mg/kg. At 1,200 mg/kg, maternal body weights were reduced throughout gestation (GS 0-20; 89.9% of control value), associated with reduced gravid uterine weight. There were no other treatment-related effects on the dams. Foetal body weights per litter were also significantly reduced at the 800 and 1,200 mg/kg dose levels, but there were no teratogenic effects. The NOAEL for maternal and developmental toxicity is 400 mg/kg/day, respectively (ECHA) [KI Score = 1]. In a rabbit developmental study, female New Zealand white rabbits were dosed by oral gavage with either 0, 120, 240 or 480 mg/kg of isopropanol during gestational days 6 to 18. At 480 mg/kg, isopropanol was unexpectedly toxic to pregnant female rabbits, resulting in the deaths of four does (26%). Maternal body weights were significantly reduced during

treatment (gestational days 6–18) and were associated with reduced maternal food consumption during this period. Profound clinical signs were noted at 480 mg/kg and included flushed and/or warm ears, cyanosis, lethargy and laboured respiration. No adverse maternal effects were noted at 120 or 240 mg/kg. There were no developmental or teratogenic effects at any dose tested. The NOAELs for maternal and developmental toxicity are 240 and 480 mg/kg/day, respectively (ECHA) [KI Score = 1].

Isopropanol was given by oral gavage to Sprague–Dawley rats from gestational days 6 to 21 in doses of 0, 200, 700 or 1,200 mg/kg. The dams were allowed to deliver, litters were culled on postnatal day (PND) 4, pups were weaned on PND 22, and their dams were killed. Weaned pups were assessed for day of testes descent or vaginal opening, motor activity, auditory startle and active avoidance. The pups were killed on PND 68. Some of the pups were taken from each dose group and were perfused in situ for pathological examination of the central nervous system. There were no biologically significant findings in the behavioural tests, no changes in organ weights and no pathological findings of note. Thus, there was no evidence of developmental neurotoxicity from isopropanol exposure (ECHA) [KI Score = 1].

Inhalation Studies

Pregnant female Sprague Dawley rats were exposed to 0, 3,500, 7,000 or 10,000 ppm isopropanol for 7 hours/day during gestational days 1–19. The animals showed unsteady gait and narcotisation during initial exposures in the mid- and high-dose groups; reduced food consumption and reduced weight gain were also noted in both the mid- and high-dose groups. Foetal body weights per litter were reduced in all dose groups. Exposure to 10,000 ppm also resulted in failure of implantation, fully resorbed litters, increased resorptions per litter and increased incidence of cervical ribs. The NOAEL for maternal toxicity is 3,500 ppm. The LOAEL for developmental toxicity is 3,500 ppm; a NOAEL was not established (ECHA) [KI Score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for isopropanol follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-cancer

Oral

The repeated-dose toxicity studies on isopropanol by the oral route are inadequate for the purposes of risk assessment. There is, however, a well-conducted two-generation reproductive toxicity study, in which rats were dosed by oral gavage up to 1,000 mg/kg/day (Bevan et al., 1995). Allen et al. (1998) calculated a benchmark dose level of 420 mg/kg/day (lower bound on dose associated with a 5% response rate for the decrease in the male mating index). The Point of Departure (POD) of 420 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 10
UF_D (database uncertainty) = 1
Oral RfD = 420/(10 x 10 x 1 x 10 x 1) = 420/1000 = 0.4 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (0.4 x 70 x 0.1)/2 = 1.4 mg/L

B. Cancer

Isopropanol was not carcinogenic to rats or mice in chronic inhalation studies. Therefore, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Isopropanol is a flammable liquid.

Isopropanol does not exhibit the following physico-chemical properties:

- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL EFFECTS SUMMARY

A. Summary

Isopropanol is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on isopropanol.

Table 3: Acute Aquatic Toxicity Studies on Isopropanol

Test Species	Endpoint	Results	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	9,640 mg/L	2	ECHA
Daphnia magna	24-hour EC_{50}	> 10,000 mg/L	2	ECHA

Chronic Studies

Table 4 lists the results of chronic aquatic toxicity studies on diethanolamine.

Table 4: Chronic Aquatic Toxicity Studies on Isopropanol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Daphnia magna	16-day NOEC	141 mg/L	4	ECHA
Daphnia magna	21-day NOEC	30 mg/L	4	OECD, 1977a,b
Scenedesmus quadricauda	7-day NOEC	1,800 mg/L	2	ECHA

C. Terrestrial Toxicity

An EC_{50} value of 2,100 mg/L was determined from a lettuce seed germination test (Reynold, 1977) [Kl score = 2].

D. Calculation of PNEC

The PNEC calculations for isopropanol follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for two trophic levels. Acute $E(L)C_{50}$ values are available for fish (9,640 mg/L) and invertebrates (> 10,000 mg/L). Results from chronic studies are available for invertebrates (16- and 21-day NOECs for *Daphnia* are 141 and 30 mg/L, respectively). On the basis that the data consists of acute studies from two trophic levels and a chronic study from one trophic level, an assessment factor of 100 has been applied to the lowest reported NOEC of 30 mg/L for invertebrates. The $PNEC_{water}$ is 0.3 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.2 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.87/1280) \times 1000 \times 0.3$
$= 0.2$ mg/kg

Where:

$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water}$ = 0.8 + [0.2 x Kp_{sed})1000 x BD_{solid}]
= 0.8 + [0.2 x 0.14/1000 x 2400]
= 0.87 m^3/m^3

Where:

Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
Kp_{sed} = K_{oc} x f_{oc}
= 3.478 x 0.04
= 0.14 L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for isopropanol calculated from EPI Suite™ using Log K_{ow} is 3.478.
f_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.014 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil}$ = (Kp_{soil}/BD_{soil}) x 1000 x $PNEC_{water}$
= (0.07/1500) x 1000 x 0.3
= 0.014 mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
Kp_{soil} = K_{oc} x f_{oc}
= 3.478 x 0.02
= 0.07 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for isopropanol calculated from EPI Suite™ using K_{ow} is 3.478 L/kg.
f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Isopropanol is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of 0.05 and a calculated BCF of 1, isopropanol does not meet the screening criteria for bioaccumulation.

The chronic toxicity data on isopropanol show a NOEC of > 0.1 mg/L. The acute E(L)C_{50} values for isopropanol are > 1 mg/L. Thus, isopropanol does not meet the screening criteria for toxicity.

The overall conclusion is that isopropanol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable Liquid Category 2

Eye Irritant Category 2

STOT Single Exposure Category 3 [Narcosis]

B. Labelling

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. If respiratory irritation, dizziness, nausea or unconsciousness occurs, seek immediate medical assistance. Give artificial respiration if victim is not breathing. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

If ingested, material may be aspirated into the lungs and cause chemical pneumonitis. Treat appropriately.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide. Do not use straight streams of water.

Specific Exposure Hazards

Highly flammable. Vapours are flammable and heavier than air. Vapours may travel across the ground and reach remote ignition sources causing a flashback fire danger. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. All equipment used when handling the material must be grounded. A vapour suppressing foam may be used to reduce vapours. Use clean non-

sparking tools to collect absorbed material. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Prevent exposure to ignition sources (i.e., use non-sparking tools and explosion-proof equipment). Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation. Use proper bonding and/or ground procedures. However, bonding and grounds may not eliminate the hazard from static accumulation. Peroxides may form upon prolonged storage. Exposure to light, heat or air significantly increases peroxide formation. If evaporated to a residue, the mixture of peroxides residue and material vapour may explode when exposed to heat or shock.

Storage

Keep container tightly closed. Store in a cool, well-ventilated area away from heat and light. Storage containers should be grounded and bonded. Fixed storage containers, transfer containers and associated equipment should be grounded and bonded to prevent accumulation of static charge. See SDS for suitable materials and coatings.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for isopropanol in Australia is 400 ppm as an 8-hour TWA and 500 ppm as a 15-min STEL.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN 1219 (Isopropanol)

Class 3

Packing Group II

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Allen, B; Gentry, R; Shipp, A; Van Landingham, C. (1998). Calculation of benchmark doses reproductive and developmental toxicity observed after exposure to isopropanol. Regul Toxicol Pharmacol 28: 38-44. http://dx.doi.org/10.1006/rtph.1998.1226

Bevan C., Tyler T.R., Gardiner T.H., Kapp Jr. R.W., Andrews L. and Beyer B.K. (1995). Two generation reproductive toxicity study with isopropanol in rats. J. Appl. Toxicol. 15(2):117-123.

Bridie, A.L., Wolff, C.J.M., and Winter, M. (1979). BOD and COD of some petrochemicals. Water Res. 13: 627-630.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

OECD. (1997a). IUCLID Data Set for 2-Propanol (CAS No. [redacted] UNEP Publications.

OECD. (1997b). Screening Information Dataset (SIDS) Initial Assessment Report for 2-Propanol (CAS No. [redacted] UNEP Publications.

Price, K.S., Waggy, G.T., and Conway, R.A. (1974) Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollut. Contr. Fed., 46: 63-77.

PubChem. National Institutes of Health. National Library of Medicine National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/

Reynold, T. (1977). An anomalous effect of isopropanol on lettuce germination. Plant Sci. Lett. 15: 25-28.

USEPA. (2017). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

MAGNESIUM SILICATE HYDRATE (TALC)

This dossier on magnesium silicate hydrate (talc) presents the most critical studies pertinent to the risk assessment of this substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): dioxosilane; oxomagnesium; hydrate

CAS RN: [redacted]

Molecular formula: $H_2Mg_3O_{12}Si_4$

Molecular weight: 379.27 g/mol

Synonyms: Talcum, oxosilanediol, trimagnesium; dioxido(oxo)silane; hydroxy-oxido-oxosilane, dioxosilane; oxomagnesium; hydrate

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Magnesium Silicate Hydrate (Talc)

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White solid odorless powder	2	ECHA
Melting Point	1,500°C @ 101.3 kPa	2	ECHA
Boiling Point	This substance is a solid that melts above 300°C	-	-
Density	2700 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	0 Pa at 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-9.4 @ 25°C	2	ECHA
Water Solubility	0.0001 g/L @ 25°C; insoluble in water	2	ECHA
Flash Point	ND	-	-
Auto flammability	ND	-	-
Viscosity	Not applicable as substance is a solid.	2	ECHA
Dissociation constant	ND because the substance is insoluble in water	-	ECHA

ND – not determined

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Magnesium silicate hydrate (talc) is an inorganic substance for which biodegradation is irrelevant. Moreover, it will not bioaccumulate and has a low potential to adsorb to soil.

B. Biodegradation

As an inorganic substance, magnesium silicate hydrate (talc) will not biodegrade. Soil and sediment degradation studies are not considered to be applicable as the test material is essentially insoluble in water and consists of materials which occur naturally in these compartments (ECHA).

C. Environmental Distribution

Magnesium silicate hydrate (talc) is insoluble in water. The log K_{OC} of was estimated to be 1.5027 which is equal to a K_{OC} value of 31.82 L/kg using the KOCWIN v2.00 QSAR method (ECHA). Based on this K_{oc} value, if released to soil, magnesium silicate hydrate (talc) is expected to have a low potential for adsorption. If released into water, the substance has a low potential for adsorption to sediment or suspended solids.

D. Bioaccumulation

There is no potential for bioaccumulation. Due to its inherent chemical-physical properties, such as absence of lipophilicity as well as the capability of the organism to excrete absorbed SiO_2 components, bioaccumulation can be disregarded. Magnesium is widespread in living cells and does not bioconcentrate in aquatic organisms (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Talc is a mineral composed of hydrated magnesium silicate. Talc is essentially non-toxic by the oral and dermal routes. Talc is non-irritating to the eyes and skin. There was no toxicity or carcinogenic effects in rats. Talc is not genotoxic. No developmental toxicity was reported in pregnant female rats, mice or rabbits given oral doses of talc.

B. Basic Toxicokinetics

Inhalation

To determine the deposition, distribution and clearance of talc, 44 female Syrian golden hamsters received a single 2-hour nose-only exposure to a neutron-activated talc aerosol and sub-groups of 4 animals were then killed at 11 different intervals from 15 minutes to 132 days after exposure.

The talc tested was a commercial baby powder. Nine unexposed control animals were used; four were killed on the day the test animals were exposed and five were killed on the final day of the study. The aerosol exposure system had 7 tiers of exposure ports, and the talc aerosol was passed through a cyclone elutriator to remove particles that were larger than ~10 µm in diameter; the activity median aerodynamic diameter was 6.4-6.9 µm. The mean aerosol concentration was 40 and 75 µg/L at the 15 to 30 and 60 to 90-minute sampling periods, respectively. In the presentation of the results, the γ-ray counts from the controls were expressed as µg talc equivalent, and the γ-ray counts of the exposed animals were not corrected for control values.

Variations among animals killed at the same time were attributed to variations in aerosol concentration at different tiers. The mean pulmonary talc content in the lungs of test animals at various time intervals was 33.08 µg (15 minutes after exposure), 24.08 µg (100 minutes), 42.70 µg (4 hours), 18.75 µg (21 hours), 21.30 µg (2 days), 21.03 µg (after 4 days), 13.85 µg (after 8 days) and 8.95 µg (after 18 days); the mean for the Day 0 control animals was 1.78 µg. The biological half-life

of the talc deposited in the lungs was 7 to 10 days. At the time of termination of the final group, i.e., 132 days, there was no statistically significant difference in the talc burden of the lungs of test (3.70 µg) and control (2.30 µg) animals. The amount of talc in the liver, kidneys and lungs was also determined; the only statistically significant differences compared to controls in any of these organs were found in the liver. There was a decrease at 4 hours compared to day 0 controls, an increase at Day 36 compared to both Day 0 and Day 132 controls, and an increase on Day 68 compared to Day 132 controls.

Analysis of the data using the Kruskal-Wallis test showed that there were no significant differences among the mean talc burden values for the liver, kidneys and ovaries, including the control values, and that there was no significant trend, indicating there was no translocation of talc to these tissues.

As noted, no translocation from the respiratory tract to other tissues was found in this study, and the clearance of talc from the lungs was complete within 4 months after exposure.

Oral

In one study, six female Syrian golden hamsters (outbred Ela:ENG strain) were dosed by gavage with 1 mL neutron-activated talc suspended in physiological saline containing 0.6% (w/w) 1% methyl cellulose, and the animals were killed 24 hours after dosing. The talc used was a commercial baby powder.

Four hamsters were dosed similarly with a non-irradiated talc solution. The neutron-activated talc was exposed to an integrated neutron flux of 7 x 1,016 n/cm^2 30 days prior to dosing. The skinned carcass, gastrointestinal (GI) tract, lungs, liver, kidneys and excreta were analysed for isotopes 60 Co and 46 Sc by gamma-ray spectrometry, and the gamma-ray counts were compared with those of four hamsters that were not dosed with talc.

The γ-ray counts of the tissue and excreta of the dose animals were equivalent to a total of 2.94 mg talc. Based on γ-ray counts, 74.5% of the neutron-activated talc was recovered in the faeces and 23.5% was recovered in the GI tract, while 1.91% was recovered in the skinned carcass, 0.09% in the urine, 0.04% in the kidneys and 0.02% in the liver. The amount found in the urine of the hamsters given irradiated talc was statistically significantly increased compared to the controls. No talc was recovered in the lungs (ECHA) [Kl score = 2].

In a second oral study, four LACA female mice were given a single oral dose of 40 mg/kg [3H] talc. Two mice were killed at 6 hours and two at 24 hours after dosing. In the mice killed 6 hours after dosing, 95 and 96% of the radioactivity was recovered in the large intestines and faeces, 9 and 7% was recovered in the small intestines and stomach, and 0.7 and 0% in the urine of each mouse. In the two mice killed 24 hours after dosing, 99 and 101% of the radioactivity was recovered in the large intestines and faeces, 4 and 6% was recovered in the small intestines and stomach, and 1.3 and 1.5% in the urine of each mouse. Less than 0.005% of the radioactivity was found in the carcass of any of the mice (ECHA) [Kl score = 2].

In a third oral study, three male Wistar albino rats were given a single oral dose and three rats were given six daily oral doses by gavage of 50 mg/kg body wt [3H] talc. After the last dose, urine and faeces were collected every 24 hours for 4 days and on Day 10; the rats were then killed. Within 24 hours after administration of the single dose, approximately 75% of the radioactivity was recovered in the faeces and only 1% was recovered in the urine. After 96 hours, a total of 95.8% of the dose was excreted in the faeces and 1.7% in the urine, with a total excretion of 97.5% of the dose. No radioactivity was recovered in the liver or kidneys 10 days after a single dose of talc. On Day 10 in

the rats given six daily doses of [3H] talc, there was no radioactivity found in the faeces or livers, and there was a trace of radioactivity (< 0.02%) in the kidneys of these rats (ECHA) [Kl score = 2].

C. Acute Toxicity

Oral

A single oral dose of 5,000 mg/kg of talc prepared as an 18.3% (w/v) suspension in saline was administered to 10 male rats. All animals survived, and there were no signs of toxicity. In conclusion, the median lethal dose of Talc (Mg3H2(SiO3)4) after a single oral administration to male rats, observed over a period of 14 days is: LD50 > 5,000 mg/kg body weight (ECHA) [Kl Score = 2].

Inhalation

Groups of 5 male and female Wistar rats were treated with magnesium hydroxide as aerosol during 4 hours. No mortality or other relevant adverse effects were observed. An inhalatory LC_{50} (4-hour) value for magnesium hydroxide exceeding 2.1 mg/L was determined, being the maximum feasible concentration that could be tested (ECHA) [Kl Score = 2].

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) was performed. Five males and five female Wistar rats were dermally exposed to a single talc dose of 2,000 mg/kg.

Approximately 24 hours before the test, the fur was removed from the dorsal area of the trunk using an electric clipper. Care was taken to avoid abrading the skin, and only animals with healthy intact skin were used. No less than 10% of the body surface was cleared for the application.

The test item was applied at a single dose, uniformly over an area which was approximately 10% of the total body surface. The test item was held in contact with the skin throughout a 24-hour period. At the end of the exposure period the residual test item was not removed.

Under the conditions of this study, single dermal application of the test item magnesium chloride hexahydrate to rats at a dose of 2,000 mg/kg body weight was associated with no mortality. The dermal LD_{50} was determined to be > 2,000 mg magnesium chloride hexahydrate/kg body weight (ECHA) [Kl Score = 2].

Dermal

No studies were available.

D. Irritation

Skin

An *in vitro* skin irritation test was carried out with the reconstituted three-dimensional human skin model EPISKIN-SM™ (Skinethic). This skin model consists of normal (non-cancerous), adult human-derived epidermal keratinocytes (NHEK) which have been cultured to form a multilayered, highly differentiated model of the human epidermis. The NHEK are cultured on chemically modified, collagen-coated cell culture inserts. A highly differentiated and stratified epidermis model is

obtained after a 13-day culture period and is comprised of the main basal, supra basal, spinous and granular layers and a functional stratum corneum.

The test item showed no irritant effects. The mean relative tissue viability (% negative control) was ≥ 50% (112.9%) after 15-minute treatment and 42-hour post incubation. The controls confirmed the validity of the study. The mean OD550 of the three negative control tissues was ≥ 0.6. The mean relative tissue viability (% negative control) of the positive control was ≤ 30% (22.6%). The standard deviation of replicate tissues of all dose groups was ≤ 30% (1.4% - 9.4%). It can be concluded that talc is non-irritating to skin (ECHA) [KI Score = 2].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) study was performed using magnesium chloride hexahydrate as a surrogate substance for talc. A dose of 0.1 g of the test item was applied at a single dose in the conjunctival sac of one eye of each test animal after pulling the lower lid away from the eyeball. The lids were then gently held together for about 1 second in order to prevent loss of the material. The untreated contralateral eye served as control. Observations of the eye were made at 1, 24, 48 and 72 hours and 4 to 6 days.

Under the conditions of the study, single ocular instillation of the test item magnesium chloride hexahydrate to rabbits at a dose of 0.1 g produced irritant effects, which were fully reversible. Neither mortalities nor significant clinical signs of toxicity were observed. The test item is deemed to be non-irritating to eyes (ECHA) [KI Score = 2].

E. Sensitisation

No experimental data are available on the Talc ($Mg_3H_2(SiO_3)_4$) powder and silicates; however, there is long experience in humans. Data collected from industrial hygiene surveillance over the last 50 years do not indicate any potential for skin sensitisation. Despite the widespread cosmetic use of talc and special studies in volunteers (BIBRA, 1991) there are no indications of any allergenic effect (ECHA) [KI score = 3].

F. Repeated Dose Toxicity

Oral

A study equivalent or similar to OECD Guideline 452 (Chronic Toxicity Studies) was performed using male and female Wistar rats. Wistar rats (16 male and 16 female) were exposed to talc in feed which resulted in an amount taken up of 100 mg/kg/day. After feeding had been carried out for 101 days, the animals were observed until death and subsequently examined histopathologically.

One of the animals treated with talc showed a leiomyosarcoma of the stomach. Sarcomas, which were not associated with the talc treatment, were found in the uterus of two animals. No chronic pathological effect was associated with oral administration of talc over 5 months. No adverse effects were seen on general toxicity endpoints. Under the condition of this study, for a period of 101 days for male and female rats, the NOAEL of talc in a feeding study was 100 mg/kg/day (ECHA) [KI score = 2].

Inhalation

A study equivalent or similar to OECD Guideline 452 (Chronic Toxicity Studies) was performed using male and female Wistar rats. The Wistar rats (12 male and 12 female) were exposed whole body to aerosolised talc at a mean respirable dust concentration of 10.8 mg/m^3 for 7.5 hours per day, 5 days a week for 6 or 12 months.

Ten days after the end of each exposure period, 6 rats per group were killed; 12 rats per group died and 2 rats per group were unaccounted for. The remaining 4 rats per group were killed one year after the end of the exposure period. Minimal fibrosis was observed. Talc exposure led to distinct fibrosis that was comparable with that after exposure to chrysotile in the parallel group. A lung adenoma was detected in 1 of 24 animals treated with talc. In rats exposed by inhalation to 10.8 mg/m^3 Italian talc (grade 00000; ready milled; mean particle size, 25 µm) for 3 months, minimal fibrosis was observed, the degree of which did not change during the observation period after exposure. Animals that were exposed for 1 year had minimal to slight fibrosis, the degree of which had increased to moderate within 1 year after cessation of exposure.

A no observed adverse effect concentration (NOAEC) of 10.8 mg/m^3 was determined (ECHA) [KI Score = 2].

Dermal

No adequate studies for human health risk assessment are available.

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on talc are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Talc

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Mammalian cell gene mutation (rat pleural mesothelial cells (RPMC)).	-*	ND	2	ECHA

*+, positive; -, negative
ND – not determined

Talc did not cause a statistically significant increase in sister chromatid exchanges (SCEs) and was not clastogenic. The test substance is non-mutagenic under the given experimental conditions (ECHA) [KI Score = 2].

In Vivo Studies

A study equivalent or similar to OECD Guideline 478 (Genetic Toxicology: Rodent Dominant Lethal Test) was performed per a rat dominant lethal assay on Sprague Dawley rats. Groups of 10 male rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3,000 or 5,000 mg/kg talc.

There were no dose-response or time trend patterns; talc did not induce dominant lethal mutations in this assay. Therefore, talc was not genotoxic in a rat dominant lethal assay (ECHA) [KI Score = 2].

H. Carcinogenicity

Oral

An OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) was performed. In a feeding study of 16 male and 16 female Wistar rats, talc was added to the diet; this resulted in a dosage rate of 100 mg/kg/day. After feeding had been carried out for 101 days, the animals were observed until death (approximately 614 days) and subsequently examined histopathologically. One of the animals treated with talc showed a leiomyosarcoma of the stomach. Sarcomas, which were not associated with the talc treatment, were found in the uterus of two animals.

However, no differences in tumour incidence were noted between treated animals and 8 male and 8 female control animals fed basal diet throughout (average survival, 641 days).

Inhalation

In a lifetime experiment, three groups of 50 male and 50 female Syrian golden hamsters, 4 weeks of age, were exposed (whole body) by inhalation to an aerosol of talc baby powder that was prepared from Vermont talc by flotation (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite and rutile) for 3, 30 or 150 minutes per day, 5 days a week for 30 days. The mean aerosol concentration was 37.1 mg/m^3, with a measurable respiratory fraction of 9.8 mg/m^3 and a MMAD of 4.9 µm. A placebo exposed group comprised 25 males and 25 females. Two further groups of hamsters, 7 weeks of age, were exposed to talc aerosol for 30 or 150 minutes per day for 300 days. The mean aerosol concentration was 27.4 mg/m^3, with a measurable respiratory fraction of 8.1 mg/m^3 and a MMAD of 6.0 µm. Another placebo-exposed group comprised 25 males and 25 females. The survivors of the last two talc-exposed groups were killed at the age of 20 months.

No clinical signs of toxicity to talc were observed. The type, incidence and severity of lesions indicated no trend toward a dose-response and no statistically significant differences between exposed and control groups. The incidence of focal alveolar cell hyperplasia (25% in treated groups; 10% in controls) appeared to be affected by treatment, but a two-way weighted analysis showed no significant association. Thus, exposure of hamsters to talc via inhalation did not produce carcinogenic effects (ECHA) [KI Score = 2].

I. Reproductive Toxicity

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed. Groups of 12-15 gravid Dutch-belted female rabbits were dosed orally with 9, 42, 195 or 900 mg/kg bw talc in corn oil on Days 6-18 of gestation. Eight gravid negative controls were given only vehicle and nine gravid positive controls were dosed with 2.5 mg/kg bw of 6-aminonicotinamide on Day 9 of gestation. The dams were killed on Day 29 of gestation. A total of 1/8, 4/15, 2/12, 5/15 and 2/13 dams of the negative control, 9, 42, 195 and 900 mg/kg bw dose groups, respectively, died or aborted before Day 29 of gestation, and the number of live litters for these groups was 6/7, 10/11, 8/10, 10/10 and 7/11, respectively. Details on Results (PO): Administration of up to 900 mg/kg bw talc on Days 6-18 of gestation had no discernible effect on nidation or on maternal survival.

The number of abnormalities did not differ between test and control animals.

Details on Results (F1): Administration of up to 900 mg/kg bw talc on days 6-18 of gestation had no discernible effect on nidation or on foetal survival. The number of abnormalities did not differ between test and control animals.

The NOAEL was considered to be 900 mg/kg bw/day for reproduction toxicity study. A NOAEL of > 900 mg/kg/day was determined for reproduction (ECHA) [KI Score = 2].

J. Developmental Toxicity

A GLP compliant study was performed. Groups of 20-22 gravid albino CD-1 mice and groups of 20-24 gravid Wistar rats were dosed by gavage with 0, 16, 74, 350 or 1,600 mg/kg bw talc as an anhydrous corn oil suspension on days 6-15 of gestation. The mice were killed on Day 17 and the rats on Day 20 of gestation and the number of implantation sites, resorptions sites, and live and dead foetuses, and the live pup body weights were recorded.

Maternal Toxicity: The administration of up to 1,600 mg/kg bw talc in corn oil had no effect on maternal endpoints.

Embryotoxic / Teratogenic Effects: The administration of up to 1,600 mg/kg bw talc in corn oil had no effect on developmental parameters and had no effect on foetal survival.

The NOAEL was considered to be 1,600 mg/kg bw/day for developmental toxicity (ECHA) [KI score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for talc follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

<u>Oral</u>

The NOAEL of 100 mg/kg/day from a chronic feeding study in rats was used to determine the oral RfD and drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

- UF_A (interspecies variability) = 10
- UF_H (intraspecies variability) = 10
- UF_L (LOAEL to NOAEL) = 1
- UF_{Sub} (subchronic to chronic) = 1
- UF_D (database uncertainty) = 1
- Oral RfD = 100/(10 x 10 x 1 x 1 x 1) = 100/100 = 1 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (1 x 70 x 0.1)/2 = 3.5 mg/L

B. Cancer

The carcinogenicity studies suggest talc is not a carcinogen. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Talc does not exhibit the following physico-chemical properties:

- Flammability
- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Talc is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Table 3 lists the results of the acute aquatic toxicity studies on magnesium silicate hydrate (talc).

Table 3: Acute Aquatic Toxicity Studies on Talc

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Fish (species unnamed)	96-hour LC_{50}	89,581 mg/L (QSAR)	2	ECHA
Daphnid	48-hour LC_{50}	36,812 mg/L (QSAR)	2	ECHA
Algae (species unnamed)	96-hour LC_{50}	7,203 mg/L	1	ECHA

<u>Chronic Studies</u>

No data are available. Short term aquatic toxicity tests reported in the literature on fish (LC_{50} *Brachydanio rerio* (Zebra fish) >100,000 mg/L/24 hr; for talc) show this substance is not toxic to aquatic life. On this basis the need for long term aquatic testing is waived (ECHA).

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

PNEC calculations for talc follow the methodology discussed in DEWHA (2009).

PNEC water

Acute experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (89,581 mg/L), *Daphnia* (36,812 mg/L), and algae (7,203 mg/L). By applying an assessment factor of 100 to the lowest E(L)C_{50} value of 7,202 mg/L from the acute studies, the $PNEC_{water}$ for talc is 72 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Moreover, the low K_{ow} indicates that talc is not expected to partition to sediments. Therefore, a $PNEC_{sed}$ was not calculated.

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Moreover, talc is biodegradable and due to its low K_{ow}, is not expected to partition to soil. Therefore, a $PNEC_{soil}$ was not calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Magnesium silicate hydrate (talc) is an inorganic substance and thus, biodegradation is not relevant. For the purposes of this PBT assessment, the persistent criteria are not considered applicable for this substance.

No data are available on bioaccumulation. However, based on the low log K_{ow}, and the inherent chemical-physical properties of magnesium silicate hydrate (talc), bioaccumulation is not expected. Thus, magnesium silicate hydrate (talc) does not meet the screening criteria for bioaccumulation.

Chronic aquatic toxicity data is not available. The E(L)C_{50} values from the acute aquatic toxicity studies on magnesium silicate hydrate (talc) are > 1 mg/L. Thus, magnesium silicate hydrate (talc) does not meet the criteria for toxicity.

Therefore, magnesium silicate hydrate (talc) is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H332- Harmful if inhaled.

B. Labelling

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Rinse out mouth then drink plenty of water. Get medical attention.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Magnesium oxide, silicon oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Avoid dust formation. Avoid breathing vapours, mist of gas. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

No specific environmental precautions required.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage and Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light. Store in cool place. Keep container tightly closed in a dry and well-ventilated place.

E. Exposure Controls/Personal Protection

Occupational Exposure Standards

Workplace Australia has established an occupational exposure standard for exposure to talc of an 8 hour time weighed average (TWA) exposure limit of 2.5 mg/m^3 (containing no asbestos fibres).

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to

maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, as well as before eating, smoking and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Talc is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council

BIBRA. (1991). The British Industrial Biological Research Association (BIBRA) Toxicity Profile – Talc. BIBRA, Carshalton, GB.

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

POLY(OXY-1,2-ETHANEDIYL), ALPHAHEXYL-OMEGA-HYDROXY-
(ETHYLENE GLYCOL-N-MONOHEXYL ETHER)

This dossier on poly(oxy-1,2-ethanediyl), alphahexyl-omega-hydroxy or ethylene glycol-n-monohexyl ether (EGMHE) does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies pertinent to the risk assessment of EGMHE in its use in in coal seam gas extraction activities. The majority of information presented in this dossier was obtained from the OECD-SIDS documents on a well-defined surrogate ethylene glycol monobutyl ether (EGBE) (CAS RN [redacted] and from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-hexoxyethanol

CAS RN: [redacted]

Molecular formula: $C_8H_{18}O_2$

Molecular weight: 146.23 g/mol

Synonyms: Poly(oxy-1,2-ethanediyl), alpha-hexyl-omega-hydroxy-; ethylene glycol monohexyl ether; EGHE; alpha-Hexyl,omega-hydroxypoly(oxy-1,2-ethanediyl); hexyl alcohol, ethoxylated

SMILES: CCCCCCOCCO

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of EGBE (CAS No. [redacted]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	A colourless liquid. Odour is mild, ether-like, and slightly rancid.	2	ECHA
Melting Point	-74.8°C @ 101.3 kPa	2	ECHA
Boiling Point	171 – 171.5°C @ 101.3 kPa	2	ECHA
Density	900 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	80 Pa @ 20°C	2	ECHA
Partition Coefficient (log K_{ow})	0.81 (temperature not available)	1	ECHA
Water Solubility	900 g/L @ 20°C (fully soluble)	2	ECHA
Flash Point	67°C	2	ECHA
Auto flammability	230°C	2	ECHA
Viscosity	3.642 mm^2/s (3.28 mPa.s)	2	ECHA
Henry's Law Constant	0.041 Pa.m^3/mol	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

EGBE is readily biodegradable. It is not expected to bioaccumulate. EGBE has a low tendency to bind to soil or sediment.

B. Biodegradation

EGBE was considered readily biodegradable in an OECD 301B test. Degradation was 90.4% after 28 days; the 10-day window was met (ECHA) [KI score = 2]. Results from another OECD 301B test showed 63% and 74-75% degradation after 10 and 28 days, respectively (ECHA) [KI score = 2]. An OECD 301 D test showed 67-75% degradation after 15 days and 73-77% after 28 days (ECHA) [KI score = 2]. In a Zahn-Wellen (OECD 302B test), degradation of EGBE was 95% after 8 days, measured as DOC removal (ECHA) [KI score = 2].

C. Environmental Distribution

No experimental data are available for EGBE. Using KOCWIN in EPI Suite™ (U.S. EPA, 2017), the estimated K_{oc} value from log K_{ow} is 7.624 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 2.823 L/kg.

D. Bioaccumulation

No bioconcentration studies have been conducted on EGBE. EGBE is not expected to bioaccumulate based on the experimental log K_{ow} of 0.81 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

EGBE has low-to-moderate acute toxicity by the oral route. Species vary greatly in their susceptibility to acute toxicity by the dermal route, with the rabbit being the most sensitive species showing moderate toxicity, with the rat and guinea pig showing low toxicity (in descending order). EGBE is a skin and eye irritant; it is not a skin sensitiser. The major target organ effect of EGBE from exposure (regardless of the route of exposure) is the red blood cell (RBC). Animal studies show a hemolytic anemia (haemolysis of RBCs) from acute and chronic exposure to EGBE, resulting in effects in the kidney, liver and spleen. The hemolytic effect of EGBE is caused by the acid metabolite, 2-butoxyacetic acid (BAA). A number of species, including humans and guinea pigs, are relatively insensitive to the hemolytic effects of EGBE. Lifetime rodent studies by the inhalation route showed no carcinogenic effects in rats; however, liver tumours and hemangiosarcomas of the liver were seen in male mice, and forestomach tumours were seen in female mice. These tumours are thought to occur by a non-genotoxic mode-of-action and are only likely to occur in humans, if at all, at unrealistically high exposures (primarily because of kinetic/dynamic differences between mice and humans). Animal studies show that EGBE can cause reproductive and developmental toxicity, but only exposures that also cause parental or maternal toxicity.

B. Toxicokinetics/Metabolism

The toxicokinetics and metabolism of EGBE have been extensively studied and are reviewed in the EU Risk Assessment Report (EU, 2006) and in the U.S. EPA IRIS Toxicological Review of EGBE (U.S. EPA, 2010).

The major metabolite of EGBE is 2-butoxyacetic acid (BAA). EGBE is metabolised to butoxyaldehyde (BAL) by alcohol dehydrogenases, which is then further metabolised to BAA by aldehyde dehydrogenases. The metabolism of EGBE to BAA appears to be a saturable process. The other metabolites of EGBE are (in order of magnitude): the glucuronide conjugate of EGBE (a competing pathway to BAA formation and whose percentage increases relative to dose), the sulfate-conjugate of EGBE and ethylene glycol. Elimination is rapid and occurs mainly by urinary excretion. EGBE does not accumulate in tissues, and the metabolic profile does not change after repeated exposures compared to acute exposures.

Physiologically-based pharmacokinetic (PBPK) models has been developed for EGBE (Corley et al., 1994, 1997, 2005).

C. Acute Toxicity

The oral LD_{50} values for EGBE are presented in Table 2.

Table 2: Acute Oral LD_{50} Values for EGBE

Species	Results (mg/kg)	Klimisch Score	Reference
Rat	1,746 (fasted) 1,746 (fed)	1	ECHA
Rat	880 (male) 614 (female)	2	ECHA
Rat	1,480	2	ECHA
Rat	~1,900	2	ECHA
Rat	2,420	2	ECHA
Rat	2,100 (male) 1,850 (female)	2	ECHA
Mouse	1,519 (fasted) 2,005 (fed)	1	ECHA
Guinea pig	1,414	1	ECHA
Guinea pig	1,200	2	ECHA

The acute inhalation LC_{50} values for EGBE are presented in Table 3.

Table 3: Acute Inhalation LC_{50} Values for EGBE

Species	Exposure	Results (mg/L)	Klimisch Score	Reference
Rat	4-hour LC_0	2.4 (males) 2.2 (females)	1	ECHA
Rat	1- to 3-hour LC_0	> 29	2	ECHA

Species	Exposure	Results (mg/L)	Klimisch Score	Reference
Rat	3-hour LC_0 8-hour LC_{100}	1.44 4.25	2	ECHA
Rat	7-hour LC_{50}	> 4.26	2	ECHA
Rat	4-hour LC_{50} 8-hour LC_{50}	> 3.9 ~3.9	2	ECHA
Rabbit	7-hour LC_{50}	~400 ppm	2	ECHA
Guinea pig	1-hour LC_0	> 3.4 (males) > 3.1 (females)	2	ECHA
Guinea pig	7-hour LC_0	>400 ppm	2	ECHA

The dermal LD_{50} values for EGBE are presented in Table 4.

Table 4: Acute Dermal LD_{50} Values for EGBE

Species	Results (mg/kg)	Klimisch Score	Reference
Rabbit	> 2,000	1	ECHA
Rabbit	> 2,000	1	ECHA
Rabbit	612 (abraded)	2	ECHA
Rabbit	405	2	ECHA
Rabbit	567	2	ECHA
Rat	> 2,000	1	ECHA
Rat	2,275	2	ECHA
Guinea pig	> 2,000	1	ECHA
Guinea pig	0.23 mL/kg (intact) 0.30 mg/kg (abraded)	2	ECHA
Guinea pig	7.3 mL/kg	2	ECHA

D. Irritation

Application of 0.5 mL EGBE to the skin of rabbits for 4 hours under occlusive conditions was irritating. The mean of the 24, 48 and 72-hour erythema scores was 1.7. The mean of the 24, 48 and 72-hour oedema scores were 0.13. The erythema was not fully reversible within 14 days observation period (ECHA) [KI score = 2]. Another study showed an irritating response to rabbit skin following a 24-hour exposure under occlusive conditions (ECHA) [KI score = 2].

Instillation of 0.1 mL EGBE into the eyes of rabbits was irritating. The 24, 48 and 72-hour mean scores were: 0.89 for corneal opacity; 0.56 for iridial lesions; 2.6 for conjunctival redness; and 1.8 for chemosis. All effects were reversible within the 21-day observation period (ECHA) [KI score = 1].

E. Sensitisation

EGBE was not considered to be a skin sensitiser in the guinea pig maximisation test (ECHA) [KI score = 1].

F. Repeated Dose Toxicity

Oral

Male CR, COBS, CD-BR rats were dosed by oral gavage with 0, 222, 443 or 885 mg/kg EBGE, 5 days/week for 6 weeks. Bloody urine, which persisted through the third week of treatment, was observed in all of the ≥ 443 mg/kg animals; only one 222 mg/kg rat had bloody urine, which disappeared after the week 3 of exposure. Lethargy, unkempt hair coats, piloerection, rates, slight weakness and inactivity were also seen in these animals. Body weights and feed consumption were significantly reduced in the 885 mg/kg animals. Haematological effects were seen in the 885 mg/kg animals and included decreased haemoglobin, total red blood cells (RBCs), and increased MCH in all dose groups and showing a dose-related response. MCHC was decreased and MCV was increased in the ≥ 443 mg/kg animals. Alkaline phosphatase levels were elevated in the ≥ 443 mg/kg animals; and SGPT and glucose levels were increased in the 885 mg/kg group. Absolute and relative spleen and liver weights were increased in the ≥ 443 mg/kg animals. Relative liver weights were also increased in the 222 mg/kg animals. Enlarged, dark spleens were seen in the ≥ 443 mg/kg animals at gross necropsy. Histopathological examination showed stomach hyperkeratosis/acanthosis and splenic congestion in virtually all treated animals at all dose levels. Extramedullary haematopoiesis was observed in the spleens of treated animals. Liver effects were also seen in treated animals and included hepatocytomegally (885 mg/kg only), anisokaryosis (22 and 443 mg/kg), and hemosiderin deposition (≥ 443 mg/kg). Kidney effects were also seen in the treated animals and included hyaline droplet degeneration, proteinaceous casts and hemosiderin in the proximal tubules. The latter two effects were seen in the ≥ 443 mg/kg animals and were considered compound-related; the hyalaine droplets were seen in the controls and its significance is uncertain. The LOAEL for this study was considered 222 mg/kg/day based on adverse effects on the RBC and splenic congestion (it is difficult to discern what were primary effects, and what were secondary to the hemolytic effects); a NOAEL was not established (ECHA) [KI score = 2].

Male and female F344/N rats were given in their drinking water 0, 750, 1,500, 3,000, 4,500 or 6,000 ppm EGBE for 13 weeks. Based on water consumption, the average daily intake was 0, 69, 129, 281, 367 or 452 mg/kg/day for males and 0, 82, 151, 304, 363 or 470 mg/kg/day for females. Supplemental groups were included for hematology and clinical chemistry observations at weeks 1 and 3. There was no mortality and no clinical signs of toxicity. Reduced body weight gain was seen in the ≥ 4,500 ppm animals, particularly in the females. Water consumption was also reduced in the higher dose groups, particularly for females. At each time point, there was a noticeable macrocytic and mildly hypochromic anemia. Reticulocyte counts were moderately increased in weeks 1 and 13; and erythrocyte counts were decreased at all time points in the ≥ 3,000 ppm males and the ≥ 1,500 ppm males. Thrombocytopenia was consistently observed at all time points in ≥ 4,500 ppm males and females; it also occurred in the 3,000 ppm females at week 13. Alkaline phosphatase was increased in the 6,000 ppm group on week 1 and in the ≥ 4,500 ppm groups on week 13. BUN and creatinine were increased, along with mild decreases in total protein and albumin, occurred at weeks 3 and 13; these changes were considered to be consistent with decreased feed intake. Absolute thymus weight were reduced in the ≥ 4,500 ppm groups. All other organ weight changes were considered secondary to body weight changes. Histopathological effects were seen in the liver, spleen and bone marrow of both male and female rats. The liver changes were primarily centrilobular hepatocellular degeneration and centrilobular Kupffer cell pigmentation. These changes were present in the majority of dosed rats, but they were more prevalent in the ≥ 3,000 ppm animals and were slightly more severe in

females. In addition, the cytoplasm of hepatocytes of treated rats was more eosinophilic and lacked the ampholytic-to-basophilic granularity typical of the controls. In the spleen, there was an increase in haematopoiesis and deposition of hemosiderin. In bone marrow there was an hyperplasia characterised by an increase of hematopoietic cells and decrease in marrow fat cells. All of these lesions were present in the majority of dosed rats, but they were more prominent in the ≥ 3,000 ppm animals. The LOAEL for this study is 750 ppm (69 and 82 mg/kg/day for males and females, respectively) based on the effects seen in the liver. A NOAEL was not obtained (NTP, 1993) [Kl score = 1].

Male and female B6C3F_1 mice were given in their drinking water 0, 750, 1,500, 3,000, 4,500 or 6,000 ppm EGBE for 14 weeks. Based on water consumption, the average daily intake was estimated to be 0, 118, 223, 553, 676 or 694 mg/kg/day for males and 0, 185, 370, 676, 861 or 1,306 mg/kg/day for females. There was no mortality and no significant clinical signs of toxicity. Reduction in body weight gain was seen in the ≥ 3,000 ppm males and females. Water consumption did not appear to be affected by treatment. Organ weight changes were considered secondary to body weight gain reduction. No treatment-related gross or microscopic lesions in male or female mice were observed. The NOAEL for this study is 223 and 370 mg/kg/day for males and females, respectively. However, this study did not include hematology measurements (NTP, 1993) [Kl score = 1].

Inhalation

Male and female F344 rats were exposed by inhalation to 0, 5, 25 or 77 ppm (0, 24, 121 or 372 mg/m^3) EGBE 6 hours/day, 5 days/week for 90 days. Effects were more pronounced in females than males. In females, there was a slight hemolytic anemia, which was indicated by a minimal depression of RBC counts, haemoglobin and hematocrit; with a slight increase in MCH that was noted at week 2 and at the end of the exposure period. The haematological effects were non-progressive in that there was no increase in severity over time. Reduced body weight gain was seen at week 2, but not at the end of the study. No effects were seen in the males. The NOAECs for males and females were 77 ppm and 25 ppm, respectively (Dodd et al., 1983; ECHA).

Male and female F344/N rats were exposed by inhalation to 0, 31, 62.5, 125, 250 or 500 ppm EGBE 6 hours/day for 14 weeks. Six female rats were found moribund and killed during the study: five in the 500 ppm group and one in the 250 ppm group. Clinical signs were mainly in the ≥ 125 ppm animals and included abnormal breathing, pallor, red urine stains, nasal and eye discharge, lethargy and either increased salivation or lacrimation. All 500 ppm females developed alternating blue and white bands on their tails, particularly during the first two weeks of treatment, that caused them to self-mutilate and loose the distal portion of their tails. The mean final body weights and body weight gains were significantly reduced in the 500 ppm females. There was a persistent and exposure-related macrocytic, normochromic, responsive anemia, characterised by decreased haematocrit, hemoglobin concentrations, and erythrocyte counts in the ≥ 125 ppm males and ≥ 31 ppm females. The anemia was dose-related and statistically significant; at the lower doses, the effect was small (~5% in the 31 ppm females). Increases in reticulocyte and nucleated erythrocyte counts were seen in the ≥ 125 ppm males and the ≥ 62.5 ppm females, which are indicative of a erythropoietic response. Kidney weight increased in the 500 ppm males and the ≥ 125 ppm females. Liver weights were increased in the ≥ 250 ppm males and the ≥ 125 ppm females. Thymus weights were decreased in the 500 ppm females. There were histopathological changes in the surviving rats. Bone marrow necrosis and infarcts were found in the tails of all surviving 500 ppm females. Minimal hematopoietic cell proliferation of the spleen was seen

in the ≥ 62.5 ppm females and ≥ 250 ppm males. Bone marrow hyperplasia was increased in the ≥ 62.5 ppm females and ≥ 250 ppm males. Increased pigmentation of Kupffer cells in the liver was seen in the ≥ 62.5 ppm females and ≥ 125 ppm males. Renal tubule pigmentation was noted in most of the 250 ppm males, in all of the 500 ppm males, and all of the ≥ 125 ppm females. Minimal forestomach inflammation and hyperplasia were noted in a few of the ≥ 250 ppm males. Epithelial hyperplasia of the forestomach were noted in one female each in the ≥ 250 ppm groups. The NOAEC for males is 62.5 ppm based on haematological changes. The LOAEC for females is 31 ppm based on haematological changes; a NOAEC was not established (NTP, 2000) [Kl score = 1].

Male and female B6C3F_1 mice were exposed by inhalation to 0, 31, 62.5, 125, 250 or 500 ppm 6 hours/day for 14 weeks. There was mortality in the 500 ppm exposure group: two males and two females died; two males and two females were found moribund and were killed. Clinical findings were limited to the 500 ppm males and females that died or were killed. By study termination, body weight gains were significantly reduced in the ≥ 125 ppm males. There was a persistent and exposure-related normocytic (unlike rats), normochromic, responsive anemia, characterised by decreased haematocrit, hemoglobin concentrations, and erythrocyte counts in the ≥ 125 ppm males and ≥ 31 ppm females. The anemia was dose-related and statistically significant; at the lower doses, the effect on erythrocyte count and haemoglobin was small (1.8% and 2.2% in the 31 and 62.5 ppm females). The normocytic and normochromic erythrocytes were demonstrated by the lack of change in the mean cell volumes and mean cell haemoglobin concentrations, respectively. Relative, but not absolute, liver weighs were increased in the 250 ppm males. At 500 ppm, there were increased relative liver weights (both sexes), absolute liver weights (males), and relative kidney and heart weights (females). The livers of the 500 ppm males and ≥ 250 ppm females showed hemosiderin deposition in the Kupffer cells. Hemosiderin pigmentation was also seen in the kidney tubular cells of the 500 ppm animals (both sexes). Extramedullary hematopoietic cell proliferation (primarily erythroid) was seen in the ≥ 125 ppm males and ≥ 250 ppm females. In the forestomach, increased incidence of inflammation was seen in the ≥ 250 ppm females and epithelial hyperplasia in the ≥ 125 ppm females. The NOAEC for males is 62.5 ppm based on haematological changes. The LOAEC for females is 31 ppm based haematological changes; a NOAEC was not established (NTP, 2000) [Kl score = 1].

Male and female F344/N rats were exposed by inhalation to 0, 31, 62.5 or 125 ppm (0, 151, 302 or 604 mg/m^3) EGBE vapour for 6 hours/day, 5 days/week for 104 weeks (NTP, 2000). For haematological and bone marrow analyses, additional groups of animals were exposed to 0, 62.5 or 125 ppm for evaluation at 3, 6 and 12 months; and to 31.2 ppm for 3 months (haematological examination only) and 6 months. Survival was similar across all groups, and there were no treatment-related clinical signs. Body weights of the 125 ppm females were generally lower than the controls from week 17 until study termination. There was a persistent and treatment-related macrocytic, normochromic, responsive anemia, characterised by decreased haematocrit, hemoglobin concentrations and erythrocyte counts at 3, 6 and 12 months in the 62.5 ppm females and the 125 ppm males. Some anemia also occurred at 3 and 6 months in the 31 ppm females and at 12 months in the 62.5 ppm males. In females, the anemia was characterised by a dose-related and significant fall in haematocrit, hemoglobin and erythrocyte count and an increase in MCV. The changes at 31 ppm were small (< 5%). Circulating reticulocyte and nucleated erythrocyte counts are indicative of an erythropoietic response to the anemia. There was about 15-35% decrease in the myeloid/erythroid ratio in the bone marrow of the 125 ppm rats (both sexes), particularly in the females. Significant changes in the ratio were also seen in the 125 ppm males and the 62.5 ppm females, but at only one time point. The severity of the response

was dose-related. Non-neoplastic changes occurred in the nose, liver and spleen. The incidence of hyaline degeneration of the olfactory epithelium were significantly increased in the ≥ 31 ppm males and in the ≥ 62.5 ppm females. The severity was minimal and did not change with increasing exposure concentration. The incidence of Kupffer cell pigmentation of the liver increased significantly in all exposed male and in the ≥ 31 ppm males and in the ≥ 62.5 ppm females; the severity increased in the 135 ppm of both sexes. The incidences of fibrosis in the spleen were significantly increased in the ≥ 62.5 ppm males, but not in females. The LOAEC for males is 31 ppm based on hematology and Kupffer cell pigmentation in the liver. The LOAEC for females is 31 ppm based on Kupffer cell pigmentation in the liver. A NOAEC for either sex was not established (NTP, 2000) [KI score = 2].

Male and female B6C3F_1 mice were exposed by inhalation to 0, 62.5, 125 or 250 ppm (0, 302, 604 or 1,208 mg/m^3) EGBE vapour for 6 hours/day, 5 days/week for 104 weeks (NTP, 2000). For haematological and bone marrow analyses, additional groups of animals were exposed to 0, 62.5, 125 or 250 ppm for evaluation at 3, 6 and 12 months. Survival of the ≥ 125 ppm males were significantly less than the controls. Body weights of exposed males were generally less than the controls during the last 25 weeks of the study. The 250 ppm females had body weights that were generally lower (20%) than controls from week 30 to the end of the study. The 62.5 and 125 ppm females had lower body weights from about week 60 until the end of the study. There was a persistent and exposure-related normocytic and normochromic, responsive anemia, characterised by haematocrit, hemoglobin concentrations and erythrocyte counts. In general, the anemia lacked changes in mean cell volumes and mean cell haemoglobin concentrations. There were no treatment-related clinical signs. The changes occurred at the 3-, 6- and 12-month time points in the ≥ 125 ppm males and females. Some anemia also occurred at 6 months in the 62.5 ppm females, and there was some indication of a macrocytosis (as seen by a minimal increase in cell volume) in the 250 ppm females at 12 months. Circulating reticulocyte counts were increased in the ≥ 125 ppm males and females at 3 and 6 months and the 250 ppm females at 12 months; these changes are indicative of an erythropoietic response to the anemia. The bone marrow had no change in either cell counts or myeloid/erythroid ratio. A thromobocytosis (increased platelet counts) developed in the ≥ 62.5 ppm animals at 12 months , in the 250 ppm males at 6 months, the 250 ppm females at 3 and 6 months, and in the 125 ppm females at 6 months. At 62.5 ppm, the females showed reduced haemoglobin, hematocrit, erythrocyte count and increased platelets. The 62.5 ppm males showed an increased platelet count. All these changes were statistically significant with a clear dose-response, but the magnitude was small (< 5%), except for the platelet count (15-20%). Splenic hematopoietic cell proliferation was increased in the ≥ 125 ppm males and 250 ppm females, but it was not accompanied by any change in myeloid/erythroid cell ratio. Increased incidence of hemosiderin pigmentation occurred in the ≥ 62.5 ppm males and ≥ 125 ppm females, and increased bone marrow hyperplasia occurred in the ≥ 125 ppm males. The incidence of hyaline degeneration of the nasal olfactory epithelium and respiratory epithelium was increased in the ≥ 62.5 ppm females (but not in males). The severity of the lesion was minimal and did not change with increasing exposure concentration. There was no clear dose-response. There were forestomach lesions which consisted of ulcers (particularly in females), epithelial hyperplasia that was usually focal, and, particularly in females, frequently associated with ulceration. There was also a number of inflammatory changes in the urogenital system in the male mice only; these changes were not considered to be primarily related to treatment. The LOAEC for this study is 62.5 ppm based on haematological changes and increased platelet counts (at 12 months); a NOAEC was not established (NTP, 2000) [KI score = 1].

Dermal

Male and female New Zealand rabbits were given dermal application of 0, 10, 50 or 150 mg/kg EGBE 6 hours/day for 13 weeks. The highest dose was the maximum that could be tolerated without irritation from prolonged exposure. There were no clinical, haematological effects, clinical chemistry or histopathological changes that were considered treatment-related. The NOAEL for this study is 150 mg/kg/day (ECHA) [KI score = 1].

G. Genotoxicity

In Vitro Studies

Table 5 presents the results of the *in vitro* genotoxicity studies on EGBE.

Table 5: *In Vitro* Genotoxicity Studies on EGBE

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	NTP, 1993; NTP, 2000
Mammalian cell gene mutation (CHO cells/HGPRT)	-	-	1	ECHA
Chromosomal aberration (CHO cells)	-	-	1	NTP, 1993; NTP, 2000

*+, positive; -, negative

In Vivo Studies

Male F344 rats were given a single daily intraperitoneal injection of 0, 7.03. 14.06, 28.12, 56.25, 112.5, 225 or 450 mg/kg EGBE for three consecutive days. Two of the five animals in the 450 mg/kg group died. There was no increase in micronuclei in the bone marrow polychromatic erythrocytes at any dose level (NTP, 2000) [KI score = 1].

Male B6C3F_1 mice were given a single daily intraperitoneal injection of 0, 17.19, 34.38, 68.78, 137.5, 275, 550 or 1,100 mg/kg EGBE for three consecutive days. All the animals in the 1,100 mg/kg group died. There was a statistically significant increase in the number of micronucleated polychromatic erythrocytes in the 137.5 mg/kg dose group only in a pairwise comparison with the controls. The analysis for trend was not significant and it was concluded that the test was negative (NTP, 2000) [KI score = 1].

H. Carcinogenicity

Oral Studies

No studies are available.

Inhalation Studies

Rats: Male and female F344/N rats were exposed by inhalation to 0, 31.2, 62.5 or 125 ppm (0, 151, 302 or 604 mg/m^3) EGBE vapour for 6 hours/day, 5 days/week for 104 weeks. Survival was similar across all groups. The incidence of benign or malignant

pheochromocytoma (combined) of the adrenal medulla in females exposed to 125 ppm EGBE was not significantly increased compared to the chamber controls, but it did exceed the historical control range. There was only one malignant pheochromocytoma, which occurred in the 125 ppm group. NTP concluded that there was no evidence for carcinogenicity in male rats and equivocal evidence for carcinogenicity in female rats (NTP, 2000) [KI score = 1].

Mice: Male and female B6C3F$_1$ mice were exposed by inhalation to 0, 62.5, 125 or 250 ppm (0, 302, 604 or 1,208 mg/m^3) EGBE vapour for 6 hours/day, 5 days/week for 104 weeks (NTP, 2000). Survival of the ≥ 125 ppm male mice was significantly less than that of the controls. Increased incidence of tumours was seen in the forestomach of females and liver hemangiosarcomas in males.

Forestomach: There was a positive trend in the incidences of forestomach squamous cell papilloma and squamous cell papilloma or carcinoma combined in female mice. The incidences were significantly increased in the 250 ppm group, in which the only squamous cell carcinoma occurred. These incidences exceeded the historical control range for female mice. There was no significant increase in the incidence of these neoplasms in male mice, but they did exceed the historical control range for male mice. There was one squamous cell carcinoma, but it was in the 125 ppm group.

Liver hemangiosarcomas: There was a positive trend in the incidence of hemangiosarcomas in male mice, which was statistically significant in the 250 ppm group. The incidence at 250 ppm also exceeded the historical control range for this tumour in male mice. There was also a positive trend in the incidence of hepatocellular carcinomas, which was statistically significant in the 250 ppm group. There was, however, no change in the incidence of hepatocellular adenomas and carcinomas combined, because of a reduced incidence of hepatocellular adenomas in the treated groups. The tumour incidence in female mice were not significantly different from the controls.

The NOAEC for tumourigenicity in mice is 125 ppm, based on an increased incidence of liver hemangiosarcomas in males and squamous cell papillomas or carcinomas in females at 250 ppm (NTP, 2000).

I. Mode of Action (MOA) for Mouse Tumours from EGBE Exposure

Liver Hemangiosarcomas

The hypothesised key steps of the MOA are metabolism of EGBE to BAA, hemolysis of RBCs with release of haemoglobin and hepatic hemosiderin accumulation, followed by oxidative stress, modulation of gene expression, cell proliferation, promotion, and neoplasm, leading to the formation of liver tumours (U.S. EPA, 2010). These tumours are unlikely to occur in humans because exposures would have to be much higher than those for rats. *In vitro* data suggest there is a 40- to 150-fold difference in the dose that produces hemolytic changes in the RBCs of humans as compared to rodents. This difference is supported by the Carpenter et al. (1956) study in which no changes in erythrocyte fragility were measured in humans at the highest tested concentration, 195 ppm, but increased erythrocyte fragility was measured in co-exposed rats. In addition, simulations from a PBPK model (Corley et al., 2005) predict that, given the vapour pressure of EGBE, the maximum blood level of BAA that can be obtained from inhalation exposure would be lower than the predicted concentrations from

bolus exposures that have not resulted in hemolytic effects, and lower than concentrations that have been shown to produce an effect on human RBCs *in vitro* (Udden, 2002).

Forestomach Tumours

The incidence of squamous cell papilloma and carcinoma of the forestomach was increased in female mice exposed to 250 ppm EGBE (NTP, 2000). There was also an increase in squamous cell papillomas in male mice, but the incidence was not statistically significant. Forestomach papillomas and carcinomas were not seen in either male or female rats in the 2-year NTP studies. In addition to the tumours, there was also a statistically significant, dose-dependent increase in hyperplasia in mice (both sexes), and for ulceration in female mice. The incidence of ulceration was significantly increased in the 125 ppm male mice.

The hypothesised steps are metabolism to BAA, followed by tissue irritation and subsequent cytotoxicity, compensatory proliferation and the induction of forestomach tumours. Forestomach tumours are unlikely to occur in humans because of the anatomical differences between the human stomach and the mouse forestomach; and because EGBE exposures would have to be higher, if at all possible, in humans than in mice because of the differences between mice and humans in the production and clearance of BAA.

J. Reproductive Toxicity

Male and female Swiss CD-1 mice were given in their drinking water 0 0.5, 1.0 or 2.0% EGBE (equivalent to daily intakes of 0, 720, 1,340 and 2,050 mg/kg/day) during a continuous breeding protocol with a 7-day pre-mating period and a 98-day cohabitation period. There were significant adverse reproductive effects in the females at very high dose levels (≥ 1,340 mg/kg) which also caused severe toxicity, including death. Marginal reductions (3%) in pup weight were noted at 720 mg/kg in the first generation, but not in the second generation. The NOAELs for reproductive and developmental toxicity are 720 mg/kg/day. A NOAEL or LOAEL was not determined for systemic parental toxicity because this protocol is not designed to assess systemic toxicity. However, it was noted that reduced water consumption occurred at all dose levels (Morrissey et al., 1988, 1989; Heindel et al., 1990) [KI score = 1].

Male and female F344/N rats were given in their drinking water 0, 750, 1,500, 3,000, 4,500 or 6,000 ppm EGBE for 13 weeks. Based on water consumption, the average daily intake was 0, 69, 129, 281, 367 or 452 mg/kg/day for males; and 0, 82, 151, 304, 363 or 470 mg/kg/day for females. Testis weights were unaffected by treatment, but the size of the uterus in the ≥ 4,500 ppm groups were reduced. Changes in uterine weight were considered by the authors to be secondary to the reduction in body weight gain rather than a direct effect of EGBE. Sperm concentration was slightly decreased in all treated males (not dose-related); all other sperm measurements were similar to controls. Oestrous cycle length was unaffected by treatment, although the ≥ 4500 ppm females spent more time in diestrous than the other groups. This correlated with the smaller uterine size, which was attributed to a secondary consequence of reduced body weight gain (NTP, 1993; ECHA) [KI score = 1].

K. Developmental Toxicity

Oral Studies

Pregnant female F344 rats were dosed by oral gavage with 0, 30, 100 or 200 mg/kg EGBE on GD 9-11; some animals sacrificed on GD 12 and others sacrificed on GD 20. Another group of pregnant female F344 rats were dosed by oral gavage with 0, 30, 100 or 300 mg/kg EGBE on

GD 11-13; some animals sacrificed on GD 14 and the others sacrificed on GD 20. At ≥ 100 mg/kg on GD 9-11 and GD 11-13, there was marked body weight reduction and/or weight gain, increased kidney and spleen weights, and severe hematotoxicity, in particular marked reduction in circulating red blood cells, haematocrit and hemoglobin, which occurred 24 hours post-treatment. By GD 20, the hematoxic effects were nearly reversed. These changes in organ weights and haematological parameters are indicative of hemolytic anemia and the compensatory haematological changes following cessation of exposure. Increased resorptions, non-live implants and adversely affected implants per litter in the 200 mg/kg treated dams (GD 9 – 11), and decreased foetal platelet count, but no embryolethality, in the 300 mg/kg treated dams (GD 11-13). There were no adverse effects seen on the cardiac system. Increased foetal lethality, but no increase in malformations, occurred in the 200 mg/kg dose (GD 9-11). Increased platelet count was also seen in the foetuses of the 300 mg/kg dose group (GD 11-13). The maternal NOAEL for this study is 30 mg/kg/day. The developmental NOAELs are 100 and 300 mg/kg/day when EGBE was given on GD 9–11 and GD 11-13, respectively (Sleet et al., 1991; ECHA) [Kl score = 1].

In a teratology probe study using the Chernoff-Kavlock assay, pregnant female CD-mice were dosed by oral gavage with 0, 350, 650, 1,000, 1,500 or 2,000 mg/kg EGBE during GD 8 to 14. Maternal toxicity was evident in the dams at dosed of ≥ 650 mg/kg. There were hemolytic effects (≥ 650 mg/kg) and mortality (≥ 1,500 mg/kg). At 1,000 and 1,500 mg/kg, increased resorption rates and numerically reduced number of viable foetuses were observed at 1,000 and 1,500 mg/kg. Cleft palates were seen in 4/43 foetuses (in one litter) at 1,000 mg/kg/day and 1/25 at 1,500 mg/kg. The NOAELs for maternal and developmental toxicity are 350 and 650 mg/kg/day, respectively (Wier et al., 1987; ECHA) [Kl score = 2].

In another Chernoff-Kavlock assay, CD-1 mice were dosed by oral gavage with 1,180 mg/kg/day EGBE (in corn oil) from GD 7 to 14, then allowed to litter and to rear pups to PND 3. Nineteen of the dams died (20%), maternal weight gain was reduced and there were only 24 viable litters (77%) from the surviving dams compared with 97% in the controls. There was no external malformations, pup survival to PND was unaffected and there was no other evidence of developmental toxicity (Schuler et al., 1984; ECHA) [Kl score = 2].

Inhalation Studies

Pregnant female F344 rats were dosed by oral gavage with 0, 25, 50, 100 or 200 mg/kg EGBE on GD 6-15. A dose-related increase in maternal toxicity was observed during the exposure period. There was hematuria (≥ 100 ppm); pale, cold extremities with necrosis of the tail tip (200 ppm); weight loss (≥ 100 ppm), reduction in food consumption (≥ 100 ppm) and water consumption (200 ppm). Absolute and relative organ weight reductions were also noted. Evidence of hemolytic anemia was found in the ≥ 100 ppm dams when blood samples were taken on GD 21. At 200 ppm, there was embryotoxicity (increased resorptions and decreased viable implants per litter) and fetotoxicity (retardations in skeletal ossification). There was no evidence of teratogenicity. The NOAECs for maternal and developmental toxicity are 50 and 100 ppm, respectively (Tyl et al., 1984; ECHA) [Kl score = 2].

Pregnant female New Zealand White rabbits were exposed by inhalation to 0, 25, 50, 100 or 200 ppm EGBE 6 hours/day during GD 6-18. At 200 ppm, four does died or were sacrificed by the third day after the onset of dosing, and four does aborted. All were pregnant. Pregnancy rates were similar across all groups. Body weight loss occurred in all groups including controls during exposure, but the highest difference was in the 200 ppm exposure group; by GD 15, body weights were significantly lower in the 200 ppm group. The high-dose group

had a significant reduction in maternal body weight (8%), gravid uterine weight (22%), and the number of total implants and viable implants. No other developmental effects (including teratogenicity) were noted. The NOAELs for maternal and developmental toxicity are 50 and 100 ppm, respectively (Tyl et al., 1984; ECHA) [Kl score = 2].

Pregnant female SD rats were exposed by inhalation to 0, 150 or 200 ppm EGBE 7 hours/day during GD 7-15. The only maternal effect noted was hematuria in the ≥ 150 ppm dams. There was no developmental toxicity. The NOAEC for developmental toxicity is 200 ppm. A conservative LOAEC for maternal toxicity is 150 ppm, with a NOAEC not established (Nelson et al., 1984) [Kl score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for EGBE follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

An oral RfD was derived by U.S. EPA (2010) based on the findings of the NTP chronic inhalation studies, the rationale being the limited oral database and because the critical endpoint, hemosiderin pigmentation, was more pronounced in the chronic inhalation study (NTP, 2000) versus the available subchronic oral study (NTP, 1993).

U.S. EPA used a route-to-route extrapolation from the NTP (2000) study for the derivation for the RfD. The dose metric used for animal-to-human and route-to-route (inhalation-to-oral) extrapolation for the derivation of the RfD is the area under the curve (AUC) of BAA at 12 months in arterial blood. This dose metric was used for dose-response modelling of chronic inhalation data to derive the point of departure (POD) of 133 µmol-hour/L, expressed as a BMDL based on animal data. The corresponding human BMDL was then back-calculated using the human PBPK model (Corley et al., 1994; Corley et al., 1997) to obtain an equivalent human oral drinking water dose ($BMDL_{HED}$) of 1.4 mg/kg/day. A simplifying assumption was used that the entire dose of drinking water EGBE was consumed over a 12-hour period each day.

Oral Reference Dose (oral RfD)

Oral RfD = $BMDL_{HED}$ / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

- UF_A (interspecies variability) = 1
- UF_H (intraspecies variability) = 10
- UF_L (LOAEL to NOAEL) = 1
- UF_{Sub} (subchronic to chronic) = 1
- UF_D (database uncertainty) = 1
- Oral RfD = 1.4/(1 x 10 x 1 x 1 x 1) = 1.4/10 = 0.14 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (0.14 x 70 x 0.1)/2 = 0.5 mg/L

B. Cancer

Male mice developed hepatocellular carcinomas and hemangiosarcomas that appear to be exposure-related. The incidence of hemangiosarcomas was statistically significant and increased over both concurrent and historical control groups. The hepatocellular carcinomas were within the range of historical controls for male mice but are considered because the dose-response trend is significant and because a similar MOA has been suggested for this tumour. The incidences in the high dose group of these two tumour types were only slightly higher than the upper end of the range for historical controls. These two tumour types were not seen in mice.

The incidence of squamous cell papilloma and carcinoma of the forestomach was increased in female mice exposed to 250 ppm EGBE (NTP, 2000). There was also an increase in squamous cell papillomas in male mice, but the incidence was not statistically significant. Forestomach papillomas and carcinomas were not seen in either male or female rats in the 2-year NTP studies. In addition to the tumours, there was also a statistically significant, dose-dependent increase in hyperplasia in mice (both sexes), and for ulceration in female mice. The incidence of ulceration was significantly increased in the 125 ppm male mice.

The MOAs for these tumours reflect the non-genotoxic nature of EGBE and its metabolites. Both of these MOAs suggests that the MOAs have only limited quantitative significance to humans, principally due to kinetic/dynamic differences from the rodents (U.S. EPA, 2010; ECHA). Because of the MOA, a non-linear approach is used for the dose-response assessment, using the RfD that was derived for the non-cancer assessment. Doses of EGBE below the RfD would not be expected to produce hemolytic effects (i.e., hemosiderin deposition) and therefore is not expected to produce any increase in cancer risk.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

EGBE does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

EGBE is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 6 lists the results of acute aquatic toxicity studies conducted on EGBE.

Table 6: Acute Aquatic Toxicity Studies on EGBE

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-hour LC_{50}	1,464	2	ECHA
Pimephales promelas	96-hour LC_{50}	2,137	2	ECHA
Pimephales promelas	96-hour LC_{50}	1,700	2	ECHA
Pimephales promelas	96-hour LC_{50}	1,580	2	ECHA
Lepomis machrochirus	96-hour LC_{50}	1,490	2	ECHA
Daphnia magna	48-hour EC_{50}	1,800	2	ECHA
Daphnia magna	48-hour EC_{50}	1,815	2	ECHA
Daphnia magna	48-hour EC_{50}	881 (cited) 1,100 (recalculated)	2	ECHA
Daphnia magna	48-hour EC_{50}	2,650	2	ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50} NOEC	911 (biomass) 88	1	ECHA
Selenastrum capricornutum	72-hour EC_{50} NOEC	720 (biomass) 280	2	ECHA

Chronic Studies

A 21-day fish (*Brachydanio rerio*) study was conducted to examine the potential for endocrine disrupting effects; the study design was based on the OECD TG 204. The NOEC was > 100 mg/L (ECHA) [KI score = 2].

The NOEC from a 21-day *Daphnia* reproduction study was 100 mg/L (ECHA) [KI score = 1].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for EGBE follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (1,000 mg/L), *Daphnia* (1,100 mg/L) and algae (911 mg/L). Results from chronic studies are also available for all three trophic levels, with the lowest NOEC being 88 mg/L for algae. On the basis that the data consists of short-term and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC of 88 mg/L for algae. The $PNEC_{water}$ is 8.8 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 6.5 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.94/1280) \times 1000 \times 8.8$
$= 6.46$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 0.30/1000 \times 2400]$
$= 0.94\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 7.624 \times 0.04$
$= 0.30$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for EGBE calculated from EPI Suite™ is 7.624 L/kg.
f_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.9 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.15/1500) \times 1000 \times 8.8$
$= 0.88$ mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
= 7.624 x 0.02
= 0.15 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for EGBE calculated from EPI Suite™ is 7.624 L/kg.
f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Based on information for read-across substance EGBE, EGMHE is readily biodegradable; thus it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of 0.81 for read-across substance EGBE, EGMHE does not meet the screening criteria for bioaccumulation.

The chronic toxicity data on read-across substance EGBE show NOECs of > 0.1 mg/L. Thus, EGMHE does not meet the screening criteria for toxicity.

The overall conclusion is that EGMHE is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity Category 4 [Oral]

Acute Toxicity Category 4 [Dermal]

Acute Toxicity Category 4 [Inhalation]

Skin Irritant Category 2

Eye Irritant Category 1

B. Labelling

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

Due to structural analogy and clinical data, this material may have a mechanism of intoxication similar to ethylene glycol.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam (alcohol-resistant is preferred), dry chemical or carbon dioxide.

Specific Exposure Hazards

Container may rupture from gas generation in a fire. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light. Store in the following materials: carbon steel, stainless steel, phenolic lined steel drums. Do not store in: aluminium, copper, galvanised iron, galvanised steel.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace exposure standards have not been established for EGMHE in Australia. The workplace exposure standard for EGBE in Australia is 20 ppm (96.9 mg/m^3) as an 8-hour TWA and a 15-min STEL of 50 ppm (242 mg/m^3) with a skin [absorption] notation.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

EGMHE is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Carpenter, C.P., Pozzani, U.C., Weil, C.S., Nair, J.H., III, Jeck, G.A., and Smyth, H.F., Jr. (1956). The toxicity of butyl cellusolve solvent. AMA Arch. Ind. Health 14: 114-131.

Corley, R.A., Bormett, G.A., and Ghanayem, B.I. (1994). Physiologically-based pharmacokinetics of 2-butoxyethanol and its major metabolite 2-butoxyacetic acid, in rats and humans. Toxicol. Appl. Pharmacol. 129: 61-79.

Corley, R.A., Markham, D.A., Banks, C., Delorme, P., Masterman, A., and Houle, J.M. (1997). Physiologically based pharmacokinetics and the dermal absorption of 2-butoxyethanol vapor by humans. Fundam. Appl. Toxicol. 39: 120-130.

Corley, R.A., Bartels, M.J., Carney, E.W., Weitz, K.K., Soelberg, J.J., Gies, R.A., and Thrall, K.D. (2005). Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. Toxicol. Sci. 85: 476-490.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Dodd, D.E., Snellings, W.M., Maranpot, R.R., and Ballantyne, B. (1983). Ethylene glycol monobutyl ether. Acute, 9 day and 90 day vapor inhalation studies in Fischer 344 rats. Toxicol. Appl. Pharmacol. 68: 405-414.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances.

EU. (2006). European Union Risk Assessment Report on 2-Butoxyethanol (CAS No. [redacted]). European Chemicals Bureau. Available at: https://echa.europa.eu/documents/10162/e74a38e1-b9e1-4568-92c5-615c4b56f92d.

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Heindel J.J., Gulati D.K., Russel V.S., Reel J.R., Lawton A.D. and Lamb J.C. (1990). Assessment of Ethylene Glycol Monobutyl and monophenol Ether reproductive toxicity using a continuous breeding protocol in Swiss CD-1 mice. Fundam. Appl. Toxicol. 15: 683-696.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Morrissey R.E., Lamb J.C., Schwetz B.A., Teague J.L. and Morris R.W. (1988). Association of sperm, vaginal cytology and reproductive organ weight data with results of continuous breeding reproduction studies in Swiss CD1 Mice. Fundam. Appl. Toxicol. 11: 359-371.

Morrissey R.E., Lamb J.C., Morris R.W., Chapin R.E., Gulati D.K. and Heindel J.J. (1989). Results and evaluations of 48 continuous breeding reproduction studies conducted in mice. Fundam. Appl. Toxicol. 13: 747-777.

National Toxicology Program [NTP]. (1993). Toxicity studies on ethylene glycol ethers administered in drinking water. NIH Publication 93- 3349. NTP Toxicity Report Series No. 26. NTP, Research Triangle Park, NC, USA.

National Toxicology Program [NTP]. (2000). Toxicology and Carcinogenesis Studies of 2-Butoxyethanol (CAS No. [redacted] in F344/N rats and B6C3F1 mice (Inhalation studies). NTP Technical Report Series No.484. NIH Publication No. 00-3974.

Nelson, B.K., Setzer, J.V., Brightwell, W.S., Mathinos, PR., Kuczuk, M.H., Weaver, T.E., and Goad, P.T. (1984). Comparative inhalation teratogenicity of four glycol ether solvents and an amino acid derivative in rats. Environ. Health Perspect. 57: 261-271.

Schuler R.L., Hardin B.D., Niemeier R.W., Booth G., Hazelden K., Piccirillo V. and Smith K. (1984). Results of testing 15 glycol ethers in a short term *in vivo* reprotoxicity assay. Environ. Health Perspect. 57: 141-146.

Sleet R.B., Price C.J., Marr M.C., Morrissey R.M. and Schwetz B.A. (1991). Cardiovascular development (CVD) in F-344 rats following phase-specific exposure to butoxy ethanol. Teratol. 43: 466.

Tyl, R.W., Millicovsky, G., Dodd, D.E., Pritts, I., France, K.A., and Fisher, L.C. (1984). Teratogenic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and new Zealand white rabbits following inhalation exposure. Environ. Health Perspect. 57: 47-68.

Udden, M.M. (2002). Rat erythrocyte morphological changes after gavage dosing with 2-butoxyethanol: a comparison with the in vitro effects of butoxyacetic acid on rat and human erythrocytes. J. Appl. Toxicol. 20: 381-387.

U.S. Environmental Protection Agency [EPA]. (2010). Toxicological Review of Ethylene Glycol Monobutyl Ether (EGBE) (CAS No. [redacted] in Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/006F. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0500tr.pdf

U.S. Environmental Protection Agency [EPA]. (2017). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Wier P.J., Lewis S.C., and Traul K.A. (1987). A comparison of developmental toxicity evident at term to postnatal growth and survival using ethylene glycol monoethyl ether, ethylene glycol monobutyl ether and ethanol. Teratog. Carcinog. Mutagen. 7: 55-64.

VINYLIDENE CHLORIDE/METHYLACRYLATE COPOLYMER

This dossier on vinylidene chloride/methylacrylate copolymer presents the most critical studies pertinent to the risk assessment of vinylidene chloride/methylacrylate copolymer in its use in coal seam gas extraction activities. It does not represent an exhaustive or critical review of all available data. Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. CHEMICAL NAME AND IDENTIFICATION

Chemical Name (IUPAC): 1,1-dichloroethene; methyl prop-2-enoate

CAS RN: [redacted]

Molecular formula: $(C_2H_2Cl_2)_x(C_4H_6O_2)_y$ [This substance is a polymer.]

Molecular weight: 183.03 g/mol (monomer); polymer assumed to be > 1,000 g/mol (NICNAS, 2017)

Synonyms: vinylidene chloride/methylacrylate copolymer; methyl acrylate-vinylidene chloride copolymer; 2-propenoic acid, methyl ester, polymer with 1,1-dichloroethene

SMILES: COC(=O)C=C.C=C(Cl)Cl

II. PHYSICO AND CHEMICAL PROPERTIES

No chemical-specific information is available. Vinylidene chloride/methylacrylate copolymer is a non-ionic synthetic polymer. It is formed by addition polymerisation, which typically affords high molecular weight polymers with stable saturated carbon-chain backbones. Water solubility is expected to be low based on the predominantly hydrophobic structure of the substance.

As noted, no information is available regarding the molecular weight and the percentage of low molecular weight (LMW) species in this polymer. However, synthetic addition polymers of this type are generally high to very high molecular weight species. It is assumed for this polymer that the number average molecular weight (NAMW) is greater than 1,000 daltons (Da) with an insignificant percentage of LMW species (DoEE, 2017).

III. ENVIRONMENTAL FATE PROPERTIES

No experimental data are available for vinylidene chloride/methylacrylate copolymer.

Polymers with a molecular weight greater than 1,000 g/mol generally have a negligible vapour pressure, which indicates that the chemical is likely to exist solely as particulate matter in the atmosphere. As particulate matter, atmospheric oxidation is not expected to be a significant route of environmental removal. Likewise, volatilisation from water or moist soil is not expected to occur at an appreciable rate (USEPA, 2013).

Non-ionic polymers such as vinylidene chloride/methylacrylate copolymer are not expected to be highly soluble in water based on its predominantly hydrophobic structure. If

discharged to the aquatic environment, this polymer is expected to partition to soil or sediment. It is not expected to be highly mobile if released to the soil compartment (Boethling and Nabholz, 1997).

Synthetic non-ionic polymers are not expected to undergo rapid degradation (NICNAS, 2017). However, the high molecular weight of the polymer is expected to preclude or minimise bioaccumulation. Polymers with a number average molecular weight (NAMW) greater than 1,000 g/mol cannot cross biological membranes (Boethling and Nabholz, 1997).

IV. HUMAN HEALTH HAZARD ASSESSMENT

These polymers are considered chemically and biologically inert. As such, no toxicity studies have been conducted on this material.

NICNAS has assessed vinylidene chloride/methylacrylate copolymer in an IMAP Tier 1 assessment and considers it a polymer of low concern[1]. In addition, based on an assessment of human health and environmental hazards, NICNAS also identified vinylidene chloride/methylacrylate copolymer as a chemical of low concern to the environment (NICNAS, 2017 and DoEE, 2017). Chemicals of low concern are unlikely to have adverse environmental effects or be a concern to human health if they are released to the environment from coal seam gas operations.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

No toxicological reference values or drinking water guidance values were developed.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Vinylidene chloride/methylacrylate copolymer does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Aquatic Toxicity

No ecotoxicity data was identified for vinylidene chloride/methylacrylate copolymer. Information on Non-Ionic Polymers Group (DoEE, 2017) is provided below.

> *"Non-ionic polymers with low water solubility, such as the methyl acrylate-vinylidene chloride copolymer, generally have low toxicity to aquatic life (Beothling and Nabholz 1997). Insoluble non-ionic polymers have low bioavailability and their adverse effects result from physical. effects such as*

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

occlusion of respiratory organs (e.g. the gills of fish). These adverse effects occur only at very high loading levels in water (Beothling and Nabholz 1997).

Water soluble or dispersible non-ionic polymers, such as polyacrylamide, are also typically of low concern for ecotoxicity. Non-ionic polymers with NAMW greater than 1 000 cannot be absorbed across biological membranes in aquatic organisms, and therefore toxicity only occurs through indirect effects such as chelation of essential nutrients (Beothling and Nabholz 1997). However, the structure of polyacrylamide suggests that it will have low potential to act by this mode of action. This is further supported by median effective concentration (EC50) and median lethal concentration (LC50) values available for other water soluble or dispersible non-ionic polymers, which are greater than 100 mg/L (Beothling and Nabholz 1997).

Water soluble or dispersible polymers with NAMW less than 1 000 Da, or significant levels of LMW substances and trapped monomers, are of potential concern because of their increased bioavailability. However, this assessment was conducted assuming that the polymers in this group have NAMW greater than 1 000 Da and the percentage of LMW species is low."

B. Terrestrial Toxicity

No data are available.

C. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Vinylidene chloride/methylacrylate copolymer is not expected to be biodegradable. Thus, it meets the criteria for persistence.

Vinylidene chloride/methylacrylate copolymer is not expected to bioaccumulate. Polymers with a NAMW greater than 1,000 g/mol cannot cross biological membranes (Boethling and Nabholz, 1997). Thus, it does not meet the screening criteria for bioaccumulation.

No aquatic toxicity studies are available for vinylidene chloride/methylacrylate copolymer. It is expected to be a low concern of toxicity to aquatic organisms because of its low potential for bioavailability. Thus, it does not meet the screening criteria for toxicity.

The overall conclusion is that vinylidene chloride/methylacrylate copolymer is not a PBT substance.

IX. CLASSIFICATION AND LABELING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictograms

None

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 5 minutes. If symptoms persist, seek medical advice.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

B. Fire Fighting Information

Extinguishing Media

Water fog, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Burning produces harmful and toxic fumes. Heat from fire may melt, decompose polymer and generate flammable vapours. Combustion products may include: carbon oxides, hydrogen chlorine gas.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Potential combustible dust hazard. Avoid generating dust. Creates dangerous slipping hazard on any hard smooth surface.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove.

D. Storage and Handling

General Handling

Avoid dust accumulation in enclosed space. Avoid generating dust; fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard. Electrostatic charge may build up during handling. Equipment, container and metal containers should be grounded and bonded.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place. Use adequate ventilation to avoid excessive dust accumulation. Store away from excessive heat and away from strong oxidising agents. Take measures to prevent the build-up of electrostatic charge.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure limit for vinylidene chloride/methylacrylate copolymer.

Engineering Controls

Use in a well-ventilated area. Avoid creating dust. Take precautionary measures against static charge.

Personal Protection Equipment

Respiratory Protection: Not normally needed; however, if significant exposures are possible, then the following respirator is recommended: Dust/mist respirator.

Hand Protection: Normal work gloves.

Skin Protection: Normal work coveralls.

Eye Protection: Wear safety glasses or goggles to protect against exposure.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Vinylidene chloride/methylacrylate copolymer is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

Boethling, R.S. and Nabholz, J.V. (1997). 'Environmental assessment of polymers under the US Toxic Substances Control Act', in Hamilton J and Sutcliffe R (eds), Ecological assessment of polymers: strategies for product stewardship and regulatory programs, Van Nostrand Reinhold, New York, USA, pp 187-234.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Environmental risks associated with surface handling of chemicals used in coal seam gas extraction in Australia, Project report Appendices A, B, C, D, F, and G prepared by the Chemicals and Biotechnology Assessments Section (CBAS) in the Department of the Environment and Energy as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

NICNAS (2017), Chemicals of low concern for human health based on an initial assessment of hazards, Project report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

United States Environmental Protection Agency (USEPA). (2013). Interpretive Assistance Document for Assessment of Polymers: Sustainable Futures Summary Assessment. June 2013.

SORBITAN, MONO-9-OCTADECENOATE, (Z)

This dossier on sorbitan, mono-9-octadecenoate, (Z) presents the most critical studies pertinent to the risk assessment of sorbitan, mono-9-octadecenoate, (Z) in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): [(2*R*)-2-[(2*R*,3*R*,4*S*)-3,4-dihydroxyoxolan-2-yl]-2-hydroxyethyl] (*Z*)-octadec-9-enoate

CAS RN: [redacted]

Molecular formula: $C_{24}H_{44}O_6$

Molecular weight: 428 g/mol

Synonyms: Sorbitan monooleate; sorbitan, mono-9-octadecenoate, (Z)

SMILES: CCCCCCCCC=CCCCCCCCC(=O)OCC(C1C(C(CO1)O)O)O

II. PHYSICO-CHEMICAL PROPERTIES

Key physical and chemical properties for sorbitan, mono-9-octadecenoate, (Z) are shown in Table 1.

Table 1: Overview of the physico-chemical properties of sorbitan mono-9-octadecenate, (Z)

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Yellow to amber liquid		HPVIS
Melting Point	223°C (estimated, pressure not provided)		HPVIS
Boiling Point	535°C (estimated, pressure not provided)		HPVIS
Density	1000 kg/m^3 @ 25°C		HPVIS
Vapour Pressure	Negligible		HPVIS
Partition Coefficient (log K_{ow})	5.89 (estimated), temperature not provided		HPVIS
Water Solubility	0.0191 (estimated) (insoluble) @ 25°C		NCBI, 2024
Flash Point	Not Available		-
Auto flammability	Not Available		-
Viscosity	100 m Pa/s		NCBI, 2024
Henry's Law Constant	Not available	-	--

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Environmental fate data of the substance or reasonable surrogates suggests that it will degrade in the environment, not persist, and due to expected metabolism is not likely to bioaccumulate.

The data supporting these conclusions are discussed below.

B. Biodegradation

Sorbitan, mono-9-octadecenoate, (Z) is readily biodegradable. In an OECD 301 C test, degradation was 58% after 14 days and 62% after 28 days (HPVIS). In a read-across, sorbitan stearate (CAS RN [redacted] is readily biodegradable. In an OECD 301 C test, degradation was 88% after 28 days (ECHA) [Kl.score=1].

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

No experimental data are available for sorbitan, mono-9-octadecenoate, (Z). Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated Koc value from log Kow is 1,599 L/kg. The estimated Koc value from the molecular connectivity index (MCI) is 2,423 L/kg. Based on these estimated K_{oc} values, the substance is likely to adsorb to soil or sediments, and unlike other more immobile Sorbitan Esters in this category, will have slight mobility.

D. Bioaccumulation

There are no bioaccumulation studies on sorbitan, mono-9-octadecenoate, (Z). Sorbitan, mono-9-octadecenoate, (Z) has an estimated log Kow of 5.89 (EPA, 2019). However, sorbitan, mono-9-octadecenoate, (Z) is expected to be metabolized and excreted. The metabolic pathway involves enzymatic hydrolysis by esterases to D-glucitol and the respective fatty acid. The fatty acids are metabolized by the beta-oxidation pathway and D-glucitol will undergo metabolism by the fructose metabolic pathway in the liver (ECHA). Using the Arnot-Gobas method involving biotransformation in the QSAR model BCFBAF v3.01, the BCF values ranged from 36 to 92 L/kg, indicating a low potential for bioaccumulation (USEPA, 2019).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Based on read-across to similar sorbitan esters, sorbitan, mono-9-octadecenoate, (Z)is a lipophilic substance with low volatility and low dermal absorption. This substance is expired as CO_2 after metabolic degradation and depending on the cleavage products, biliary excretion with the faeces (fatty acids) and via urine (D-glucitol) is likely. It has low acute oral, inhalation and dermal toxicity. Sorbitan, mono-9-octadecenoate, (Z)is not expected to be irritating to the eyes, or the skin and it is not a skin sensitiser. It has low oral repeated dose toxicity, and it was not reported as genotoxic in any in vitro assay. It is not carcinogenic nor is it a reproductive or developmental toxicant.

B. Toxicokinetics/Metabolism

Metabolism of the sorbitan esters in animals has been reported to occur initially via enzymatic hydrolysis, leading to sorbitan and the corresponding natural fatty acids. Oral gavage studies in rats with radiolabeled sorbitan monostearate (CAS RN [redacted] which is structurally similar to sorbitan, mono-9-octadecenoate, (Z), have demonstrated that about 90% of the sorbitan monostearate dose was absorbed and hydrolyzed to stearic acid and sorbitan (Elder, 1985; Wick, 1953). The resulting sorbitan and fatty acid metabolites, in turn would be expected to be metabolized further (via fatty acid beta-oxidation or carbohydrate metabolic pathways) to either smaller and more polar water-soluble metabolites, which can be excreted in the urine or as carbon dioxide exhaled in the lungs.

As the molecular weight of sorbitan stearate (CAS RN [redacted] ranges between 402.57 and 981.56 g/mol, an absorption of the molecule in the gastrointestinal tract is in general improbable. Sorbitan stearate has a low vapour pressure of < 0.0001 Pa at 25 °C, thus, being of low volatility. Therefore, under normal use and handling conditions, inhalation exposure and thus availability for respiratory absorption of the substance in the form of vapours, gases, or mists is not expected to be significant. However, the substance may be available for respiratory absorption in the lung after inhalation of aerosols, if the substance is melted and sprayed. In humans, particles with aerodynamic diameters below 100 µm have the potential to be inhaled. Particles with aerodynamic diameters below 50 µm may reach the thoracic region and those below 15 µm the alveolar region of the respiratory tract (ECHA, 2008). Lipophilic compounds with a log Pow > 4 that are poorly soluble in water (1 mg/L or less) like sorbitan stearate can be taken up by micellar solubilisation. Overall, a systemic bioavailability of Sorbitan stearate in humans is considered likely after inhalation of aerosols with aerodynamic diameters below 15 µm. Dermal absorption of sorbitan stearate was predicted to be very low with an estimated dermal permeability coefficient (Kp) of 0.068 cm/h and a dermal absorption rate of 0.000037 mg/cm²/h (=0.00000918 mg/cm²/event) (ECHA) [KI.score=2]. The high log P_{ow} of > 5 implies that Sorbitan stearate may have the potential to accumulate in adipose tissue (ECHA). Sorbitan fatty acid esters will undergo esterase-catalysed hydrolysis, leading to the cleavage products D-glucitol and fatty acids. The log Pow of the first cleavage product D-glucitol is -2.2, indicating a high solubility in water. Consequently, there is no potential for D-glucitol to accumulate in adipose tissue. The second cleavage product, the fatty acids, can be stored as triglycerides in adipose tissue depots or be incorporated into cell membranes. At the same time, fatty acids are also required as a source of energy. Thus, stored fatty acids underlie a continuous turnover as they are permanently metabolized and excreted. Bioaccumulation of fatty acids only takes place, if their intake exceeds the caloric requirements of the organism. Due to the high molecular weight and the insolubility in water, excretion of Sorbitan stearate via urine is unlikely after oral administration. After oral ingestion, sorbitan fatty acid esters will undergo stepwise chemical changes in the gastro-intestinal fluids as a result of enzymatic hydrolysis. As the physico-chemical characteristics of the cleavage products (e.g. physical form, water solubility, molecular weight, log Pow vapour pressure, etc.) will be different from those of the parent substance the predictions based upon the physico-chemical characteristics of the parent substance do no longer apply (ECHA) However, also for both cleavage products, it is anticipated that they will be absorbed in the gastro-intestinal tract. Overall, the available information indicates that sorbitan stearate is expired as CO_2 after metabolic degradation. Moreover, depending on the cleavage products, biliary excretion with the faeces (fatty acids) and via urine (D-glucitol) is likely (ECHA).

C. Acute Toxicity

No studies are available on sorbitan, mono-9-octadecenoate, (Z).

Oral

The oral LD_{50} in rats for sorbitan monopalmitate is >15,900 mg/kg (ECHA) [Kl.score=2].

An OECD Guideline 401 (Acute Oral Toxicity) study was conducted using male and female Wistar rats exposed to 2000 mg/kg bw/day sorbitan stearate (CAS RN [redacted] via oral gavage. No mortality occurred during the study period. The LD_{50} was reported as >2,000 mg/kg bw/day (ECHA) [Kl.score=2].

Inhalation

The 4-hour inhalation LC_{50} value for sorbitan monolaurate (CAS RN [redacted] was reported as >5000 mg/m^3 based on a study conducted using male and female Wistar rats exposed to sorbitan monolaurate via a nose only aerosol for four hours. No mortality was reported in this study. (ECHA) [Kl.score=2].

Dermal

No acute dermal toxicity studies are available.

D. Irritation

Skin

Application of 0.5 g sorbitan palmitate (CAS RN [redacted] to the skin of New Zealand white rabbits for 24 hours under occlusive conditions was not irritating (ECHA) [Kl.score=2].

Eye

An OECD guideline 405 (Acute Eye irritation/Corrosion) study was conducted using an unspecified strain for rabbits exposed to 0.1 grams of sorbitan stearate (CAS RN [redacted] for 7 days. Sorbitan stearate was reported as non irritating in under the conditions of this study (ECHA) [Kl.score =2].

E. Sensitisation

No studies are available for sorbitan, mono-9-octadecenoate, (Z)

F. Repeated Dose Toxicity

Oral

Sorbitan stearate was tested in a combined repeated dose toxicity study with a reproductive/developmental screening (OECD 422) test. Male and female SD rats were dosed by oral gavage with 0, 40, 200, or 1,000 mg/kg sorbitan stearate (CAS RN [redacted] There were no systemic effects that were considered to be treatment-related. The NOAEL for systemic toxicity is 1,000 mg/kg-day, the highest dose tested (ECHA) [Kl.score=2].

Inhalation

No studies are available.

Dermal

No reliable studies are available.

G. Genotoxicity

In Vitro Studies

There are no *in vitro* genotoxicity studies on sorbitan mono-9-octadecenate, (Z). Table 2 shows the results of *in vitro* genotoxicity studies on read-across substances sorbitan stearate (CAS RN [redacted] and sorbitan laurate (CAS RN [redacted]

Table 2: *In vitro* genotoxicity studies on sorbitan stearate and sorbitan laurate

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)**	-	-	2	ECHA
Chromosomal aberration (human lymphocytes)**	-	-	2	ECHA

*+, positive; -, negative

In Vivo Studies

No studies are available.

H. Carcinogenicity

No studies are available on sorbitan mono-9-octadecenoate, (Z). Furthermore, there is no evidence that sorbitan fatty acid esters induce gene mutations in bacteria or chromosome aberrations in mammalian cells, as the results of all genotoxicity studies were consistently negative. Furthermore, in the available repeated dose toxicity studies and developmental studies, no substance-related increases in the incidence of hyperplasia or pre-neoplastic lesions were observed. The available and relevant studies do not indicate that sorbitan fatty acid esters fulfil the criteria for classification as germ cell mutagen or that they are able to induce hyperplasia and/or pre-neoplastic lesions. Furthermore, the weight of evidence from all available information leads to the conclusion that sorbitan fatty acid esters are not carcinogenic. Therefore, a carcinogenicity study is scientifically unjustified (ECHA).

Oral

Male and female TO mice were given in their diet 0, 0.5, 2, or 4% sorbitan stearate (CAS RN [redacted] for 80 weeks. The estimated daily intakes were 0, 650, 2,600, and 5,200 mg/kg. Body weights were similar across all groups throughout the study. There were no increases in tumour incidence that were considered to be treatment-related (ECHA) [KI.score=2].

Inhalation

There are no studies available.

Dermal

There are no studies available.

I. Reproductive Toxicity

No studies are available on sorbitan mono-9-octadecenoate, (Z).

Sorbitan stearate (CAS RN [redacted] was tested in a combined repeated dose toxicity study with a reproductive/developmental screening (OECD 422) test. Male and female SD rats were dosed by oral gavage with 0, 40, 200, or 1,000 mg/kg sorbitan stearate. There were no systemic, reproductive, or developmental effects that were considered to be treatment-related. The NOAEL for reproductive and developmental toxicity is 1,000 mg/kg-day, the highest dose tested (ECHA) [Kl.score=2].

J. Developmental Toxicity

Oral

A combined repeated dose/developmental toxicity screening study was performed according to OECD 422 with sorbitan stearate (CAS RN [redacted] in male and female Sprague-Dawley rats. Seven to 12 rats were daily orally treated with 40, 200, 1000 mg/kg bw/d of the sorbitan stearate. Females were treated 2 weeks before mating through day 4 of lactation (about 40 days) and the males for 42 days. Control animals were treated with the vehicle. In parental animals, no mortality was observed, and no abnormalities related to the treatment. In the offspring, mortality was observed as follows: 2 dams of the 40 mg/kg bw/d dose group lost all pups and an additional dam lost 9/13 pups, potentially due to lack of lactation on day 1. No further mortalities of newborns were observed at any dose. The number of abnormalities seen in the visceral and skeletal tissues in test animals did not differ from spontaneously occurring abnormalities in the controls. The only exception was the occurrence of a filamentous tail in one pup of the 1000 mg/kg bw/d dose group. The effect was considered as not treatment-related but as common effect in Sprague-Dawley rats. With regard to the described effects, a developmental NOAEL of≥1000 mg/kg bw/d was determined (ECHA) [Kl.score=2].

The effects of sorbitan stearate (CAS RN [redacted] on foetal development after oral administration to pregnant animals was also investigated in Wistar rats. The rats were given oral doses 500 or 1000 mg/kg bw/d of sorbitan stearate from day 0 to day 20 of gestation. At sacrifice on day 20 of gestation, no differences between dose and control groups were observed with regard to clinical signs, body weights and post-mortem examinations of organs. One foetus of the highest dose group showed retardation (no further details were given). As this effect was not observed in other foetuses of the same dose group, it was considered to be incidental and not treatment-related. Two foetuses of the 500 mg/kg bw dose group and one fetus of the 1000 mg/kg bw dose groups showed incomplete ossification of cervical vertebral arches. A cervical rib was observed in one control group animal, in four animals of the 500 mg/kg bw/day dose group, and in three foetuses at dosing of 1000 mg/kg bw/d. Asymmetry of sternebrae was observed in four foetuses of the 500 mg/kg bw group and five foetuses of the highest dose group. Incompletely ossified sternebrae was found in 27 foetuses at dosing of 500 mg/kg bw and in 39 foetuses at dosing of 1000 mg/kg bw/d. A lumber rib was observed in one fetus of the 500 mg/kg bw/d dose group and in three control group animals. Since the effects described occurred to the same extent in control and test group animals, the changes were not assumed to be caused by sorbitan stearate, but as natural occurrence in comparison with background data of the test laboratory. In the 1000 mg/kg bw/d dose group, body weight gain of foetuses was slightly suppressed but there was no significant difference when

compared to controls. Therefore, a developmental NOAEL of≥1000 mg/kg bw/d was determined (ECHA) [Kl.score=2].

Inhalation

There are no studies available.

Dermal

There are no studies available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for sorbitan mono-9-octadecenoate, (Z) follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

There are no repeated dose toxicity studies on sorbitan mono-9-octadecenoate, (Z). Sorbitan monostearate, a structurally similar substance to sorbitan mono-9-octadecenoate, (Z) has been tested in an OECD 422 rat oral gavage study. The NOAEL for systemic, reproductive, and developmental toxicity is 1,000 mg/kg-day. The NOAEL of 1,000 mg/kg-day will be used to derive an oral RfD and drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / ($UF_A \times UF_H \times UF_L \times UF_{Sub} \times UF_D$)

Where:

- UF_A (interspecies variability) = 10
- UF_H (intraspecies variability) = 10
- UF_L (LOAEL to NOAEL) = 1
- UF_{Sub} (subchronic to chronic) = 10
- UF_D (database uncertainty) = 1
- Oral RfD = 1,000/(10 × 10 × 1 × 10 × 1) = 1,000/1,000 = 1.0 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) × (human weight) × (proportion of intake from water) / (volume of water consumed) × (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) × (human weight) × (proportion of water consumed) / (volume of water consumed)

Where:

- Human weight = 70 kg (ADWG, 2011)
- Proportion of water consumed = 10% (ADWG, 2011)
- Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (1.0 × 70 × 0.1)/2 = 3.5 mg/L

B. Cancer

There are no carcinogenicity studies on sorbitan mono-9-octadecenoate, (Z). Sorbitan monostearate (CAS RN [redacted] was not carcinogenic to mice. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sorbitan mono-9-octadecenoate, (Z) does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Acute and chronic studies indicate that the substance is of relatively low toxicity to aquatic organisms. Data to support this conclusion are discussed below.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on sorbitan, mono-9-octadecenoate, (Z) or sorbitan stearate.

Table 3: Acute aquatic toxicity studies on sorbitan, mono-9-octadecenoate, (Z) and sorbitan stearate

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Salmo gairdneri	96-hr LL_{50}	>1,000 [WAF]	2	HPVIS
Oryzias latipes	96-hr LL_{50}	>1,000 [WAF]*	1	ECHA
Daphnia magna	48-hr EL_{50}	>1,000 [WAF]*	2	ECHA
Pseudokirchneriella subcapitata	72-hr EL_{50}	>1,000 [WAF]*	1	ECHA

*Studies conducted on sorbitan stearate (CAS No. [redacted]

Chronic Studies

The 21-day NOELR (no-observed-effect-loading-rate) in a *Daphnia* reproduction test for sorbitan stearate (CAS No. [redacted] is 16 mg/L WAFA (ECHA) [Kl.score=2].

The 72-hr NOELR (no-observed-effect-loading-rate) to *Pseudokirschneriella subcapitata* for sorbitan stearate is 560 mg/L [WAF] (ECHA) [Kl.score=1].

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

The PNEC calculations for sorbitan, mono-9-octadecenoate, (Z) follow the methodology discussed in DEWHA (2009).

PNEC Water

Experimental results are available for three trophic levels. Acute E(L)L_{50} values are available for fish (>1,000 mg/L WAF), invertebrates (>1,000 mg/L WAF), and algae (>1,000 mg/L WAF). Results from chronic studies are available for invertebrates (16 mg/L WAF) and algae (560 mg/L WAF). On the basis that the data consists of short-term studies for three trophic levels and long-term results studies for two trophic levels, an assessment factor of 50 has been applied to the lowest reported NOELR of 16 mg/L for invertebrates. The $PNEC_{water}$ is 0.32 mg/L WAF.

PNEC Sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 11.83 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (47.3/1280) \times 1000 \times 0.32$
$= 11.83$ mg/kg

Where:

$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 96.9/1000 \times 2400]$
$= 47.3\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 2,423 \times 0.04$
$= 96.9$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for sorbitan, mono-9-octadecenoate, (Z) calculated from EPISUITE™ using the MCI is 2,423 L/kg.
f_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC Soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 10.3 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (48.46/1500) \times 1000 \times 0.32$
$= 10.3$ mg/kg

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 2,423 \times 0.02$
$= 48.46\ m^3/m^3$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for sorbitan, mono-9-octadecenoate, (Z) calculated from EPISUITE™ using the MCI is 2,423 L/kg.
F_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (IChEMS, 2022; ECHA, 2023).

Sorbitan, mono-9-octadecenoate, (Z) is readily biodegradable. Thus, it does not meet the screening criteria for persistence.

The estimated BCF values (involving biotransformation) for sorbitan, mono-9-octadecenoate, (Z) ranged from 36 to 92 L/kg. Thus, it does not meet the criteria for bioaccumulation.

The lowest chronic NOELR for sorbitan stearate, the surrogate for sorbitan, mono-9-octadecenoate, (Z), is >0.1 mg/L. The acute $E(L)L_{50}$ values are >1 mg/L. Thus, sorbitan, mono-9-octadecenoate, (Z) does not meet the screening criteria for toxicity.

The overall conclusion is that sorbitan, mono-9-octadecenoate, (Z) is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

No classified.

B. Labelling

No signal word.

C. Pictogram

None

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Please refer to the product SDS for additional information and confirmation of the information provided herein.

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention.

Ingestion

Rinse mouth with water and then drink a glass of water. Get medical attention. Never give anything by mouth to an unconscious person.

B. Firefighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Keep product and empty container away from heat and sources of ignition. May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Handle in accordance with good industrial hygiene and safety practice.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

For large amounts: dike spillage and pump off product. For residues: pick up with suitable absorbent material. Dispose of contaminated material as prescribed.

D. Storage and Handling

General Handling

Keep product and empty container away from heat and sources of ignition. Ensure adequate ventilation, especially in confined areas.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for sorbitan, mono-9-octadecenoate, (Z).

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Sorbitan, mono-9-octadecenoate, (Z) is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

Australian Drinking Water Guidelines [ADWG]. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council. Updated September 2022. https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Elder, R. L. (1985). Final report on the safety assessment of sorbitan stearate, sorbitan laurate, sorbitan sesquioleate, sorbitan oleate, sorbitan tristearate, sorbitan palmitate, and sorbitan trioleate. *J. Amer. Coll. Toxicol., 4*(3), 65–121.

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health. https://www1.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-publicat-environ.htm

European Chemicals Agency [ECHA]. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances.

European Chemicals Agency [ECHA]. (2023). Chapter R.11: vPvB assessment. In *Guidance on information requirements and chemical safety assessment*. Version 4.0. https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Industrial Chemicals Environmental Management Standard [IChEMS]. (2022). Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals. https://www.dcceew.gov.au/sites/default/files/documents/australian-pbt-criteria.pdf

Klimisch, H. J., Andreae, M., & Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol., 25*, 1–5.

National Center for Biotechnology Information [NCBI]. (2024). PubChem Compound Summary for CID 9920342, Sorbitan Monooleate. https://pubchem.ncbi.nlm.nih.gov/compound/Sorbitan-Monooleate.

U.S. Environmental Protection Agency [USEPA] (2019). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.Wick, A.N., and Joseph, L. (1953). The metabolism of sorbitan monostearate. Food Res. 18: 79

U.S. Environmental Protection Agency High Production Volume (HPV) Information System [HPVIS]. (2003, November 26). U.S. HPV Test Plan and Robust Summaries for Sorbitan Esters Category of the Aliphatic Esters Chemicals. https://ofmpub.epa.gov/oppthpv/Public_Search.PublicDetails

SILICON DIOXIDE

This dossier on silicon dioxide presents the most critical studies pertinent to the risk assessment of silicon dioxide in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the OECD-SIDS documents on synthetic amorphous silica and silicates (OECD, 2004a,b), and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch *et al.*, 1997).

1 SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Silicon dioxide

CAS RN: [redacted]

Molecular formula: $nSiO_2$

Molecular weight: 60.08

Synonyms: Silicon dioxide; synthetic amorphous silica; silica gel; precipitated silica, crystalline-free

SMILES: O=[Si]=O

2 PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Silicon Dioxide

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Powder, granules, pellets	2	ECHA
Melting Point	1,713°C	2	ECHA
Boiling Point	2.2 g/cm^3	2	ECHA
Water Solubility	76 – 128 mg/L* (slightly soluble)	1	ECHA

*Based on dissolved SiO_2.

3 ENVIRONMENTAL FATE PROPERTIES

A. Summary

Silicon oxides are the most abundant compounds in the earth's crust mass. Silicon dioxide (CAS No. [redacted] released into the environment is expected to combine indistinguishably with the soil layer or sediment due to their chemical similarity with inorganic soil matter (OECD, 2004a).

Biodegradation is not applicable to silicon dioxide (CAS No. [redacted] The bioavailable form of silicon dioxide (CAS No. [redacted] is the dissolved form which exists exclusively

as monosilicic [$Si(OH)_4$] acid under environmental pH (OECD, 2004a). Although the water-soluble fraction of silicon dioxide (CAS No. [redacted] acts as weak acid, pH changes are not likely to occur in the environment due to low aquatic releases and sufficient natural buffer capacities (OECD, 2004a).

Bioaccumulation of silicon dioxide (CAS No. [redacted] is generally unlikely to occur. However, dissolved silica can be actively assimilated by some marine and terrestrial organisms as normal natural processes mainly related to structural function.

4 HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The oral bioavailability of silicon dioxide in animals and humans is low. Absorbed silicon dioxide is rapidly eliminated and there is no accumulation in the body. The bioavailability of silicon dioxide by the inhalation route is low. While there is deposition in the lungs following inhalation exposure to silicon dioxide, it is rapidly eliminated. The acute toxicity of silicon dioxide is low by the oral, inhalation and dermal routes. Silicon dioxide is not irritating to the skin and eyes. Repeated oral exposures to rodents showed no adverse effects. Repeated inhalation exposure to high respirable levels of silicon dioxide resulted in an inflammatory response in the respiratory tract and lungs, which was reversible following cessation of exposure. Silicon dioxide is not genotoxic. Although the study was of poor quality, there was no evidence of adverse effects on reproduction in rats given silicon dioxide in the diet. Animal studies showed no adverse effects on foetal development from oral exposure to silicon dioxide.

B. Toxicokinetics/Metabolism

The oral bioavailability of silicon dioxide in animals and humans is low. Absorbed silicon dioxide is rapidly eliminated and there is no accumulation in the body. The bioavailability of silicon dioxide by the inhalation route is low. While there is deposition in the lungs following inhalation exposure to silicon dioxide, it is rapidly eliminated (OECD, 2004a,b).

C. Acute Toxicity

The oral LD_{50} of silicon dioxide (CAS No. [redacted] in rats from two different studies is >5,000 mg/kg (ECHA) [Kl. scores = 1].

The 4-hour inhalation LC_{50} in rats for an aerosol of silicon dioxide (CAS No. [redacted] is >0.69 mg/L, which was the maximum technically attainable concentration. The mass median aerodynamic diameter (MMAD) was approximately 0.6 µm, and approximately 65% of the mass was <6 µm (ECHA) [Kl. score = 2].

The 4-hour inhalation LC_{50} in rats for an aerosol of silicon dioxide (CAS No. [redacted] is >2.08 mg/L. The MMAD was approximately 0.76 µm, and approximately 98-99.4% of the mass was <10 µm (ECHA) [Kl. score = 2].

The 4-hour inhalation LC_{50} in rats for an aerosol of silicon dioxide (CAS No. [redacted] from a nose-only exposure is >0.14 mg/L, which was the maximum technically attainable concentration. The MMAD was 3.2 µm, and 47-50% of the mass was <6 µm (ECHA) [Kl. score = 2].

The dermal LD_{50} in rabbits is >5,000 mg/kg (no deaths) (ECHA) [Kl. score = 2].

D. Irritation

Application of 0.5 g silicon dioxide (CAS No. [redacted] to the skin of rabbits for 4 hours under occlusive conditions was not irritating (ECHA) [Kl. score = 1].

Instillation of 0.1 g silicon dioxide (CAS No. [redacted] to the eyes of rabbits was minimally irritating (ECHA) [Kl. score = 1].

E. Sensitisation

No studies are available.

F. Repeated Dose Toxicity

Oral

Male and female Wistar rats were given diets containing silicon dioxide (CAS No. [redacted] for 90 days. The dietary concentrations as silica concentrations were 0, 0.4-0.7, 1.7-1.9 or 6.5-7.0% silica; this equates to 0, 300-330, 1,200-1,400 or 4,000-4,500 mg/kg CAS No. [redacted] There were no treatment-related effects. The NOAEL is 4,000 to 4,500 mg/kg-day (ECHA) [Kl. score = 1].

Male and female CD rats were given diets containing silicon dioxide (CAS No. [redacted] for 6 months. The estimated daily intakes were 0, 2,170 and 7,950 mg/kg-day for males, and 0, 2,420 and 8,980 mg/kg-day for females. There were no treatment-related effects. The NOAEL is 7,950 and 8,980 mg/kg-day for males and females, respectively (ECHA) [Kl. score = 1].

Male and female Fischer 344 rats were fed a diet containing a synthetic amorphous silica (CAS No. not stated) for 102 weeks. The dose levels were 0, 12,500, 25,000 and 50,000 ppm. There were no treatment-related effects on body weight gain, feed consumption, survival, or hematology parameters. Liver weights were lower (up to 15%) in the ≥25,000 ppm females from 12 to 24 months; a dose-related trend was not apparent. The NOAEL is 50,000 ppm. Using a body specific food consumption rate, the NOAEL corresponds to 2,500 mg/kg-day (ECHA) [Kl Score = 2].

Male and female $B6C3F_1$ mice were fed a diet containing a synthetic amorphous silica (CAS No. not stated) for 93 weeks. The dose levels were 0, 12,500, 25,000 and 50,000 ppm. There were no treatment-related effects on survival or clinical signs. Body weight gain was lower in the 5% group from week 15 to week 50 for the males and from 30 to 50 for the females. Mean body weights for 5% group animals for the remainder of the study were similar to controls. The NOAEL is 50,000 ppm in the diet. Using 0.13 as the fraction of body weight that mice consume per day as food (U.S. EPA), the NOAELs corresponds to 6,500 mg/kg-day (ECHA) [Kl Score = 2].

Inhalation

Male and female Wistar rats were exposed by inhalation to 0, 1, 6 or 30 mg/m^3 silicon dioxide (CAS No. [redacted] 6 hours/day, 5 days/week for 13 weeks. There were no

deaths during the study. Respiration rates were increased in a concentration-dependent manner. Body weight and body weight gain were unaffected in females, but were lower in the males with the 30 mg/m^3 groups significantly affected throughout the study. At ≥6 mg/m^3, there were haematological changes, increased lung weights and histopathologic changes in the lungs (including collagen increase and sporadic focal fibrosis). At 1 mg/m^3, there was a slight, but fully reversible, pulmonary response indicative of an inflammatory reaction. The NOAEC for this study is 1.3 mg/m^3 (ECHA) [Kl. score = 1].

Dermal

No adequate studies are available.

G. Genotoxicity

In Vitro Studies

The results of *in vitro* genotoxicity studies on silicon dioxide are presented below in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Silicon Dioxide

Test System	Test substance	Results*		Klimisch Score	Reference
		-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	CAS No. [redacted]	-	-	2	Prival *et al.* (1991)
Bacterial reverse mutation (*E. coli* strains)	CAS No. [redacted]	-	-	2	Prival *et al.* (1991)
Bacterial reverse mutation (*S. typhimurium* strains)	CAS No. [redacted]	-	-	1	ECHA
Mammalian cell gene mutation (CHO cells)	CAS No. [redacted]	-	-	1	ECHA
Chromosomal aberration (Human embryonic lung cells, WI-38)	CAS No. [redacted]	NA	-	2	ECHA
Chromosomal aberration (CHO cells)	CAS No. [redacted]	-	-	1	ECHA
Unscheduled DNA synthesis (primary rat hepatocytes)	CAS No. [redacted]	NA	-	1	ECHA

*+, positive; -, negative; NA, not applicable.

In Vivo Studies

Male F344 rats were exposed by inhalation to 0 or 50 mg/m^3 silicon dioxide (CAS No. [redacted] 6 hours/day, 5 days/week for 13 weeks. When tested in a HPRT assay, there was no increase in mutation frequency in the alveolar Type II cells from exposed rats compared to controls (ECHA) [Kl. score = 2].

Male SD rats were given by oral gavage either a single dose of 0, 1,4, 14, or 140 mg/kg silicon dioxide (CAS No. [redacted] or five consecutive daily doses of 0, 500, or 5,000 mg/kg

silicon dioxide (CAS No. [redacted] Chromosomal aberrations were not significantly increased in the treated animals compared to controls (ECHA) [Kl. score = 2].

In a dominant lethal mutation assay, male SD rats were given by oral gavage either a single dose of 0, 1, 4, 14 or 140 mg/kg silicon dioxide (CAS No. [redacted] or five consecutive daily doses of 0, 500, or 5,000 mg/kg silicon dioxide (CAS No. [redacted] There was no indication of a mutagenic effect by silicon dioxide (CAS No. [redacted] (ECHA) [Kl. score = 2].

H. Carcinogenicity

Oral

Male and female Fischer 344 rats were fed a diet containing a synthetic amorphous silica (CAS No. not stated) for 102 weeks. The dose levels were 0, 12,500, 25,000 and 50,000 ppm. The incidence of tumours was similar between treated and control animals. The number of animals used in this study was small (ECHA) [Kl Score = 2]. Male and female $B6C3F_1$ mice were fed a diet containing a synthetic amorphous silica (CAS No. not stated) for 93 weeks. The incidence of tumours was similar between treated and control animals (ECHA) [Kl Score = 2].

I. Reproductive Toxicity

A one-generation reproductive toxicity study has been conducted on silicon dioxide (CAS No. [redacted] Male and female Wistar rats were given diets containing 0 or 497 mg/kg-day (males) or 509 mg/kg-day (females). In the parental animals, there were no treatment-related effects on mortality, clinical symptoms, feed consumption, body weight gain and measured hematology parameters. There was no reproductive or developmental toxicity (ECHA) [Kl. score = 3].

J. Developmental Toxicity

Pregnant female rats were given by oral gavage doses up to 1,350 mg/kg silicon dioxide (CAS No. [redacted] on GD 6-15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 1,350 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 2].

Pregnant female mice were given by oral gavage doses up to 1,340 mg/kg silicon dioxide (CAS No. [redacted] on GD 6-15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 1,340 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 2].

Pregnant female rabbits were given by oral gavage doses up to 1,600 mg/kg silicon dioxide (CAS No. [redacted] on GD 6-18. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 1,600 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 2].

Pregnant female Syrian hamsters were given by oral gavage up to 1,600 mg/kg silicon dioxide (CAS No. [redacted] on GD 6-10. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 1,600 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 2].

5 DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for silicon dioxide (CAS No. [redacted] follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

Oral

There were no adverse effects seen in rats or mice fed a diet containing up to 50,000 ppm silicon dioxide (CAS No. not stated) for 102 and 93 weeks, respectively (Takizawa *et al.*, 1988). The NOAELs for rats and mice were 2,500 and 6,500 mg/kg-day, respectively. The lowest NOAEL of 2,500 mg/kg-day will be used for determining the oral Reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:
UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1

Oral RfD = 2,500/(10 x 10 x 1 x 1 x 1) = 2,500/100 = 25 mg/kg-day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:
Human weight = 70 kg (ADWG, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (25 x 70 x 0.1)/2 = 88 mg/L

B. Cancer

Silicon dioxide was not carcinogenic to rats or mice in chronic dietary studies. Hence, a cancer reference value was not derived.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Silicon dioxide does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

7 ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Silicon dioxide has a low acute toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on silicon dioxide.

Table 3: Acute Aquatic Toxicity Studies on Silicon Dioxide

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Danio rerio	96-h LL_0	10,000*	1	ECHA
Danio rerio	96-h LL_0	10,000	1	ECHA
Daphnia magna	48-h EL_{50}	>1,000**	2	ECHA
Daphnia magna	24-h EL_{50}	>10,000	2	ECHA

*Silica, amorphous, fumed, crystalline-free (CAS No. [redacted]

**Mortality may have occurred from physical effects of unfiltered medium.

Chronic Studies

No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for silicon dioxide follow the methodology discussed in DEWHA (2009).

PNEC water

Silicon dioxide is a solid in powder form, which is slightly soluble in water. Acute aquatic toxicity studies on fish and *Daphnia* using excess loadings of silicon dioxide showed no acute toxicity (Table 3). Physical effects of silicon dioxide on *Daphnia* were seen in tests using unfiltered test medium (OECD, 2004a,b; ECHA). Because of the physico-chemical properties of silicon dioxide, the $PNEC_{water}$ was not determined.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. The $PNEC_{sed}$ cannot be derived using the equilibrium partitioning method.

PNEC soil

There are no toxicity data for terrestrial or soil organisms. The $PNEC_{soil}$ cannot be derived using the equilibrium partitioning method.

8 PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REAC Criteria methodology (DEWHA, 2009; ECHA, 2008).

Silicon dioxide (CAS No. [redacted] released into the environment is expected to combine indistinguishably with the soil layer or sediment due to their chemical similarity with inorganic soil matter. Biodegradation is not applicable to silicon dioxide (CAS No. [redacted] For the purposes of this PBT assessment, the persistent criteria is not considered applicable to silicon dioxide (CAS No. [redacted]

Silicon dioxide (CAS No. [redacted] is an inorganic substance that is a slightly soluble powder. Bioaccumulation of silicon dioxide (CAS No. [redacted] is generally unlikely to occur, given its low bioavailability. However, dissolved silica can be actively assimilated by some marine and terrestrial organisms as normal natural processes mainly related to structural function. For the purposes of this PBT assessment, silicon dioxide (CAS No. [redacted] does not meet the criteria for bioaccumulation.

The acute toxicity of the water-soluble fraction of silicon dioxide (CAS No. [redacted] is >1 mg/L. Thus, it does not meet the criteria for toxicity.

The overall conclusion is that silicon dioxide (CAS No. [redacted] is not a PBT substance.

9 CLASSIFICATION AND LABELLING

A. Classification

No classified.

B. Labelling

No signal word.

C. Pictogram

None.

10 SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. If symptoms persist, seek medical advice.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

No data are available.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Prevent from entering sewers, waterways, or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for silica gel (silicon dioxide, CAS No. [redacted] in Australia is 10 mg/m^3 as an 8-hour TWA.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Use respiratory protection if airborne dust levels are expected to exceed the occupational exposure guidance value.

Hand Protection: Use gloves.

Skin *Protection*: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Silicon dioxide is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

11 DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

12 REGULATORY STATUS

Australian AICS Inventory: Listed.

13 REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA] (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

OECD (2004a). Screening Information Dataset (SIDS) Initial Assessment Report for Synthetic Amorphous Silica and Silicates: Silicon Dioxide (CAS No. [redacted] [redacted] [redacted] Silicic Acid, Aluminum Sodium Salt (CAS No. [redacted] Silicic Acid, Calcium Salt (CAS No. [redacted] UNEP Publications.

OECD (2004b). IUCLID Data Set for Synthetic Amorphous Silica and Silicates: Silicon Dioxide (CAS No. [redacted] [redacted] [redacted] Silicic Acid, Aluminum Sodium Salt (CAS No. [redacted] Silicic Acid, Calcium Salt (CAS No. [redacted] UNEP Publications.

Prival, M.J., Simmon, V.F., and Mortelmans, K.E. (1991). Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. Mutat. Res. 260: 321-329.

CRYSTALLINE SILICA, QUARTZ (CAS NO. [redacted]
CRYSTALLINE SILICA, CRISTOBALITE (CAS NO. [redacted]
CRYSTALLINE SILICA, TRIDYMITE (CAS NO. [redacted]
NON-CRYSTALLINE SILICA (IMPURITY) (CAS NO. [redacted]
DIATOMACEOUS EARTH (CAS NO. [redacted]
DIATOMACEOUS EARTH, CALCINED (CAS NO. [redacted]

This dossier on crystalline silica, quartz, cristobalite and tridymite; non-crystalline silica (impurity); diatomaceous earth; and diatomaceous earth, calcined presents the most critical studies pertinent to the risk assessment of these substances in their use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

For the purpose of this dossier, crystalline silica, quartz (CAS No. [redacted] has been reviewed as representative of crystalline silica cristobalite and tridymite, and non-crystalline silica (impurity). Crystalline silica, quartz is also considered representative of diatomaceous earth and diatomaceous earth, calcined, as they both consist mainly of silicon dioxide.

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): dioxosilane

CAS RN: [redacted]

Molecular formula: SiO_2

Molecular weight: 60.084 g/mol

Synonyms: Cristobalite, Dioxide, Silicon

SMILES: O=[Si]=O

II. PHYSICAL AND CHEMICAL PROPERTIES

Silica is an off-white granule that occurs naturally in various crystalline and amorphous or other non-crystalline forms. Crystalline silica is characterised by silicon dioxide (SiO_2) molecules oriented in fixed, periodic patterns to form stable crystals. The primary crystalline form of silica is quartz. Other crystalline forms of silica include cristobalite, tripoli and tridymite. Particle size is a key determinate of silica toxicity, since toxicity is restricted to particles that are small enough to be deposited into the target regions of the respiratory tract (OECD, 2011).

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Crystalline silica is characterised by silicon dioxide (SiO_2) molecules oriented in fixed, periodic patterns to form stable crystals. The primary crystalline form of silica is quartz. It is a stable solid under typical environmental conditions. It will not biodegrade, bioaccumulate, nor will it sorb to sediments or soils.

B. Biodegradation

No data are available. Based on the crystalline form of the substance, it is not expected to biodegrade.

C. Environmental Distribution

No experimental data are available for crystalline silica. As a stable inorganic solid, it is not soluble in water, and it will not sorb to soils or sediment.

D. Bioaccumulation

There are no bioaccumulation studies on crystalline silica.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Human exposure to crystalline silica via inhalation can lead to silicosis, lung cancer and pulmonary tuberculosis (WHO, 2000).

B. Acute Toxicity

No adequate acute oral, dermal or inhalation exposure studies are available for quartz, cristobalite or tridymite.

Most acute toxicity studies for quartz or cristobalite were conducted using intratracheal instillation. Intratracheal instillation is the introduction of the substance directly to the trachea and is used to test respiratory toxicity of a substance.

Single intratracheal instillation of quartz caused inflammatory effects and formation of discrete silicotic nodules in rats, mice and hamsters (IARC, 2012; WHO, 2000). Other effects like oxidative stress, cellular proliferation and increases in water, protein and phospholipid content of rat lungs, apoptosis (programmed cell death) and lung cancer were also noted.

In an acute dose study, rats were dosed once with 0, 0.75, 1.5, 3.0, 6.0 or 12 mg/kg bw/day quartz by intratracheal instillation (Seiler et al., 2001). The lowest observed adverse effect level (LOAEL) of 0.75 mg/kg bw/day was derived from these studies.

Two other similar studies of single intratracheal instillation of quartz reported higher LOAELs in rats (3 and 40 mg/kg bw/day) based on inflammation and fibrosis (Saffiotti et al., 1996).

C. Irritation

No data available.

D. Sensitisation

No data available.

E. Repeated Dose Toxicity

Oral

No data available.

Inhalation

Repeated inhalation exposure of crystalline is known to cause adverse effects (IARC, 2012). Silicosis has been identified as the main non-cancer effect of silica exposure, although available epidemiologic data as well as animal data provide evidence for several other effects associated with silica exposure, such as silicotuberculosis, enlargement of the heart (cor pulmonale), interference with the body's immune system and damage to the kidneys (Health Canada, 2013).

Dermal

No data available.

F. Genotoxicity

No data available.

G. Carcinogenicity

Oral

No data available.

Inhalation

The International Agency for Research on Cancer (IARC) has classified crystalline silica as a Group 1 carcinogen, as there was sufficient evidence for carcinogenicity in experimental animals and sufficient evidence for carcinogenicity of inhaled crystalline silica from occupational sources (IARC, 1997; IARC, 2012).

H. Reproductive Toxicity

No data available.

I. Developmental Toxicity

No data available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicity information on crystalline silica is inadequate and/or unreliable for deriving toxicological reference and drinking water guidance values for this substance.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Crystalline silica does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Although no data are available, crystalline silica is expected to exhibit low acute toxicity to aquatic organisms.

B. Aquatic Toxicity

No aquatic toxicity data were available.

C. Terrestrial Toxicity

No terrestrial toxicity data were available.

D. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Crystalline silica is an inorganic mineral. Thus, biodegradation is not applicable to this substance. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to crystalline silica.

As an inorganic complex it is not expected to bioaccumulate. Thus, crystalline silica does not meet the screening criteria for bioaccumulation.

Crystalline silica is not expected to cause adverse effects in environmental receptors. Thus, this substance does not meet the screening criteria for toxicity.

Therefore, crystalline silica is not a PBT substance.

IX. CLASSIFICATION AND LABELING

A. Classification

H373 – may cause damage to organs through prolonged or repeated exposure.

B. Labelling

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention if symptoms persist.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Get medical attention if respiratory irritation develops or breathing becomes difficult.

Ingestion

Rinse mouth. Do not induce vomiting. Get medical attention if symptoms occur.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use extinguishing media appropriate for surrounding material.

Specific Exposure Hazards

Reacts with hydrofluoric acid (HF) forming toxic gas (SiF_4).

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Pick up mechanically – vacuum up. Avoid generating dust. If formation of dust cannot be avoided, use respiratory filter device. Dispose of the material collected according to regulations.

D. Storage And Handling

General Handling

Handle in accordance with good industrial hygiene and safety practice. Avoid contact with eyes, skin and clothing. Avoid dust formation. Do not breathe dust. Wash thoroughly after handling. Use with adequate ventilation.

Storage

Provide adequate exhaust ventilation at places where dust is formed. Keep airborne concentrations below exposure limits. Keep containers tightly closed in a dry, cool, well-ventilated area.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has established an occupational exposure standard for exposure to crystalline silica of an 8-hour time weighed average (TWA) exposure limit of 0.05 mg/m^3.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls

to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; as well as before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Crystalline silica is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Health Canada. (2013). Environment Canada, Health Canada. Screening Assessment for the Challenge: Quartz (CAS [redacted] and Cristobalite (CAS [redacted] June 2013. https://www.ec.gc.ca/ese-ees/1EB4F4EF-88EE-4679-9A6C-008F0CBC191C/FSAR_B12%20-%[redacted]20%26%[redacted]20%28QC%29_EN.pdf

IARC. (1997). Silica, some silicates, coal dust and Para-aramid fibrils. International Agency for Research on Cancer (IARC) working group on the evaluation of carcinogenic risks to humans, Lyon, France, 15-22 October 1996. IARC Monogr Eval Carcinog Risks Hum. 1997;68:1–475.

IARC. (2012). Silica dust, crystalline, in the form of quartz or cristobalite. International Agency for Research on Cancer (IARC) working group on the evaluation of carcinogenic risks to humans, Lyon, France, 17-24 March, 2009. IARC Monogr Eval Carcinog Risks Hum. 2012;100C:355–405

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

OECD. (2011). OECD -SIDS Initial Targeted Assessment Profile on Quartz and Cristobalite, SIAM 32, 19-21 April 2011. https://hpvchemicals.oecd.org/ui/handler.axd?id=b68bb357-e6dd-4db9-b05c-8148223fc0ff.

Saffiotti, U., Williams, O., Lambert, N., Daniel, N., Kaighn, M.E., Mao, Y., Shi, X. (1996). Carcinogenesis by crystalline silica: animal, cellular, and molecular studies. In:Castranova V, Vallyathan V, Wallace WE, eds. Silica and silica-induced lung diseases. Boca Raton, FL, CRC Press, pp. 345–381.

Seiler, F., Rehn, B. and Bruch, J. (2001). Evidence of a no-effect level in silica–induced rat lung mutagenicity but not in fibrogenicity. Archives of Toxicology 74: 716-719.

WHO. (2000). Concise International Chemical Assessment Document 24 - Crystalline Silica, Quartz. Produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals. WHO Geneva.

CHOLINE CHLORIDE

This dossier on choline chloride (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the OECD-SIDS documents on choline chloride (OECD, 2004), and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-hydroxy-N,N,N-trimethylethanaminium chloride

CAS RN: [redacted]

Molecular formula: $C_5H_{14}NO.Cl$

Molecular weight: 139.6 g/mol

Synonyms: Choline chloride; 2-hydroxy-N,N,N-trimethylethanaminium chloride; trimethyl(2-hydroxyethyl)ammonium chloride; cholinium chloride; 2-hydroxyethyl(trimethyl)azanium chloride

SMILES: C[N+](C)(C)CCO.[Cl-]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Choline Chloride

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa*	White crystalline solid*	2	OECD (2004)
Melting Point	~ 200°C @ 101.3 kPa	1	ECHA
Boiling Point	Decomposition at 305°C @ 101.3 kPa prior to boiling	2	ECHA
Density	70% aq. solution: 1110 kg/m³@ 20°C	4	OECD (2004)
Partition Coefficient (log K_{ow})	75% aq. solution: -3.77 @ 25°C	1	ECHA
Vapour Pressure	2287.2 Pa @ 25°C (QSAR)	2	ECHA
Water Solubility	Powder containing 50% choline chloride: 650 g/L (temperature unknown	4	OECD (2004)
Auto flammability	330°C	2	ECHA

Property	Value	Klimisch score	Reference
Viscosity	75% aq. solution: 26.2 mPa.s @ 20°C; 14.1 mPa.s @ 40°C	1	ECHA
Henry's Law Constant	2.06 x 10-11 Pa.m^3/mol @ 25 °C (estimated using HENRYWIN v3.10)	-	OECD (2004)

*Choline chloride is a white crystalline solid; it is marketed as an aqueous solution (70-75% w/w in water), which is colourless with an amine-like odour.

Choline chloride is a quaternary amine salt that will dissociate in water into choline ($C_5H_{14}NO^+$) ions and chloride (Cl^-) ions.

III. ENVIRONMENTAL FATE PROPERTIES

A. Partitioning

Choline chloride is highly water soluble and non-volatile. When released to water under typical environmental conditions, the quaternary ammonium salt dissociates to release a positively charged choline ion and a negatively charged chloride ion (OECD, 2004). It is unlikely to partition to the atmosphere based on its low volatility (OECD, 2004).

B. Biodegradation

Choline chloride is readily biodegradable (93% within 14 days) in a MITI-I test (MITI, 1992; OECD, 2004). In another MITI-I test, biodegradation was $\geq$60%, indicating ready biodegradation (Tunkel *et al.*, 2000; OECD, 2004). A $BOD_5/ThOD_5$ ratio of 75% was obtained in a BOD_5 test performed according to DIN 38409 part 43 (BASF AG, 1984; OECD, 2004).

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

No experimental data are available for choline. Choline is a quaternary ammonium compound (QAC); these compounds are not included in the training set for the K_{oc} estimation of the QSAR model KOCWIN v. 2.00 in EPISuite™ (USEPA, 2016), and therefore outside the program's prediction domain. A K_{oc} value of 2.3 had been estimated using the older QSAR model PCKOCWIN v. 1.66 (OECD, 2004), indicating a low potential for soil adsorption.

Results from Mackay Level I modelling indicate that choline chloride will be distributed completely into water (OECD, 2004).

D. Bioaccumulation

No measured data on bioaccumulation of choline chloride is available. An experimental log K_{ow} is -3.77, which indicates a low potential to accumulate in organisms (OECD, 2004). Bioaccumulation is not expected in aquatic organisms.

E. Summary

Choline chloride is readily biodegradable. Distribution modelling using Mackay Level 1 shows choline to be distributed completely into water. Choline chloride will not adsorb on soil and sediments. It is not expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Choline is a vitamin-like essential nutrient. It has low acute toxicity by the oral route and is slightly irritating to the skin and eyes. Repeated high intake of choline in humans has been reported to cause a slight hypotensive effect. No adverse effects (including tumours) were seen in rats given choline in the diet for 72 weeks. Choline is not genotoxic. High dietary doses of choline to pregnant mice resulted in developmental toxicity (but no teratogenic effects) at levels that were maternally toxic.

NICNAS has assessed fumaric acid in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to human health[1]

B. Metabolism

Choline is a vitamin-like essential nutrient. Although the body can synthesise choline in small amounts, it is insufficient to maintain health and must be consumed in the diet. Choline is required for the synthesis of phospholipids in cell membranes, methyl group metabolism and acetylcholine synthesis (neurotransmitter) (Zeisel and Blusztajn, 1994).

Dietary choline is taken up into the body by transporter proteins present in the cells lining the small intestine (IOM, 2000). In the small intestine, prior to uptake into the small intestinal cells, some choline is metabolised by bacteria to betaine and methylamines (Zeisel et al., 1980). Dietary choline can be present as free choline or in esterified forms (i.e., phosphocholine, glycerophosphocholine, sphingomyelin, and phosphatidylcholine) (Zeisel and Blusztain, 1994). Free choline is formed from these esterified choline compounds by pancreatic enzymes.

Choline is involved in a number of biochemical pathways in eukaryotic and prokaryotic cells. It is a precursor for acetylcholine (a neurotransmitter); phospholipids (structural integrity and signaling roles for cell membranes); and a major source for methyl groups (IOM, 2000).

C. Acute Toxicity

<u>Oral</u>

The oral LD_{50} values of choline in rats are approximately 3,500 and 5,500 mg/kg (ECHA) [Kl. scores = 2].

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber= [redacted] 2C+

Inhalation

No acute inhalation or dermal toxicity studies are available.

D. Irritation

Skin

Application of a 70% aqueous solution to the skin of rabbits for 20 hours under occlusive conditions resulted in ambiguous skin irritation (BASF AG, 1963a; OECD, 2004) [Kl. score = 2].

Eye

Slight eye irritation was seen in the eyes of rabbits after instillation of a 70% aqueous solution of choline chloride; no effects were seen 24 hours after exposure (BASF AG, 1963b; OECD, 2004) [Kl. score = 2].

E. Sensitisation

No data are available in animals. In a Human Repeated Insult Patch Test (HRIPT), there was no evidence of dermal sensitisation in 200 subjects given 0.5% (w/v) aqueous solution of choline chloride during the induction phase and 0.2% (w/v) aqueous solution during the challenge phase (Colgate-Palmolive, 2003; OECD, 2004).

F. Repeated Dose Toxicity

Oral

A 72-week feeding study was conducted to investigate the impact of choline chloride on the liver tumour promoting activity of phenobarbital and DDT in diethylnitroamine-initiated Fischer 344 rats. Animals received approximately 500 mg/kg/day choline chloride. Following the end of the exposure period, the animals were kept on the same untreated diet as the control group until study termination at week 103. Histopathology was limited to the liver and organs that developed gross abnormalities. There were no significant differences between treated and control animals on survival rates, body weights, and relative liver weights. There were no increased number of neoplastic liver nodules, hepatocellular carcinomas, lung tumours, leukemia or other tumours between treated and control animals. The NOAEL for choline chloride in this study is 500 mg/kg-day (Shivapurkar *et al.*, 1986) [Kl. score = 3].

In humans, oral administration of 10,000 mg/day choline chloride in a pilot study treating a small number of patients with Alzheimer's disease resulted in a slight hypotensive effect (Boyd *et al.*, 1977). This dose was regarded as a LOAEL by the U.S. Institute of Medicine (IOM) Standing Committee on the Scientific Evaluation of Dietary Reference Intake (2000).

Inhalation

No adequate or reliable studies are available.

Dermal

No adequate or reliable studies are available.

G. Genotoxicity

In Vitro Studies

Choline chloride was not mutagenic to bacteria in reverse mutation assays (Haworth *et al.*, 1983, Litton Bionetics, 1977).

A small, but statistically significant, and dose-related increase in chromosomal aberrations was reported in Chinese Hamster Ovary (CHO) cells at doses of 50 and 500 µg/mL choline chloride in the absence of S9 only (Bloom *et al.*, 1982). No higher concentrations were examined. These results could not be confirmed in two studies using CHO cells at concentrations of choline chloride up to 5,000 µg/mL (Galloway *et al.*,1985).

In sister chromatid exchange (SCE) assays, ambiguous results were obtained in two parallel studies (at two different laboratories) in CHO cells at concentrations up to 50 and 5,000 µg/mL choline chloride, respectively. Cytotoxicity was observed at 5,000 µg/mL. In laboratory 2, the increase in SCEs, which was sporadic and not dose-related, that was observed with metabolic activation was not reproduced in laboratory 1. Laboratory 1 showed a weak positive at the top dose without metabolic activation, but a comparison with laboratory 2 was not possible due to the insufficient number of cells analysed (Bloom *et al.*, 1982; Galloway *et al.*, 1985).

Choline chloride was negative in a gene conversion assay with *Saccharomyces cerevisiae* strain D4 in the presence or absence of metabolic activation (Litton Bionetics, 1977; OECD, 2004).

In Vivo Studies

No studies are available.

H. Carcinogenicity

Oral

No studies are available.

Inhalation

No studies are available.

I. Reproductive Toxicity

No reliable studies have been conducted that address female fertility or reproductive toxicity by a relevant route of exposure.

J. Developmental Toxicity

Oral

Pregnant female mice were given in their feed 0, 1, 2.5, 5, or 10% choline chloride (0 or approximately 1,250, 4,160, 10,800, or 20,000 mg/kg choline chloride) on gestational days 1 to 18. Maternal body weight gain was reduced in all treated groups except for the 1,250

mg/kg group. Maternal weight gain of dams with embryonic/foetal absorptions showed no net weight gain at >4,160 mg/kg, but there was net weight loss in the 20,000 mg/kg group. All foetuses were resorbed in the 20,000 mg/kg group. Embryonic/foetal lethality of 35% and 69% were seen in the 4,160 and 10,800 mg/kg groups, respectively. No resorptions occurred in the 1,250 mg/kg group. Developmental toxicity was seen at >4,160 mg/kg group. There were no statistically significant increases in malformations in any dose group. The NOAEL for maternal and developmental toxicity is 1,250 mg/kg/day (BASF AG, 1966; OECD, 2004) [Kl. score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for choline chloride follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes selected hypotension as the critical effect from the study by Boyd *et al.* (1977) when deriving a Tolerable Upper Intake Level. Boyd *et al.* (1977) reported a LOAEL of 10,000 mg/day choline chloride (7,500 mg/day choline). An uncertainty factor of 2 was chosen because of the limited data regarding hypotension and the inter-individual variation in response to cholinergic effects. Thus, the value for the Tolerable Upper Intake Level or repeated exposure of adults to choline is 3,500 mg/day choline.

Note that the Australian National Health and Medical Research Council (2014) concluded that there are no data to suggest that there is increased susceptibility to choline during pregnancy or lactation; thus, the upper level of intake choline is the same for women during pregnancy or lactation as it is for adults (3,500 mg/day choline).

Oral Reference Dose (oral RfD)

An oral RfD for choline is derived as follows: the LOAEL of 7,500 mg/day from the Boyd *et al.* (1977) study is divided by an uncertainty factor of 2 to obtain a value of 3,500 mg choline/day or 50 mg choline/kg/day for a 70 kg person.

Oral RfD = 50 mg/kg/day [choline]

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (50 x 70 x 0.1)/2 = 175 mg/L [choline]

The Australian drinking water guideline value for chloride ions is 250 mg/L based on aesthetics (ADWG, 2021).

B. Cancer

There are no carcinogenicity studies on choline chloride. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Choline chloride does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL EFFECTS SUMMARY

A. Summary

Choline chloride is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies conducted on choline chloride.

Table 2: Acute Aquatic Toxicity Studies on Choline Chloride

Test Species	Endpoint	Results (mg/L)[1]	Klimisch score	Reference
Oryzias latipes	96-hour LC_{50}	>100 (nominal and measured)	1	MOE Japan (1999a); OECD (2004)
Leuciscus idus	96-hour LC_{50}	>10,000*	2	OECD (2004); ECHA
Daphnia magna	48-hour EC_{50}	349 (nominal and measured)	2	MOE Japan (1999b); OECD (2004)
Daphnia magna	48-hour EC_{50}	>500*	2	OECD (2004)
Pseudokirchneriella subcapitata	72-hour EC_{50}	>1,000 (nominal and measured)	1	MOE Japan (1999a); OECD (2004)

*78% aqueous solution of choline chloride

Chronic Studies

In a 21-day *Daphnia magna* reproduction test, the nominal and measured NOEC was reported to be 30.2 mg/L (MOE Japan, 1999d) [Kl. score = 1].

The NOEC from a 72-hr algae *Pseudokirchneriella subcapitata* study is 30.2 mg/L (MOE Japan, 1999c; OECD, 2004) [Kl. score = 1].

C. Terrestrial Toxicity

No data is available.

Choline is present in all plant and animal cells, mostly in the form of phospholipids (phosphotidylcholine or lecithin, lysophosphatidylcholine, choline plasmalogens and sphingomyelin), which are essential components of membranes (IOM, 2000).

D. Calculation of PNEC

The PNEC calculations for choline chloride follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (>100 mg/L), invertebrates (349 mg/L) and algae (>1,000 mg/L). Results from chronic studies are available for invertebrates (21-day NOEC = 30.2 mg/L) and algae (72-hour NOEC = 32 mg/L). On the basis that the data consists of chronic studies on two trophic level (albeit not on the species with the lowest $E(L)C_{50}$), an assessment factor of 100 has been applied to the lowest reported NOEC of 30 mg/L for *Daphnia*. The $PNEC_{aquatic}$ is 0.3 mg/L (0.22 mg/L for choline).

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.15 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1{,}000 \times PNEC_{water}$
$= (0.844/1280) \times 1{,}000 \times 0.22$
$= 0.15$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1{,}000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 0.092/1{,}000 \times 2400]$
$= 0.844\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg).

BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$

= 2.3 x 0.04

= 0.092 L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for choline is estimated to be 2.3 L/kg (OECD, 2004).

F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ for choline is 0.007 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1{,}000 \times PNEC_{water}$

= (0.05/1500) x 1,000 x 0.22

= 0.007 mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)

BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$

= 2.3 x 0.02

= 0.05 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for choline is estimated to be 2.3 L/kg (OECD, 2004).

F_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Choline chloride is readily biodegradable and thus it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of -3.77, choline chloride does not meet the criteria for bioaccumulation.

The NOEC values from chronic toxicity studies on choline chloride are >0.1 mg/L. Thus, choline chloride does not meet the criteria for toxicity.

The overall conclusion is that choline chloride is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not Classified

B. Labelling

No signal word.

C. Pictogram

None

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Keep product and empty container away from heat and sources of ignition. May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide, nitrogen oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Prevent from entering sewers, waterways, or low areas.

Steps to be Taken if Material is Released or Spilled

Soak up with inert absorbent material.

D. Storage And Handling

General Handling

Keep product and empty container away from heat and sources of ignition. Ensure adequate ventilation, especially in confined areas.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for choline chloride.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Choline chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Australian National Health and Medical Research Council (2014). Nutrient Reference Values for Australia and New Zealand: Choline. Accessed at: https://www.nrv.gov.au/nutrients/choline

BASF AG (1963a). Toxicity of choline chloride 70 % in water; skin irritation after exposure to choline chloride. Department of Toxicology. Unpublished results. Study No. XIII 9. 01 Mar. 1963.

BASF AG (1963b). Toxicity of choline chloride 70% in water; eye irritation. Department of Toxicology. Unpublished results. Study No. XIII 9. 01 Mar. 1963.

BASF AG (1966). Study on teratogenic effects of choline chloride in the mouse after oral application. Department of Toxicology. Unpublished results. Study No. XIV/156. 14 Oct. 1966.

BASF AG (1984). Department of Product Safety. Laboratory of Ecology. Pruefbericht ueber eine Untersuchung auf biologische Abbaubarkeit im BSB5-Test - Cholinchlorid (German). Test No. 01606. 16 Feb. 1984.BASF AG (2004b). Department of Product Safety. Unpublished calculation. Mackay Level I V2.11. 29 Jun. 2004.

Bloom A., Galloway, S., Nakamura, F.T., Teteviri, A., Armstrong, M., Lavappa, K.L., Duk, S., and Ahmed, M.A. (1982). Comparison of results for SCE and chromosome aberrations for eleven compounds tested in two laboratories by standardized methods. Environ. Mutagen. 4: 397.

Boyd, W.D., Graham-White, J., Blackwood, G., Glen, I., and McQueen, J. (1977). Clinical effects of choline in Alzheimer senile dementia. Lancet 2: 711.

Colgate-Palmolive (2003). Study No. DCR-200-137-TKL. TKL Research Inc. Paramus, NJ, USA. In: SCCNFP. Scientific Committee on Cosmetic Products and Non-Food Products. Choline Chloride. SCCNFP/0672/03. 9 Dec. 2003.

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA] (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Galloway, S.M., Bloom, A..D, Resnick, M., Margolin, B.H., Nakamura, F., Archer, P., and Zeiger, E, (1985). Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7: 1-51.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagenesis Suppl. 1: 3-142.

Institute of Medicine [IOM] (2000). Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. . Standing Committee on the Scientific Evaluation of Dietary Reference Intake, Institute of Medicine, National Academy Press, Washington D.C.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Litton Bionetics (1977). Mutagenic evaluation of compound FDA75-[redacted] choline chloride. FCC. Report No. PB-266 891. Mar. 1977.

MITI (1992). Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan. Edited by Chemicals Inspection & Testing Institute Japan, published by Japan Chemical Industry Ecology-Toxicology & Information Center. October 1992.

MOE Japan (1999a). Ministry of Environment. Acute toxicity study of choline chloride on the Orange killifish *Oryzias latipes*. Unpublished study. No. 1998-16.

MOE Japan (1999b). Ministry of Environment. Acute toxicity study of choline chloride on *Daphnia magna*. Unpublished study. No. 1998-14.

MOE Japan (1999c). Ministry of Environment. Acute toxicity study of choline chloride on the freshwater alga *Pseudokirchnerialla subcapitata*. Unpublished study. No. 1998-13.

MOE Japan (1999d). Ministry of Environment. Chronic toxicity study of choline chloride on the freshwater invertebrate *Daphnia magna*. Unpublished study. No. 1998-15.

OECD (2004). SIDS Initial Assessment Report for Choline chloride (CAS No. [redacted] UNEP Publications. Available at: http://www.inchem.org/documents/sids/sids/67481.pdf

Shivapurkar, N., Hoover, K.L., and Poirier, L.A. (1986). Effect of methionine and choline on liver tumor promotion by phenobarbital and DDT in diethylnitrosamine-initiated rats. Carcinogenesis 7: 547- 550.

Tunkel J., Howard, P.H., Boethling, R.S., Sitteler, W., and Loonen, H. (2000). Predicting ready biodegradability in the Japanese Ministry of international trade and industry test. Environ. Toxicol. Chem. 19: 2478-2485.

U.S. Environmental Protection Agency [EPA] (2016). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Zeisel, S.H., Story, D.C., Wurtman, R.J., and Brunengraber, H. (1980). Uptake of free choline by isolated perfused rat liver. Proc. Natl. Acad. Sci. USA 77(8): 4417-4419.

Zeisel, S.H., and Blusztajn, J.K. (1994). Choline and human nutrition. Ann. Rev. Nutr. 14: 269-296.

GUAR GUM

This dossier on guar gum (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the chemistry database PubChem. Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): disodium;[[[5-(6-aminopurin-9-yl)-3-hydroxyoxolan-2-yl]oxy-methoxyphosphoryl]oxy-oxidophosphoryl] hydrogen phosphate

CAS RN: [redacted]

Molecular weight: 535.15 g/mol; 200,000 to 300,000 daltons (Glickman, 1969)

Molecular formula: $C_{10}H_{14}N_5Na_2O_{12}P_3$

Synonyms: GU-052, guar flour, guaran, gum guar, slocose

SMILES:: COP(=O)(OC1C(CC(O1)N2C=NC3=C(N=CN=C32)N)O)OP(=O)([O-])OP(=O)(O)[O-].[Na+].[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Guar Gum

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Off-white to yellowish-white powder	-	PubChem
Vapour Pressure	Negligible	-	PubChem
Water Solubility	< 1 g/L @ 20°C (insoluble)	-	PubChem

III. ENVIRONMENTAL FATE PROPERTIES

Guar gum is a carbohydrate polymer consisting of D-mannose and D-galactose sugars from the guar plant or cluster bean. As a high molecular weight polysaccharide polymer, guar gum is expected to have a negligible vapour pressure. If released to air, a negligible vapour pressure indicates guar gum will exist solely in the particulate phase in the atmosphere. Particulate-phase guar gum will be removed from the atmosphere by wet and dry deposition. If released to soil, guar gum is expected to have no mobility since it is a polymer that binds strongly with soil particles. Volatilisation from moist soil surfaces is not expected to be an important fate process based upon a negligible Henry's Law constant. Likewise, guar gum is not expected to volatilise from dry soil surfaces based upon its vapour pressure. If released into water, guar gum is expected to adsorb to suspended solids and sediment (PubChem). Half-life data was not available.

Guar gum is expected to readily undergo microbial biodegradation in the environment (on the basis that it is a polysaccharide and expected to be readily biodegradable), and the potential to bioaccumulate in organisms is considered to be low (DoEE, 2017 and USEPA, 2005).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Guar gum exhibits very low acute toxicity by the oral route. It is non-irritating to the skin and minimally irritating to the eyes. Repeated dose toxicity studies in rats showed minimal toxicity from exposure to guar gum in the diet. Guar gum is not genotoxic or carcinogenic. Oral exposure to guar gum did not affect fertility in rats; nor was there any indication of developmental toxicity in either rats or mice.

NICNAS has assessed Guar Gum in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to human health[1]

B. Acute Toxicity

The oral LD_{50} in rats was reported to be 7,060 mg/kg (Graham *et al.*, 1981) [Kl. Score = 2].

C. Irritation

Guar gum is non-irritating to the skin and minimally irritating to the eyes (McCarty *et al.*, 1990). Nonetheless, ECHA warns that the substance may cause serious eye irritation.

D. Sensitisation

There were reports of workers sensitised to guar gum in a carpet-manufacturing plant. Immediate skin reactivity to guar gum was observed in 8 out of 162 employees, and 11 of 133 participants had serum IgE antibodies to guar gum. These findings are difficult to interpret since carbohydrates, such as guar gum, are generally not associated with allergenicity (Malo, 1990).

E. Repeated Dose Toxicity

<u>Oral</u>

Male and female Osborne-Mendel rats were given diets containing 0, 1, 2, 4, 7.5, or 15% guar gum for 91 days. The average daily intakes are: 0; 580; 1,187; 2,375; 4,561 and 10,301 mg/kg/day for males; and 0; 691; 1,362; 2,762; 5,770 and 13,433 mg/kg/day for females. There were no deaths during the study. Body weights were significantly decreased in the ≥1% females and the ≥7.5% males; biologically significant changes (>10%) were seen in the 7.5% females and the 15% males. Liver weights were decreased in the ≥1% dietary groups. Kidney weights were decreased in the ≥7.5% dietary groups and were borderline significant in the 4% group. The 15% group males had reduced bone marrow cellularity; although the level was within normal limits, several of the rats were at the lower end of the normal range.

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]2C+

The NOAEL for this study is 4% in the diet or 2,762 mg/kg/day based on reduced body weights in the female rats (Graham *et al.*, 1981) [Kl. Score = 2].

Male and female F344 rats and B6C3F_1 mice were given diets containing 0; 6,300; 12,500; 25,000; 50,000 or 100,000 ppm guar gum for 13 weeks. Mean body weights were decreased in the 100,000 ppm male rats and in the ≥50,000 ppm female mice. A dose-related decrease in feed consumption was observed for male and female rats; male and female mice were comparable or higher than that of controls. There were no compound-related clinical signs or histopathological effects. The NOAELs for this study are 50,000 and 25,000 ppm for rats and mice, respectively. Using the fraction of body weight that rats and mice consume per day as food (0.05 and 0.13, respectively; USEPA), the NOAELs corresponds to 2,500 mg/kg/day for rats and 3,250 mg/kg/day for mice (NTP, 1982) [Kl. Score = 2].

Male and female F344 rats and B6C3F_1 mice were given diets containing 0 ppm, 25,000 ppm or 50,000 ppm guar gum for 103 weeks. Mean body weights of the high-dose females were lower than those of the controls after week 20 for mice and week 40 for rats. No compound-related clinical signs or adverse effects on survival were observed. Feed consumption by dosed rats and mice of either sex was lower than that of controls. There were no non-neoplastic histopathological effects in either rats or mice that were treatment-related. The NOAEL for both rats and mice is 25,000 ppm. Using the fraction of body weight that rats and mice consume per day as food (0.05 and 0.13, respectively; USEPA), the NOAELs correspond to 1,250 mg/kg/day for rats and 3,250 mg/kg/day for mice (NTP, 1982) [Kl. Score = 2].

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

Guar gum was not mutagenic to *S. typhimurium* strains TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535, TA 1537, and TA1538 in the presence or absence of metabolic activation (Zeiger *et al.*, 1992) [Kl. Score = 2].

In Vivo Studies

Guar gum was inactive in a rat bone marrow cytogenetic assay at doses up to 5,000 mg/kg (Johnson *et al.*, 2015) Kl. Score = 4].

In a rat dominant lethal mutation test, rats were dosed by oral gavage with either a single or multiple doses of up to 5,000 mg/kg guar gum. There was no indication of a mutagenic effect by guar gum (Lee *et al.*, 1983) [Kl. Score = 2].

G. Carcinogenicity

Male and female F344 rats were given diets containing 0 ppm, 25,000 ppm or 50,000 ppm guar gum for 103 weeks in an NTP chronic bioassay. There were increased incidences of

adenomas of the pituitary in male rats and pheochromocytomas of the adrenal medulla in female rats that were statistically significant, but these differences were considered to be unrelated to guar gum administration. When pituitary adenomas or carcinomas and when pheochromocytomas or malignant pheochromocytomas were combined, the statistical differences disappeared. NTP concluded that, under conditions of this bioassay, guar gum was not carcinogenic for F344 rats (NTP, 1982) [Kl. Score = 2].

Male and female $B6C3F_1$ mice were given diets containing 0 ppm, 25,000 ppm or 50,000 ppm guar gum for 103 weeks in an NTP chronic bioassay. Hepatocellular carcinomas occurred in treated male mice at incidences that were significantly lower than that in controls. The combined incidence of male mice with either hepatocellular adenomas or carcinomas was also significantly lower in the high-dose group. NTP concluded that, under conditions of this bioassay, guar gum was not carcinogenic for $B6C3F_1$ mice (NTP, 1982) [Kl. Score = 2].

H. Reproductive Toxicity

Oral

Male and female Osborne-Mendel rats were fed diets containing 0, 1, 3, 4, 7.5, or 15% guar gum for 13 weeks before mating, during mating and throughout gestation. The daily intakes for the female rats during gestation were 0; 700; 1,400; 2,700; 5,200 or 11,800 mg/kg/day. Fertility was unaffected by treatment. There were slightly fewer corpora lutea and implantations in the 15% dietary group, but implantation efficiency was unaffected. The NOAEL for reproductive toxicity is 5,200 mg/kg/day (Collins *et al.*, 1987) [Kl. Score = 2].

I. Developmental Toxicity

Oral

Male and female Osborne-Mendel rats were fed diets containing 0, 1, 3, 4, 7.5, or 15% guar gum for 13 weeks before mating, during mating and throughout gestation. The daily intake for the female rats during gestation were 0; 700; 1,400; 2,700; 5,200 or 11,800 mg/kg/day. There were no deaths during the study. In the 15% group, the number of viable foetuses per litter were slightly reduced but was not statistically significantly different from controls. The authors indicated that the reduction may have been an effect of the decreased number of corpora lutea because the number of resorptions was unaffected in this treatment group. There was no treatment-related effect on foetal development or sex distribution, and there were no teratogenic effects (Collins *et al.*, 1987) [Kl. Score = 2].

Pregnant female rats were dosed by oral gavage with 0, 9, 42, 200 or 900 mg/kg guar gum on GD 6 to 15. There was no maternal or developmental toxicity at any dose level. The NOAEL for maternal and developmental toxicity is 900 mg/kg/day (FDRL, 1973) [Kl. Score = 2].

Pregnant female CD-1 mice were dosed by oral gavage with 0, 8, 37, 170, or 800 mg/kg guar gum on GD 6 to 15. A significant number of deaths (6 out of 29) occurred in the 800 mg/kg dose group. There were indications of maternal toxicity in the surviving high-dose dams. There was no developmental toxicity at any dose level. The NOAELs for maternal and developmental toxicity are 170 and 800 mg/kg/day, respectively (FDRL, 1973) [Kl. Score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for guar gum follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

In a two-year NTP chronic bioassay, female rats and mice given 50,000 ppm guar gum in their feed had lower body weights. There were no treatment-related non-neoplastic lesions in either rats or mice. The NOAEL for this study is 25,000 ppm for rats and mice, which corresponds to 1,250 mg/kg/day for rats and 3,250 mg/kg/day for mice.

The NOAEL of 1,250 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

- UF_A (interspecies variability) = 10
- UF_H (intraspecies variability) = 10
- UF_L (LOAEL to NOAEL) = 1
- UF_{Sub} (subchronic to chronic) = 1
- UF_D (database uncertainty) = 1
- Oral RfD = 1,250/(10 x 10 x 1 x 1 x 1) = 1,250/100 = 13 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

- Human weight = 70 kg (ADWG, 2021)
- Proportion of water consumed = 10% (ADWG, 2021)
- Volume of water consumed = 2L (ADWG, 2021)
- Drinking water guidance value = (13 x 70 x 0.1)/2 = 46 mg/L

B. Cancer

Guar gum was not carcinogenic to rats or mice in two-year dietary studies. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Guar gum does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Guar gum is a polysaccharide polymer. It has low acute toxicity concern for fish but exhibits moderate acute toxicity to invertebrates (*Daphnia*).

B. Aquatic Toxicity

Acute Studies

The 96-hour LC_{50} for *Oncorhynchus mykiss* is 218 mg/L (Biesinger *et al.*, 1976) [Kl. Score = 2].

The 48-hour and 96-hour LC_{50} values for *Daphnia magna* are 42 mg/L and <6.2 mg/L, respectively (Biesinger *et al.*, 1976) [Kl. Score = 2].

Chronic Studies

No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for guar gum follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for two trophic levels. The acute LC_{50} values are available for fish (218 mg/L) and *Daphnia* (<6.2 mg/L). No chronic studies are available. On the basis that the data consists of acute studies from two trophic levels, an assessment factor of 1,000 has been applied to the lowest reported LC_{50} value of 6.2 mg/L for *Daphnia*. The $PNEC_{water}$ is 0.006 mg/L.

PNEC sediment

No experimental toxicity data on sediment organisms are available. The K_{ow} and K_{oc} of guar gum cannot be calculated using EPI Suite because the molecular weight of guar gum greatly exceeds the limit of 1,000. Thus, the equilibrium partition method cannot be used to determine a $PNEC_{sediment}$ and the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No experimental toxicity data on soil organisms are available. The K_{ow} and K_{oc} of guar gum cannot be calculated using EPI Suite because the molecular weight of guar gum greatly exceeds the limit of 1,000. Thus, the equilibrium partition method cannot be used to determine a $PNEC_{soil}$ and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU Reach Criteria methodology (DEWHA, 2009; ECHA, 2008).

Guar gum is a naturally occurring polysaccharide from the guar plant or cluster bean; it expected to be readily biodegradable. Thus it is not expected to meet the screening criteria for persistence.

The potential to bioaccumulate in organisms is considered to be low. Thus guar gum is not expected to meet the criteria for bioaccumulation.

There are no adequate chronic aquatic toxicity studies available on guar gum. The acute LC_{50} values for guar gum are >1 mg/L in fish and invertebrates. Therefore, guar gum does not meet the screening criteria for toxicity.

The overall conclusion is that guar gum is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Aquatic Toxicity Category 2

B. Labelling

Warning!

According to the classification provided by companies to ECHA in CLP notifications, this substance causes serious eye irritation.

C. Pictogram

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Remove contaminated clothing. Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

Notes to Physician

May cause asthma-like (reactive airways) symptoms.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus for fire fighting.

C. Accidental Release Measures

Personal Precautions

Avoid dust formation.

Environmental Precautions

No special environmental precautions required.

Steps to be Taken if Material is Released or Spilled

Sweep up and dispose in suitable, closed containers.

D. Storage And Handling

General Handling

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard specifically for guar gum.

Engineering Controls

Ensure adequate ventilation.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Handle with gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Guar gum is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Biesinger, K.E., Lemke, A.E., Smith, W.E., and Tyo, R.M. (1976). Comparative toxicity of polyelectrolytes to selected aquatic animals. J. Water Pollut. Control Fed. 48: 183-187; cited in U.S. EPA ECOTOX database.

Collins, T.F.X., Welsh, J.J., Black, T.N., Graham, S.L., and O'Donnell, M.W., Jr. (1987). Study of the teratogenic potential of guar gum. Food Chem. Toxicol. 25: 807-814.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Food and Drug Research Laboratories, Inc. [FDRL]. (1973). Teratologic evaluation of FDA 71-16 (guar gum) in mice, rats, hamsters, and rabbits. Final report prepared under DHEW contract No. FDA 71-260. Maspeth, NY. NTIS No. PB-223-819/4; cited in CIR (2015).

Glickman M. (1969). Gum technology in the Food Industry, pp. 590, Academic Press, New York; cited in Yoon *et al.* (1998).

Graham, S.L., Arnold, A., Kasza, L., Ruffin, G.E., Jackson, R.C., Watkins, T.L., and Graham, C.H. (1981). Subchronic effects of guar gum in rats. Fd. Cosmet. Toxicol. 19: 287-290.

Johnson, W., Jr., Heldreth, B., Bergfeld, W.F., Belsito, D.V., Hill, R.A., Klaassen, C.D., Liebler, D.C., Marks, J.G., Jr., Shank, R.C., Slaga, T.J., Snyder, P.W., and Andersen, F.A. (2015). Safety assessment of galactomannans as used in cosmetics. Int. J. Toxicol. 34(Suppl. 1): 35S-65S.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Lee, W.R., Abrahamson, S., Valencia, R., Von Halle, E.S., Wuergler, F.E., and Zimmering, S. (1983). The sex-linked recessive lethal test for mutagenesis in *Drosophila melanogaster*. A report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat. Res. 123: 183-279.

Malo, J.L., Cartier, A., L'Archevêque, J., Ghezzo, H., Soucy, F., Somers, J., and Dolovich, J. (1990). Prevalence of occupational asthma and immunologic sensitization to guar gum among employees at a carpet-manufacturing plant. J. Allergy Clin. Immunol. 86: 562-569.

McCarty, J.D., Weiner, M., Freeman, C., Aguinaldo, E.R., and Fletcher, M.J. (1990). Primary skin and ocular irritation studies on five food additive plant gums. J. Am. Coll. Toxicol. 1(1): 50-51.

NTP. (1982). NTP Technical Report on the Carcinogenesis Bioassay of Guar Gum (CAS No. [redacted] in F344 Rats and B6C3F_1 Mice (Feed Study), National Toxicology Program, Research Triangle Park, NC.

PubChem. PubChem open chemistry database: https://pubchem.ncbi.nlm.nih.gov

United States Environmental Protection Agency [USEPA]. (2005). Science Assessment for Hydroxypropyl Guar Gum, Lower Risk Pesticide Chemical Focus Group, Office of Prevention, Pesticides and Toxic Substances, US Environmental Protection Agency. Accessed: http://www.epa.gov/opprd001/inerts/hydroxypropyl.pdf

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1992). Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen. 21: 2-141.

ULEXITE

This dossier on ulexite presents the most critical studies pertinent to the risk assessment of ulexite in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Sodium-calcium pentaborate octahydrate

CAS RN: [redacted]

Molecular formula: $(NaCaB_5O_6(OH)_6 \bullet 5H_2O)$

Molecular weight: 405 g/mol

Synonyms: Ulexite; sodium-calcium pentaborate octahydrate

Smiles: B1(OB2OB(O1)OB(O2)OB([O-])[O-])[O-].O.O.O.O.O.O.O.O.[Na+].[Ca+2]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Commercially Available Ulexite

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, granular, ground or powder form	4	Etimine USA, Inc. (2016)
Melting Point	870°C	4	Etimine USA, Inc. (2016)
Boiling Point	Not Applicable	-	-
Bulk Density	1,410 to 1,500 kg/m^3	4	Etimine USA, Inc. (2016)
Water solubility	26.67% as dissolved Ulexite @ 25°C by weight of solution	4	American Borate Company (2016)

Ulexite is a naturally-occurring mineral that is slightly soluble in water. Limited measured data are available for ulexite. In a study investigating the relative rates of boron from soluble and controlled-release boron fertilizers, ulexite showed releases of boron of 20% in just under 10 weeks; 40% in approximately 25 weeks; 60% by 40 weeks; and 80% by 60 weeks (Broschat, 2008). In the environment, borates will dissociate and/or hydrolyse to release boron as boric acid [$B(OH)_3$ (also formulated as H_3BO_3)] and/or borate anions. Therefore, the information presented within this dossier is for boron (CAS No. [redacted]

III. ENVIRONMENTAL FATE PROPERTIES

Boron is found almost exclusively in the environment in the form of boron-oxygen compounds, which are often referred to as borates. In the environment, borates and compounds of boric acid will dissociate and/or hydrolyse to form the same boron species. For example, when borax dissolves in dilute solutions, it dissociates into Na+ ions and the tetraborate anion ($B_4O_5(OH)_4^{2-}$). Boric acid ($B(OH)_3$) is formed following acid catalysed hydrolysis of the tetraborate anion. Under alkaline conditions, dilute solutions of the tetraborate anion depolymerise rapidly to the mononuclear borate anion ($B(OH)_4^-$) (DoEE, 2017).

Boron is an inorganic, elemental compound and can therefore not be biodegraded by micro-organisms or other biotic-related processes (ECHA).

The WHO (1998) review of boron noted that highly water-soluble materials are unlikely to bioaccumulate to any significant degree and that borate species are all present essentially as undissociated and highly soluble boric acid at neutral pH. The available data indicate that both experimental data and field observations support the interpretation that borates are not significantly bioaccumulated (ECHA).

Bioconcentration factors of < 0.1 to 10.5 L/kg have been reported from laboratory tests of fish and oysters (Thompson et al. 1976). Saiki et al. (1993) measured boron levels in aquatic food chains and observed the highest concentrations of boron in detritus and filamentous algae. Invertebrates and fish had lower concentrations, indicating that bioaccumulation was not occurring. Based on these data, boron does not bioaccumulate in the aquatic environment (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

No information is available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

No values were derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Ulexite does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

There are no mammalian or aquatic toxicity studies on ulexite. Toxicity for boron is provided within this section.

Boron is of a low toxicity concern to aquatic organisms. Although boron is required by plants at low concentrations, at high concentrations it is toxic. In Australia, it is generally accepted that boron toxicity will pose a risk to terrestrial plants when soil concentrations exceed 15 mg/kg of extractable boron. The phytotoxicity of boron is dependent on the plant species and soil type (DoEE, 2017).

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies on boron.

Table 2: Acute Aquatic Toxicity Studies on Boron[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
P. promelas	4-day LC_{50}	79.7 mg/B/L	2	ECHA
Freshwater invertebrates	48-hr LC_{50}	64 to >544 mg/B/L	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	52.4 mg/B/L	2	ECHA

1 – CAS No. [redacted]

Chronic Studies

Table 3 lists the results of chronic aquatic toxicity studies on boron.

Table 3: Chronic Aquatic Toxicity Studies on Boron[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Micropterus salmoides	4d-EC_{10}	36.8 mg/B/L	2	ECHA
Oncorhynchus mykiss	long term NOEC-LOEC	19.2. mg/B/L	2	ECHA
Brachydanio rerio	long term NOEC-LOEC	36.mg/B/L	2	ECHA
Pimephales promelas	long term NOEC-LOEC	21.3 mg/B/L	2	ECHA
Daphnia magna	NOEC	13.9 mg/B/L	2	ECHA
Hyalella Azteca	NOEC	6.3 mg/B/L	2	ECHA
Chironomus riparius	NOEC	20.1 mg/B/L	2	ECHA
Brachionus calyciflorus	NOEC	24.6 mg/B/L	2	ECHA
Lampsilis siliquoidea	NOEC	30 mg/B/L	2	ECHA

1 – CAS No. [redacted] for boron

ANZG has developed a water quality guideline for boron (ANZG, 2021). Very high reliability default guideline values (DGVs) for (dissolved) boron in freshwater were derived from 22 chronic (long-term) toxicity data, comprising eight fish, two amphibians, three crustaceans,

one bivalve, three macrophytes, one green microalga, three diatoms and one blue–green alga. The DGVs for 99, 95, 90 and 80% species protection are 340 µg/L, 940 µg/L, 1,500 µg/L and 2,500 µg/L, respectively. The 95% species protection level for boron in freshwater (940 µg/L) is recommended for adoption in the assessment of slightly-to-moderately disturbed ecosystems.

C. Terrestrial Toxicity

Relevant and reliable chronic no-effects values were identified for 39 terrestrial species or microbial processes. No-effect levels for dissolved boron ranged between 7.2 mg B/kg soil dw and 86.7 mg B/kg soil dw. The plant *Zea mays* was the most sensitive trophic level. The least sensitive species was the nematode *C.elegans*. A Species Sensitivity Distribution (SSD) has been developed for the assessment of boron in the terrestrial compartment, using the reliable species-specific chronic toxicity effect levels that have been generated in various research studies (ECHA) [KI Score = 2].

D. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Ulexite is a naturally-occurring mineral. For the purposes of this PBT assessment, the persistence criteria is not considered applicable to this inorganic substance.

Bioaccumulation is not applicable to naturally-occurring minerals, such as ulexite. Although boron is slowly released from ulexite, limited data indicate that bioaccumulation is not significant in aquatic and terrestrial food chains. Thus, it does not meet the criteria for bioaccumulation.

There are no aquatic toxicity studies on ulexite. The lowest chronic toxicity value for boron is > 0.1 mg/L. The acute E(L)C_{50} values for boron is > 1 mg/L. Thus, based on boron, ulexite does not meet the criteria for toxicity.

Therefore, ulexite is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

GHS07, GHS08

B. Labelling

Warning!

Danger!

According to the classification provided by companies to ECHA in CLP notifications this substance may damage fertility or the unborn child and causes serious eye irritation.

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. If symptoms persist, seek medical advice.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Ulexite is non-flammable, combustible, or explosive. It is a flame retardant.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Ulexite is slightly water-soluble; at high concentrations it may cause damage to trees or vegetation by root absorption. Do not flush to drains.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for ulexite.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Ulexite is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

American Borate Company. (2016). Technical specifications on Ulexite 45 micron ground. Available at: http://www.americanborate.com/media/19191/ulexite-[redacted]2016-technical-specification.pdf.

ANZG. (2021). Toxicant default guideline values for aquatic ecosystem protection: Boron in freshwater. Australian and New Zealand Guidelines for Fresh and Marine Water Quality. CC BY 4.0. Australian and New Zealand Governments and Australian state and territory governments, Canberra, ACT, Australia.

Broschat, T.K. (2008). Release rates of soluble and controlled-release boron fertilizers. HorTechnology 18(3): 471-474.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DoEE. (2017). Environmental risks associated with surface handling of chemicals used in coal seam gas extraction in Australia, Project report Appendices A, B, C, D, F, and G prepared by the Chemicals and Biotechnology Assessments Section (CBAS) in the Department of the Environment and Energy as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

Etimine USA, Inc. (2016). Safety Data Sheet on Ulexite. Available at: http://www.etimineusa.com/sites/etimineusa.com/files/SDS%20-%20Ulexite%202016%20-%202018_0.pdf

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Saiki, M.J., Jennings, M.R., and Brumbaugh, W.B. (1993). Boron, Molybdenum, and Selenium in aquatic food chains from the Lower San Joaquin River and its tributaries, California. Archives of Environmental Contamination and Toxiciology. 24, 307-319.

Thompson et al. (1976). Toxicity, uptake and survey studies of boron in the marine environment. Water Research Vol. 10. pp 869 to 875, 1976.

WHO. (1998). World Health Organisation, Environmental health criteria 204 – boron, viewed 26 August 2015. http://www.inchem.org/documents/ehc/ehc/ehc204.htm.

ETHYLENE GLYCOL

This dossier on ethylene glycol presents the most critical studies pertinent to the risk assessment of ethylene glycol in its use in hydraulic fracturing fluids. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Ethane-1,2-diol

CAS RN: [redacted]

Molecular formula: $C_2H_6O_2$ ($HOCH_2CH_2OH$)

Molecular weight: 62.07 g/mol

Synonyms: Ethylene glycol; ethane-1,2-diol; 1,2-ethanediol, 2-hydroxyethanol; monoethylene glycol; MEG; glycol alcohol; EG

SMILES: C(CO)O

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Ethylene Glycol

Property	Value	Klimisch score	Reference
Physical state at 20oC and 101.3 kPa	Colourless and odourless syrupy liquid	2	ECHA
Melting Point	-13°C @ 101.3 kPa	2	ECHA
Boiling Point	197.4°C @ 101.3 kPa	2	ECHA
Density	1110 kg/m3@ 20°C	2	ECHA
Vapour Pressure	12.3 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-1.36 (calculated) @ 25°C	2	ECHA
Water Solubility	1000 g/L @ 20°C	2	ECHA
Flash Point	111°C	2	ECHA
Auto flammability	398°C	2	ECHA
Viscosity	16.1 mPa s @ 25°C	2	ECHA
Henry's Law Constant	0.133 @ 25°C (QSAR)	2	ECHA

III. ENVIRONMENTAL FATE SUMMARY

A. Summary

Ethylene glycol is readily biodegradable, and it is not expected to bioaccumulate. Ethylene glycol has low potential to adsorb to soil and sediment.

B. Biodegradation

Ethylene glycol was readily biodegradable in an OECD 301A test. After 10 days, degradation was 90-100% (ECHA) [Kl. score = 1]. There was 97% degradation after 20 days in a BOD test; and 96% degradation after 28 days in an OECD 301D test (Waggy et al., 1994; OECD, 2004a,b) [Kl. score = 2]. If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

The aerobic degradation of ethylene glycol was measured from grab river water samples at 4, 8 and 20°C. At 20°C, ethylene glycol was completely degraded in three days in all river waters tested; at 8°C, degradation was complete within 14 days. Degradation at 4°C was substantially slower, with degradation of < 20% after 14 days in river samples with limited suspended matter and a starting concentration of 10 mg/L (Evans and David, 1974).

C. Environmental Distribution

No experimental data are available for ethylene glycol. Using KOCWIN in EPISuite™ (USEPA, 2017), the estimated K_{oc} values from the molecular connectivity index (MCI) and from the log K_{ow} are 1 and 0.2239 L/kg, respectively.

Based upon these K_{oc} values, if released to soil, ethylene glycol is expected to have low potential for adsorption and a high potential for mobility. If released to water, based on its K_{oc} and high water solubility values, ethylene glycol is likely to remain in water and not adsorb to sediment. From the water surface, the substance will not evaporate into the atmosphere (ECHA).

D. Bioaccumulation

The calculated log K_{ow} for ethylene glycol is -1.36 (ECHA). The BCF for ethylene glycol in golden ide (*Leuciscus idus melanotus*) after three days of exposure was determined to be 10 (Freitag *et al.*, 1985). Bioaccumulation is not to be expected.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Following acute ingestion of ethylene glycol, the critical effects in humans in three subsequent stages are central nervous system toxicity, metabolic acidosis and kidney toxicity. The lethal effects of ethylene glycol in human adults occur at oral doses of $\geq$ 1,600 mg/kg. Ethylene glycol is not a skin irritant or a skin sensitiser in laboratory animals. In humans, ethylene glycol may cause skin irritation; there is also a low potential for skin sensitisation. It is not an eye irritant. The kidney is the primary target organ from repeated exposures. The proposed mode-of-action (MOA) for the kidney damage involves the formation of a precipitate or crystals from the ethylene glycol metabolite oxalic acid with calcium in the urine. Ethylene glycol is not genotoxic or carcinogenic to rodents. Ethylene glycol did not affect fertility in animal studies, but it did cause developmental effects. In rodents, the

developmental effects caused by oral doses of ethylene glycol include teratogenic effects (craniofacial and axial-skeletal malformations and variations). In contrast, no developmental toxicity was seen in rabbit studies. The relevant metabolite for the developmental toxicity seen in rodent, but not rabbit, studies appears to be glycolic acid. This metabolite can be reached at higher concentrations in rats than in rabbits. Based on a physiologically-based pharmacokinetic (PBPK) model for ethylene glycol, humans are unlikely to achieve blood levels of glycolic acid necessary for developmental toxicity.

B. Metabolism

Ethylene glycol is almost completely absorbed in laboratory animals by the oral route (OECD, 2004a; Frantz et al., 1996a). A range of 1-51% of ethylene glycol is absorbed by the dermal route based on *in vivo* studies in rodents (Frantz et al., 1996a,b).

The main metabolic pathway for metabolism of ethylene glycol is oxidation via alcohol dehydrogenases and aldehyde dehydrogenases. The main metabolites of ethylene glycol are carbon dioxide, oxalic acid and glycolic acid (OECD, 2004a).

The relevant metabolite for the repeated dose toxicity studies is oxalic acid, which is slowly transported from the liver to the kidneys, where is forms calcium-oxalate crystals (Corley et al., 2005a).

The relevant metabolite for the developmental toxicity seen in rodent, but not rabbit, studies appears to be glycolic acid. This metabolite can be reached at higher concentrations in rats than in rabbits (Carney et al., 1998).

A physiologically-based pharmacokinetic (PBPK) model has been developed for ethylene glycol. When internal dose surrogates were compared in rats and humans over a wide range of exposures, it has been concluded that humans are unlikely to achieve blood levels of glycolic acid necessary for developmental toxicity (Corley et al., 2005b).

C. Acute Toxicity

The oral LD_{50} in rats was reported to be 7,712 mg/kg (ECHA) [Kl. score = 2]. The 6-hour inhalation LC_{50} value for male and female rats was > 2.5 mg/L (Tyl et al., 1995a) [Kl. score = 2]. The dermal LD_{50} for male and female mice is > 3,500 mg/kg (Tyl et al., 1995b) [Kl. score = 2].

Following acute ingestion of ethylene glycol, the critical effects in humans in three subsequent stages are central nervous system toxicity, metabolic acidosis and kidney toxicity (ECHA). The lethal effects of ethylene glycol in human adults occur at oral doses of $\geq$ 1,600 mg/kg (Hess et al., 2004).

D. Irritation

Application of 0.5 mL of ethylene glycol to the skin of rabbits for 23 hours under occlusive conditions was not irritating (Guillot et al., 1982) [Kl. score = 2].

In a Human Repeated Insult Patch Test (HRIPT), ethylene glycol was applied to the skin for 24 hours under occlusive or semi-occlusive conditions for nine times during the induction phase. The induction phase was followed by a rest period of two weeks, followed by a 24-hour challenge on the sixth week of the study. Erythema was seen in a small proportion of the 401 subjects that completed the study. Under the conditions of the study, three subjects had reactions on challenge that were

indicative of possible irritation and/or low-level sensitisation. These three subjects were re-challenged under occlusive or semi-occlusive conditions one or two weeks later. Re-challenge testing was negative for one subject, but the other two subjects were judged to have irritant reactions to ethylene glycol since their reactions were similar or lesser compared to the skin responses observed during the induction period, and the skin reactions were not greater over time after the challenge or re-challenge (ECHA).

Instillation of 0.05 mL of ethylene glycol into the eyes of rabbits was not irritating (ECHA) [Kl. score = 2].

E. Sensitisation

Ethylene glycol was not a skin sensitiser to guinea pigs in a Magnusson and Kligman test (Kurihara et al., 1996) [Kl. score = 2]. In a HRIPT, ethylene glycol was considered to have a low potential for dermal sensitisation in humans (ECHA).

F. Repeated Dose Toxicity

Oral

Male and female Fischer 344 rats were given in their feed 0, 0.32, 0.63, 1.25, 2.5 or 5% ethylene glycol for 13 weeks. Mortality was seen in the 5% males, but not in females. Mean weight gain was significantly decreased in the 2.5 and 5% males; there was no significant differences in female rats. Feed consumption was similar across all groups. A significant increase was seen in the left kidney weight in the 2.5 and 5% dose groups (both sexes); this was not seen in the right kidneys. Mean thymus ratio to terminal body weight was significantly decreased in the 5% males. Serum urea nitrogen levels were significantly increased in the 2.5 and 5% males, and significantly increased in the ≥ 0.32% females. Creatinine levels were decreased in the 0.32% groups and significantly increased in the 2.5 and 5% groups. The 2.5% and 5% male rats had kidneys that were rough, granular and/or pitted appearances. The 5% females showed nephrosis, and the 5% males had clusters of crystals in the brain. The NOAEL for this study is 1.25%, which was estimated to be 600 to 1,000 mg/kg/day (Melnick, 1984) [Kl. score = 2]

Male and female Sprague Dawley rats were given in their drinking water ethylene glycol for 90 days. The concentrations for females were 0, 0.5, 1.0, 2.0 or 4.0% (0, 597, 1,145, 3,087 or 5,744 mg/kg/day). The concentrations for males were 0, 0.25, 0.5, 1.0 or 2.0% (0, 205, 407, 947 or 3,134 mg/kg/day). In the 4% groups, there was mortality and decreased body weights (males only). Significant organ weights were noted only in males. Kidney weights were significantly increased in the 1% and 2% males; heart, liver and lung were significantly decreased in the 2% males. The 4% males also had a significant increase in the brain and gonads relative to body weights. Leukocyte levels were significantly decreased in the 0.5, 2 and 4% females, but not in males. Significant differences were noted in LDH, creatinine, ALT, calcium and glucose in the 1% males; and phosphorus, BUN and creatinine in the 2% males. There were significant increases in phosphorus in the 1% females and glucose in the 0.5 and 4% females. Kidney lesions were seen in the ≥ 2% females and in the ≥ 1% males, with the lesions more prominent in males than in females. The kidney changes consisted of tubular dilation, tubular degeneration, acute inflammation, birefringent crystals in tubules and pelvic epithelium. The NOAEL for this study is 407 mg/kg/day for males. The LOAEL for females is 597 mg/kg/day; a NOAEL was not established (Robinson et al., 1990) [Kl. score = 2]

Male and female B6C3F$_1$ mice were given in their feed 0, 0.32, 0.63, 1.25, 2.5 or 5.0% ethylene glycol for 13 weeks. There was no mortality and no treatment-related effect on mean weight gain and feed consumption. Organ/body weight ratios were similar across all groups. Serum urea nitrogen and creatinine levels were unaffected. Kidney effects were seen in the male, but not female, mice. Kidney lesions were observed in half of the 5% male mice and one mouse in the 2.5% dose level. Lesions were tubular dilation, cytoplasmic vacuolisation and regenerative hyperplasia of tubular cells. There was no evidence of crystal formation in the tubules. These changes were focal, randomly distributed and of minimal to mild severity. Hyaline degenerative of the liver was present in the centrilobular hepatocytes in all of the 2.5% and 5% males. These cells showed cytoplasmic accumulations of non bifringent, eosinophilic (hyaline), globular or crystalline material which resembled erythrocytes in size, shape and tinctorial properties. The NOAEL for this study is 1.25%, which was estimated to be 600 to 1,000 mg/kg/day (Melnick, 1984) [Kl. score = 2].

Male Fischer 344 and Wistar rats were given in their feed 0, 150, 500 or 1,000 mg/kg ethylene glycol for 16 weeks. At 1000 mg/kg, the following effects were seen: mortality in Wistar strain (2/10) with prior clinical observations of emaciation and dermal atonia and macroscopic findings of changes in kidneys (pale, calculi) and small seminal vesicles in these animals; mean body weight losses, lower mean body weights and mean cumulative body weight changes in Wistar strain (weeks 2 – 16); lower mean food consumption in Wistar strain; higher mean water consumption in both F344 and Wistar strains; lower mean specific gravity and higher mean total urine volume in both F344 and Wistar strains; macroscopic findings of pale kidneys, presence of calculi, rough surface and dilated pelvis; higher mean absolute and relative kidney weights in both F344 and Wistar strains; renal macroscopic findings of crystal nephropathy in Wistar and F-344 rats, with more severe nephropathy in Wistar strain than in the F344 strain. At 500 mg/kg, the following effects were seen: lower mean body weights (study weeks 3, 6-8 and 10-12) and mean cumulative body weight changes in the Wistar strain throughout the study with slightly lower mean food consumption throughout the study; higher mean water consumption in the Wistar strain; lower mean urine specific gravity and higher mean total urine volume in the Wistar strain; macroscopic findings in the Wistar strain consisting of predominantly pale kidneys, presence of calculi, rough surface and dilated pelvis; higher mean absolute and relative kidney weight in the Wistar strain; renal macroscopic findings of crystal nephropathy in Wistar and F-344 strains, with more severe nephropathy in the Wistar strain than in the F344 strain. The NOAEL in both the F344 and Wistar rats is 150 mg/kg/day (Cruzan et al., 2004) [Kl. score = 2].

Male Wistar rats were given in their feed 0, 50, 150, 300 or 400 mg/kg ethylene glycol for 12 months. There was mortality in the 300 and 400 mg/kg dose groups (5/20 and 4/20, respectively); the remaining 400 mg/kg animals were euthanised early (Day 203) due to excessive weight loss. The 300 mg/kg animals had increased water consumption and urine volume with decreased specific gravity, most likely due to osmotic diuresis. Calculi (calcium oxalate crystals) were found in the bladder and kidney pelvis in the ≥ 300 mg/kg animals. The ≥ 300 mg/kg rats that died prematurely had transitional cell hyperplasia with inflammation and haemorrhage of the bladder wall. Crystal nephropathy (basophilic foci, tubule or pelvic dilatation, birefringent crystals in the pelvic fornix, or transitional cell hyperplasia) was seen in all of the 400 mg/kg and most of the 300 mg/kg rats. These effects were not seen in the 50 or 150 mg/kg rats. Kidney oxalate levels, the metabolite responsible for the kidney toxicity, was not increased in the 50 and 150 mg/kg animals compared to the controls. The NOAEL for this study is 150 mg/kg/day (Corley et al., 2005) [Kl. score = 1].

Male and female Sprague-Dawley rats were given in their feed 0, 0.1, 0.2, 0.5, 1.0 or 4.0% ethylene glycol for two years. There was significant reduction in growth in the 4% males after week 16, and in the 1% males after week 70. The 4% females did not gain any weight past the first year of the study. Water consumption was double that of the controls in the 4% males that initiated soon after the

start of the study. The 1% males had significant increases in water consumption after 6 months and some increase was observed in the 0.5% males. Females only showed increased water consumption in the 4% group. There was 100% mortality in the 1 and 4% males, while mortality of additional dose levels were below that of the controls. There was 100% mortality in the 4% females, while the 1% females were similar to the controls; the 0.1, 0.2 and 0.5% females were increased compared to the controls. Since the 1 and 4% males and the 4% females all died before the study termination date, there are no data for these groups on terminal organ weight. For males, the terminal organ weights were decreased in all dose levels compared to the controls. For females, the organ weights were similar to the controls. The 1 and 4% males and females had kidneys with stones and crystals. The NOAEL for this study is 0.2% (data was insufficient to calculate the dose) (Blood, 1965) [Kl. score = 2].

Male and female Fischer 344 rats were given in their feed 0, 40, 200 or 1,000 mg/kg ethylene glycol for 24 months. There were numerous adverse effects in the 1,000 mg/kg males and, to a lesser degree, in the 1,000 mg/kg females. The most remarkable effect was the production of urinary calculi in the kidneys, ureters and urinary bladders of the 1,000 mg/kg males, along with the presence of high levels of calcium oxalate in the urine. Increased incidences of tubular cell hyperplasia, tubular dilation, peritubular nephritis and focal granulomatous nephritis occurred in the 1,000 mg/kg males. Other significant findings in these males were markedly lower body weight gain, increased absolute and relative kidney weights, decreased absolute and relative liver weights, various hematopoietic changes and increased water consumption (likely a result of impaired kidney function). Histopathological changes in the 1,000 mg/kg males were mineralisation of the heart, lungs, stomach and vas deferens being the most noteworthy. The various adverse effects in these males resulted in reduced survival; there was increased mortality which became apparent by 8 months, with all males in this group died by month 16. Although calcium oxalate crystals were found in the urine of the 1,000 mg/kg females, no urinary calculi were seen. Absolute and relative kidney weights were increased in these rats. The most significant histopathologic finding in the 1,000 mg/kg females was fatty metamorphosis of the liver. There were transient changes in organ weights, erythroid parameters, water consumption rates and urine specific gravity in the 200 and 40 mg/kg rats; these effects were considered to be statistical artifacts attributable to chance. Focal soft mineralisation was observed in certain organs of the 200 and 40 mg/kg rats, which were considered to be the result of altered calcium metabolism associated with ingestion of ethylene glycol. The NOAEL for this study is considered to be 200 mg/kg/day (DePass et al., 1986a; ECHA) [Kl. score = 2].

Male and female B6C3F_1 mice were given in their feed 0, 6,250 ppm (males only), 12,500 and 25,000 ppm (males and females) or 50,000 ppm (females only) for 103 weeks. These concentrations are approximately equivalent to 0, 1,500, 3,000, 6,000 or 12,000 mg/kg/day. Survival, mean body weights and feed consumption was similar across all groups. There were no treatment-related clinical signs of toxicity. Liver lesions (males only) and arterial hyperplasia (females only) were observed at 12,500 ppm, but no adverse effects were observed at 6,250 ppm. The NOAEL for this study is 6,250 ppm in males, which corresponds to 1,500 mg/kg/day (NTP, 1993) [Kl. score = 2].

Inhalation

No studies are available.

Dermal

No studies in rodents or rabbits are available.

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on ethylene glycol are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Ethylene Glycol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	1	ECHA
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	+/-	-	2	McGregor et al. (1991)
Chromosomal aberration (CHO cells)	-	-	2	ECHA

*+, positive; -, negative

In Vivo Studies

A dominant lethal study was conducted in F344 rats given 0, 40, 200 or 1,000 mg/kg/day ethylene glycol in feed. There were slight increases in the dominant lethal mutation index in the high-dose and low-dose groups; these appear to be random occurrences and were not considered to be treatment-related. It was concluded that ethylene glycol was not genotoxic in this study (DePass et al., 1986b) [Kl. score = 2].

H. Carcinogenicity

Oral

Male and female Fischer 344 rats were given in their feed 0, 40, 200 or 1,000 mg/kg ethylene glycol for 24 months. There was increased mortality in the 1,000 mg/kg males, starting at 8 months and resulting in all males in this group dead by 16 months. Survival for the 1,000 mg/kg females and the 200 and 40 mg/kg males and females were similar to the controls. The incidence of mononuclear cell leukemia was statistically significantly higher in the 200 mg/kg males compared to the male controls, but not when compared to the pooled controls (males and females). Evaluation of the data by the method of Thomas et al. (2007), however, showed no treatment-related effect. It was concluded that ethylene glycol was not carcinogenic to rats in this study (DePass et al., 1986) [Kl. score = 2].

Male and female B6C3F_1 mice were given in their feed 0, 6,250 ppm (males only), 12,500 and 25,000 ppm (males and females) or 50,000 ppm (females only) ethylene glycol. These concentrations were approximately equivalent to 0, 1,500, 3,000, 6,000 or 12,000 mg/kg/day. Body weights, survival and incidence of tumours were similar between treated and control mice (NTP, 1993) [Kl. score = 2].

Inhalation

No studies are available.

Dermal

No studies are available.

I. Reproductive Toxicity

Ethylene glycol was assessed in a Reproductive Assessment by Continuous Breeding (RACB) protocol (Chapin and Sloane, 1997). The parental mice were administered ethylene glycol via drinking water during pre-mating exposure, cohabitation, pregnancy and lactation. The F_1 generation received prenatal exposure via maternal exposure during gestation, with the exposure continuing during lactation, weaning and mating of F_1 animals and production of an F_2 litter. The doses were 0, 0.25, 0.5 or 1% ethylene glycol, which corresponded to approximately 0, 410, 840 or 1,640 mg/kg/day. No adverse effects were noted in the parental animals at doses up to 1%. There was a small, but statistically significant, effects on the numbers of litters per fertile pair, the number of live pups per litter, and live pup weight in the 1% dose group. Neither the 0.25 nor 0.5% dose groups were significantly affected. The number of live pups per litter was lower in the treated groups, but differences were not statistically significant. Unusual facial features (i.e., shorter snout and wide-set eye) and skeletal defects (shortened frontal, nasal and parietal bones; fused ribs abnormally shaped or missing sternebrae, abnormally shaped vertebrae; and twisting of the spine) were noted on some of the offspring of the treated mice in the 1% group, but not in the controls. The parental NOAEL is 1% (approximately 1,640 mg/kg/day), and the NOAEL for reproductive toxicity is 0.5% (approximately 840 mg/kg/day (Lamb et al., 1985) [Kl. score = 2].

In a three-generation reproductive toxicity study, Fischer 344 rats were given in their diet 0, 40, 200 or 1,000 mg/kg/day ethylene glycol. There were no treatment-related effects on clinical signs of toxicity or survival in the parental animals. There were no significant effects on fertility index, gestation index, gestation survival for all three generations. Mean pup weights for each of the hree generations were similar between treated and control animals. The NOAEL for parental and reproductive toxicity is 1,000 mg/kg/day (DePass et al., 1986b) [Kl. score = 2].

J. Developmental Toxicity

Pregnant Sprague-Dawley rats were dosed by oral gavage with 0, 50, 150, 500, 1,000 or 2,500 mg/kg ethylene glycol during gestational days (GD) 6-15. Maternal toxicity was observed in the 2,500 mg/kg group and consisted of significantly decreased body weights, increased water consumption, decreased uterine weights, increased kidney weights and increased relative liver weights. At 500 mg/kg, there were developmental effects, which included reduced foetal body weights, extra or missing ribs, missing arches and poor ossification in thoracic and lumbar centra. In the 2,500 mg/kg group, in addition to skeletal malformations, there was gastroschisis, hydrocephaly, lateral ventricle dilated (tissue depressed), umbilical hernia and atelectasis. The NOAELs for maternal and developmental toxicity are 1,000 and 500 mg/kg/day, respectively (Neeper-Bradley et al., 1995) [Kl. score = 2].

Pregnant CD rats were dosed by oral gavage with 0, 1,250 2,500 or 5,000 mg/kg ethylene glycol during GD 6-15. In the ≥ 2,500 mg/kg groups, the dams had increased relative kidney weights, decreased gravid uterine weight and increased water consumption. Maternal body weight gain was significantly decreased in the 1,250 mg/kg group. Live litter size was significantly decreased in the 5,000 mg/kg group and foetal body weights were decreased in the 1,250 and 5,000 mg/kg groups. Litters with malformed foetuses were observed in the ≥ 1,250 mg/kg groups. The LOAELs for maternal and developmental toxicity are 1,250 mg/kg/day; NOAELs were not established (Price et al., 1985) [Kl. score = 2].

Pregnant Fischer 344 rats were given by oral gavage 0, 40, 200 or 1,000 mg/kg ethylene glycol during GD 6-15. No maternal toxicity was observed at any dose level. There were no significant effects on preimplantation loss, foetal length, foetal weight, total implantations or litter size. There was an increased incidence of skeletal alterations in the 1,000 mg/kg group, which consisted of poorly ossified and unossified vertebral centra. No significant increases in the incidence of major malformations were observed. The NOAELs for maternal and developmental toxicity are 1,000 and 400 mg/kg/day (Maronpot et al., 1983) [Kl. score = 2].

Pregnant CD-1 mice were dosed by oral gavage with 0, 50, 150, 500 or 1,500 mg/kg ethylene glycol during gestational days (GD) 6 to 15. There was no maternal toxicity. At 1,500 mg/kg, there were reduced foetal body weights, fused ribs and arches, poor ossification in thoracic and lumbar centra and increased occurrence of an extra 14^{th} rib. At 500 mg/kg, there was slight reductions in foetal body weight and increased incidences of extra ribs. The NOAELs for maternal and developmental toxicity were 1,500 and 150 mg/kg/day, respectively (Neeper-Bradley et al., 1995) [Kl. score = 2].

Pregnant CD-1 mice were dosed by oral gavage with 0, 750, 1,500 or 3,000 mg/kg ethylene glycol during GD 6 to 15. There was a significant decrease in maternal gain, gravid uterine weights and liver weights in the 1,500 mg/kg group. A decreased number of implantation sites per litter was observed in the 1,500 mg/kg group. Significant decrease in liver litter size was observed in the 3,000 mg/kg group and decreased foetal body weights were seen at ≥ 750 mg/kg. Litters with a significant increase in malformed foetuses were observed in the ≥ 750 mg/kg groups. There was a significant dose-related increase in post-implantation loss per litter, though there were no significant pairwise comparisons. The NOAEL for maternal toxicity is 750 mg/kg/day. The LOAEL for developmental toxicity is 750 mg/kg/day; the NOAEL was not established (Price et al., 1985) [Kl. score = 2].

In a short-term reproductive and developmental toxicity screen test, male and female Swiss Crl:CD-1 mice were allowed to mate over a three-day period. The males were dosed by oral gavage from study Day 3 to study Day 20. The Group A females were exposed throughout the 21-day test period; the Group B females were exposed during GD 8-14. The doses were 0, 250, 700 or 2,500 mg/kg ethylene glycol. The Group A females were sacrificed after 19 days of treatment, and the Group B females were allowed to litter and rear to postnatal day (PND) 4. There was no maternal or paternal toxicity. The 2,500 mg/kg females in Group A had significantly fewer liver implants and more dead implants. The 2,500 mg/kg in Group B had significantly lower total litter weights on PND 1 and 4. The NOAELs for parental and developmental toxicity are 2,500 and 700 mg/kg/day (Harris et al., 1992) [Kl. score = 2].

In a Chernoff/Kavlock assay, pregnant CD-1 mice were dosed by oral gavage with 0 or 11,090 mg/kg ethylene glycol during GD 7-14. The females were allowed to litter and rear to PND 3. Ten percent of the maternal animals died. The number of surviving pups per litter (40% survived), birth weight and pup weight gain were reduced. The LOAELs for maternal and developmental toxicity are 11,090 mg/kg; NOAELs were not established (Schuler et al., 1984; Hardin et al., 1987) [Kl. score = 2].

Pregnant female New Zealand White rabbits were dosed by oral gavage with 0, 100, 500, 1,000 or 2,000 mg/kg ethylene glycol on GD 6 to 19. At 2,000 mg/kg, eight of the 17 does (42.1%) died. Maternal body weights and body weight gain were similar across all groups. There was no developmental toxicity. The NOAEL for maternal toxicity is 1,000 mg/kg/day. The NOAEL for developmental toxicity is 2,000 mg/kg/day, the highest dose tested (ECHA) [Kl. score = 2].

Pregnant female CD rats were dosed by oral gavage with 0, 250, 1,250 or 2,250 mg/kg ethylene glycol on GD 6 to 20. At 2,250 mg/kg, maternal body weight, body weight gain, kidney weight and postpartum uterine weight were significantly reduced. At 1,250 mg/kg, the gestational period was

lengthened and maternal kidney histopathological effects were noted. Developmental toxicity was noted in the 2,250 mg/kg group and included reduced pup weight, reduced viability and increased malformations (primarily hydrocephaly and abnormalities of the axial skeleton). No developmental toxicity was seen in the 1,250 mg/kg group. The NOAEL for maternal and developmental toxicity is 250 mg/kg/day (ECHA) [Kl. score = 2].

Inhalation

Pregnant female CD rats were exposed by inhalation (whole-body) to 0, 150, 1,000 or 2,500 mg/m^3 ethylene glycol aerosol 6 hours/day on gestational days 6 to 15. There was no treatment-related mortality; a dose-related increased in clinical signs (red fur discoloration on the head and neck) was noted, which was considered to be a non-specific indication of stress. Body weights and body weight gain were unaffected by treatment. There was some evidence of treatment-related reductions in ossification of the foetal skeleton at 1,000 and 2,500 mg/m^3 (considered as fetotoxicity). The NOAECs from inhalation exposure cannot be determined due to confounding oral exposure during whole-body exposure. However, there was no maternal or embryotoxicity at 150 mg/m^3 and no teratogenicity at any aerosol concentration tested (Tyl et al., 1995a) [Kl. score = 2].

Pregnant female CD-1 mice were exposed by inhalation (whole-body) to 0, 150, 1,000 or 2,500 mg/m^3 ethylene glycol aerosol 6 hours/day on gestational days 6 to 15. Reduced maternal body weight was observed in the 2,500 mg/m^3 group on GD 12,15 and 18 and in the 1,000 mg/m^3 group on GD 18. Reduced maternal weight gain was also seen during GD 6-12, 6-15 and GD 6-18 for the ≥ 1000 mg/m^3 groups and for GD 5-18 for the 2,500 mg/m^3 group. Terminal body weights were reduced in the ≥ 1,000 mg/m^3 groups. Gravid uterine weight was also reduced in the ≥ 1,000 mg/m^3 groups, so that body weight corrected for gravid uterine weight was unaffected. The number of viable implantations per litter was reduced at 2,500 mg/m^3. The number of non-viable implantations per litter was elevated at ≥ 1,000 mg/m^3 because of a significant increase in late resorptions at 1,000 mg/m^3, and a significant increase in late resorptions and in dead foetuses at 2,500 mg/m^3. The number of early resorptions at 2,500 mg/m^3 was also elevated but not statistically. foetal body weights per litter (male, female and total) were reduced at ≥ 1,000 mg/m^3. There was a significant increase in the incidence of a number of external, visceral and skeletal malformation, as well as skeletal variations, at ≥ 1,000 mg/m^3. There was no observable maternal or developmental toxicity at 150 mg/m^3. However, a NOAEC cannot be determined because of the amount of ethylene glycol that may have been ingested from the presence of ethylene glycol on the fur (Tyl et al., 1995a) [Kl. score = 2].

Pregnant female CD-1 mice were exposed by inhalation (nose-only) to 0, 500, 1,000 or 2,500 mg/m^3. The study also included a group exposed to 2,100 mg/m^3 (not discussed here). Reduced maternal body weight gain were seen in the 2,500 mg/m^3 for GD 9-12, 12-15, 6-15 and 0-18. Absolute kidney weights were increased in the ≥ 1,000 mg/m^3 groups. foetal body weights per litter were significantly reduced for the 2,500 mg/m^3. In the 2,500 mg/m^3, there was a significant increase in one skeletal malformation (fusion of the ribs) and an increased incidence of skeletal variations. No other teratogenic effects were observed. The NOECs for maternal and developmental toxicity are 500 and 1,000 mg/m^3, respectively (Tyl et al., 1995c) [Kl. score = 2].

Dermal

Pregnant CD-1 mice were administered by dermal applications of 0, 400, 1,677 or 3,549 mg/kg ethylene glycol 6 hours/day on GD 6-15. There was minimal, if any, treatment-related maternal toxicity. Copora lutea, total implants, percentage of live foetuses per litter, foetal body weights and incidence of external or visceral malformations were unaffected by treatment. There was, however,

a significant increase in two skeletal variations in the 3,549 mg/kg group. The NOAELs for maternal and developmental toxicity were considered to be 3,549 mg/kg/day (Tyl et al., 1995b) [Kl. score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for ethylene glycol follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The NOAEL from a 24-month rat dietary study was reported to be 200 mg/kg/day based on kidney lesions in male F344 rats at 1,000 mg/kg/day (DePass et al., 1986b). A subsequent 12-month rat dietary study using male Wistar rats reported a NOAEL of 150 mg/kg/day also based on kidney toxicity at 300 mg/kg/day and higher (Corley et al., 2008). The Wistar rat strain was shown to be more sensitive (approximately three-fold) to the kidney toxicity of ethylene glycol than F344 rats (Cruzan et al., 2004). The NOAEL of 150 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Snellings et al. (2013) derived an oral reference dose for ethylene glycol using benchmark dose modelling, with toxicokinetic (PBPK modelling) and toxicodynamic data. The human equivalent dose ($[BMDL_{05}]_{HED}$) was calculated to be 150 mg/kg/day.

Oral RfD = $[BMDL_{05}]_{HED}$ / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 1
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 150/(1 x 10 x 1 x 1 x 1) = 150/10 = 15 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (15 x 70 x 0.1)/2 = 53 mg/L

B. Cancer

Ethylene glycol was not carcinogenic to rats and mice in two-year dietary studies. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Ethylene glycol does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Ethylene glycol is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on ethylene glycol.

Table 3: Acute Aquatic Toxicity Studies on Ethylene Glycol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	>72,860	1	Pillard (1995)
Oncorhynchus mykiss	96-hour LC_{50}	22,810 24,591	2	OECD (2004a,b)
Daphnia magna	48-hour EC_{50}	>100	1	ECHA
Daphnia magna	48-hour EC_{50}	46,300	2	Gersich et al. (1986)
Ceriodaphnia dubia-affinis	48-hour EC_{50}	25,800 (20°C) 10,000 (24°C)	2	Cowgill et al. (1985)
Daphnia magna	48-hour EC_{50}	46,300 (20°C) 51,000 (24°C)	2	Cowgill et al. (1985)
Selenastrum capricornutum	96-hour IC_{50} NOEC	10,940 10,000	2	Pillard and DuFresne (1999)

Chronic Studies

Table 4 lists the results of chronic aquatic toxicity studies conducted on ethylene glycol.

Table 4: Chronic Aquatic Toxicity Studies on Ethylene Glycol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	7-day NOEC	15,380	2	Pillard (1995)
Ceriodaphnia dubia	7-day NOEC (reproduction)	8,590	2	Pillard (1995)
Pseudokirchneriella subcapitata	72-hr NOEC	>100 *	2	ECHA

*Read-across to pentaethylene glycol (CAS No. [redacted]

C. Terrestrial Toxicity

No guideline studies have been conducted on ethylene glycol.

D. Calculation of PNEC

The PNEC calculations for ethylene glycol follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (22,810 mg/L), *Daphnia* (>100 mg/L), and algae (10,940 mg/L). NOEC values from long-term studies are available for fish (15,380 mg/L), invertebrates (8,590 mg/L) and algae (10,000 mg/L). On the basis that the data consists of short-term and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported E(L)C_{50} value of 100 mg/L for fish. The E(L)C_{50} value is used because the value for fish is lower than the NOEC values for all three trophic levels. The $PNEC_{aquatic}$ is 10 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 6.4 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.82/1280) \times 1000 \times 10$
$= 6.4$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.04/1000 \times 2400]$
$= 0.82\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg)

BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$

= 1 x 0.04

= 0.04 L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for ethylene glycol calculated from EPISUITE™ using the MCI is 1 L/kg.

F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.13 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$

= (0.02/1500) x 1000 x 10

= 0.13 mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)

BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$

= 1 x 0.02

= 0.02 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for ethylene glycol calculated from EPISUITE™ using the MCI is 1 L/kg.

F_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Ethylene glycol is readily biodegradable and thus does not meet the screening criteria for persistence.

The measured BCF in fish is 10. Thus, ethylene glycol does not meet the criteria for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on ethylene glycol are > 0.1 mg/L. The acute $E(L)C_{50}$ values from the acute aquatic toxicity studies on ethylene glycol are > 1 mg/L. Thus, ethylene glycol does not meet the criteria for toxicity.

The overall conclusion is that ethylene glycol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

STORE Category 2 (target organ: kidney)

B. Labelling

Warning

A. Pictogram

IX. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention.

Ingestion

Rinse mouth with water and then drink a glass of water. Get medical attention. Never give anything by mouth to an unconscious person.

Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Keep product and empty container away from heat and sources of ignition. May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

B. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Handle in accordance with good industrial hygiene and safety practice.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

For large amounts: dike spillage and pump off product. For residues: pick up with suitable absorbent material. Dispose of contaminated material as prescribed.

C. Storage And Handling

General Handling

Keep product and empty container away from heat and sources of ignition. Ensure adequate ventilation, especially in confined areas.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

D. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standards for ethylene glycol in Australia is as follows: 10 mg/m^3 as an 8-hour TWA for ethylene glycol (particulate); 20 ppm (52 mg/m^3) as an 8-hour TWA for ethylene glycol (vapour). There is also a skin notation indicating that absorption through the skin may be significant source of exposure.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. Ensure that eyewash stations and safety showers are close to the workstation location.

X. TRANSPORT INFORMATION

Ethylene glycol is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Blood, F.R. (1965). Chronic toxicity of ethylene glycol in the rat. Food Cosmet. Toxicol. 3: 229-234.

Carney, E.W., Pottenger, L.H., Bartels, M.J., Jaeckh, R., and Quast, J.F. (1998). Comparative pharmacokinetics and metabolism of ethylene glycol in pregnant rats and rabbits. Toxicol. Lett. 95: 208.

Chapin, R.E. and R.A. Sloane. (1997). Reproductive assessment by continuous breeding: evolving study design and summaries of ninety studies. Environ Health Perspect. 1997 Feb; 105(Suppl 1): 199–205.

Corley, R.A., Meek, M.E., and Carney, E.W. (2005a). Mode of action: oxalate crystal-induced renal tubule degeneration and glycolic acid-induced dysmorphogenesis – renal and developmental effects of ethylene glycol. Crit. Rev. Toxicol. 35: 691-702.

Corley, R.A., Bartels, M.J., Carney, E.W., Weitz, K.K., Soelberg, J.J., and Gies, R.A. (2005b). Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. Toxicol. Sci. 85: 476-490.

Corley, R.A., Wilson, D.M., Hard, G.C., Stebbins, K.E., Bartels, M.J., Soelberg, J.J., Dryzga, M.D., Gingell, K.E and Snellings, W.M.(2008). Dosimetry considerations in the enhanced sensitivity of male Wistar rats to chronic ethtlene glocol-induced nephrotoxicity. Toxicology and Applied Pharmacology. Volume 228, Issue 2: 165-178.

Cowgill, U.M., Takahash, I.T., and Applegath, S.L. (1985). A comparison of the effect of four benchmark chemicals on Daphnia magna and Ceriodaphnia dubia-affinis tested at two different temperatures. Environ. Toxicol. Chem. 4: 415-422.

Cruzan, G., Corley, R.A., Hard, G.C., Mertens, J.J., McMartin, K.E., Snellings, W.M., Gingell, R., and Deyo, J.A. (2004). Subchronic toxicity of ethylene glycol in Wistar and F-344 rats related to metabolism and clearance of metabolites. Toxicol Sci. 81: 502-11.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DePass, L.R., Garman, R.F., Woodside, M.D., Giddens, W.E., Maronpot, R.R., and Weil, C.S. (1986a). Chronic toxicity and oncogenicity studies of ethylene glycol in rats and mice. Fundam. Appl. Toxicol. 7: 547-565.

DePass, L.R., Woodside, M.D., Maronpot, R.R., and Weil, C.S. (1986b). Three-generation reproduction and dominant lethal mutagenesis studies with ethylene glycol in the rat. Fundam. Appl. Toxicol. 7: 566-572.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Evans, W.H., and David, E.J. (1974). Biodegradation of mono-, di-, and triethylene glycols in river waters under controlled laboratory conditions. Water Res. 8: 97-100.

Frantz, S.W., Beskitt, J.L., Grosse, C.M., Tallant, M.J., Dietz, F.K., and Ballantyne, B. (1996a). Pharmacokinetics of ethylene glycol. I. Plasma disposition after single intravenous, peroral, or percutaneous doses in female Sprague-Dawely rats and CD-1 mice. Drug Metab. Dispos. 24: 911-921.

Frantz, S.W., Beskitt, J.L., Grosse, C.M., Tallant, M.J., Dietz, F.K., and Ballantyne, B. (1996b). Pharmacokinetics of ethylene glycol. II. Tissue distribution, dose dependent elimination, and identification of urinary metabolites following single intravenous, peroral, or percutaneous doses in female Sprague-Dawely rats and CD-1 mice. Xenobiotica 26: 1195-1220.

Freitag, D., Ballhorn, L., Geyer, H., and Korte, F. (1985). Environmental hazard profile of organic chemicals. Chemosphere 14: 1589-1616.

Gersich, F.M., Blanchard, F.A., Applegath, S.L., and Park, C.N. (1986). The precision of Daphnid (Daphnia magna Straus, 1820) static acute toxicity tests. Arch. Environ. Contam. Toxicol. 15: 741-749.

Guillot, J.P., Martini, M.C., Giauffret, J.Y., Gonnet, J.F., and Guyot, J.Y. (1982). Safety evaluation of some humectants and moisturizers used in cosmetic formulations. Int. J. Cosmetic Science 4: 67-80.

Hardin, B.D., Schuler, R.L., Burg, J.R., Booth, G.M., Hazelden, K.P., MacKenzie, K.M., Piccirillo, V., Jr, and Smith, K.N. (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. Terat. Carcinogen. Mutagen. 7: 29-48.

Harris, M.W., Chapin, R.E., Lockhart, A.C., and Jokinen, M.P. (1992). Assessment of a short-term reproductive and developmental toxicity screen. Fundam. Appl. Toxicol. 19: 186-196.

Hess, R., Bartels, M.J., and Pottenger, L.H. (2004). Ethylene glycol: an estimate of tolerable levels of exposure based on a review of animal and human data. Arch. Toxicol. 78: 671-680.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Kurihara, A., Manabe, A., Katsuno, K., Itoh, K., Hisamitsu, H., Wakumoto, S., and Yoshida, T. (1996). Evaluation of skin irritation and sensitization of two diol solutions used as experimental dentin primers in humans and guinea pigs. Dent. Mater. J., 15: 226-232.

Lamb, J.C., IV, Maronpot, R.R., Gulati, D.K., Russel, V.S., Hommel-Barnes, L., and Sabharwa, l. P.S. (1985). Reproductive and developmental toxicity of ethylene glycol in the mouse. Toxicol. Appl. Pharmacol. 81: 100-112.

McGregor, D.B., Brown, A.G., Howgate, S., McBride, D., Riach, C., and Caspary, W.J. (1991). Responses of the L5178Y mouse lymphoma cell forward mutation assay. V: 27 coded chemicals. Environ. Mol. Mutagen. 17: 196-219.

Melnick, R.L. (1984). Toxicities of ethylene glycol and ethylene glycol monoether in Fischer 344/N rats and B6C3F1 mice. Environ. Health Perspect. 57: 147-155.

Neeper-Bradley, T.L., Tyl, R.W., Fisher, L.C., Kubena, M.F., Vrbanic, M.A., and Losco P.E. (1995). Determination of a no-observed-effect level for developmental toxicity of ethylene glycol administered by gavage to CD rats and CD-1 mice. Fundam. Appl. Toxicol. 27: 121-130.

National Toxicology Program [NTP]. (1993). Toxicology and Carcinogenesis Studies of Ethylene Glycol in B6C3F1 Mice (Feed Studies). National Toxicology Program Technical Report Series No. 413.

OECD. (2004a). SIDS Dossier on the HPV Chemical Ethylene Glycol (CAS No. [redacted]

OECD. (2004b). SIDS Initial Assessment Report on the Ethylene Glycol Category: Ethylene Glycol (CAS No. [redacted] Diethylene Glycol (CAS No. [redacted]), Triethylene Glycol (CAS No. [redacted] Tetraethylene Glycol (CAS No. [redacted] Pentaethylene glycol (CAS No. [redacted]

Pillard, D. (1995). Comparative toxicity of formulated glycol deicers and pure ethylene and propylene glycol to Ceriodaphnia dubia and Pimephales promelas. Environ. Toxicol. Chem. 14: 311-315.

Pillard, D.A. and DuFresne, D.L. (1999). Toxicity of formulated glycol deicers and ethylene and propylene glycol to lactuca sative, lolium perenne, selenastrum capricornutum, and lemna minor. Arch Environ. Contam. Toxicol. 37(1):29-35.

Price, C.J., Kimmel, C.A., Tyl, R.W., and Marr, M.C. (1985). The developmental toxicity of ethylene glycol in rats and mice. Toxicol. Appl. Pharmacol. 81: 113-127.

Robinson, M., Pond, C.L., Laurie, R.D., Bercz, J.P., Henningsen, G., and Condie L.W. (1990). Subacute and subchronic toxicity of ethylene glycol administered in drinking water to Sprague-Dawley rats. Drug Chem. Toxicol .13: 43-70.

Schuler, R.L., Hardin, B.D., Niemeier, R.W., Booth, G., Hazelden, K., Piccirillo, V., and Smith, K. (1984). Results of testing 15 glycol ethers in a short-term in vivo reproductive toxicity assay. Environ. Health Perspect. 57: 141-146.

Snellings, W.M., Corley, R.A., McMartin, K.E., Kirman, C.R., and Bobst, S.M. (2013). Oral reference dose for ethylene glycol based on oxalate crystal-induced renal tubule degeneration as the critical effect. Regul. Toxicol. Pharmacol. 65: 229-241.

Thomas, J., Haseman, J.K., Goodman, J.I., Ward, J.M., Loughran, Jr., T.P., and Spencer, P. (2007). A review of large granular lymphocytic leukemia in Fischer 344 rats as an intial step toward evaluating the implication of the endpoint to human cancer risk assessment. Toxicol. Sci. 99: 3-19.

Tyl, R.W., Ballantyne, B., Fisher, L.C., Fait, D.L., Savine, T.A., Dodd, D.E., Klonne, D.R., and Pritts, I.M. (1995a). Evaluation of the developmental toxicity of ethylene glycol aerosol in the CD rat and CD-1 mouse by whole-body exposure. Fundam. Appl. Toxicol. 24: 57-75.

Tyl, R.W., Fisher, L.C., Kubena, M.F., Vrbanic, M.A., and Losco, P.E. (1995b). Assessment of the developmental toxicity of ethylene glycol applied cutaneously to CD-1 mice. Fundam. Appl. Toxicol. 27: 155-166.

Tyl, R.W., Ballantyne, B., Fisher, L.C., Dodd, D.E., Klonne, D.R., Pritts, M., and Losco, P.E. (1995c). Evaluation of the developmental toxicity of ethylene glycol aerosol in CD-1 mice by nose-only exposure. Fundam. Appl. Toxicol. 27: 49-62.

U.S. Environmental Protection Agency [EPA]. (2017). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Waggy, G.T., Conway, R.A., Hansen, J.L., and Blessing, R.I. (1994). Comparison of 20-d BOD and OECD closed-bottle biodegradation tests. Environ. Toxicol. Chem. 13: 1277-1280.

SODIUM HYDROXIDE

This dossier on sodium hydroxide presents the most critical studies pertinent to the risk assessment of sodium hydroxide in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the OECD-SIDS documents on sodium hydroxide (OECD, 2002a,b) and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Sodium hydroxide

CAS RN: [redacted]

Molecular formula: HNaO

Molecular weight: 40 g/mol

Synonyms: Caustic soda, soda lye, NaOH

SMILES: O[Na]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-Chemical Properties of Sodium Hydroxide

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid	2	Lide, 2009; ECHA
Melting Point	318°C (solid, 100%); 52°C (60% solution)	2	ECHA
Boiling Point	1,388°C @ 101.3 kPa	2	Lide, 2009; ECHA
Density	2130 kg/m^3, 20°C (100%) 1430 kg/m^3, 20°C (40%)	2	Lide, 2009; ECHA
Vapour Pressure	1 Pa @ 513°C	2	Lide, 2009; ECHA
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	Very soluble (>10 g/L @ 25°C)	2	Lide, 2009; ECHA
Dissociation Constant (pKa)	14.8 @ 25°C	2	Lide, 2009; ECHA
pH of 5% NaOH solution	14	2	O'Neil, 2006

Sodium hydroxide (NaOH) is a strong alkaline substance that dissociates completely in water to sodium (Na^+) and hydroxyl (OH^-) ions.

III. ENVIRONMENTAL FATE PROPERTIES

Due to its high water solubility and low vapour pressure, sodium hydroxide will be found predominantly in the aquatic environment where it dissociates completely to sodium (Na^+) and hydroxyl (OH^-) ions. Both ions are ubiquitous in the environment (UNEP, 1995).

The addition of sodium hydroxide to an aquatic ecosystem may increase the pH depending on the buffer capacity of the receiving water. In general, the buffer capacity is regulated by the equilibria between CO_2, HCO_3^- and CO_3^{2-}:

$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$ ($pKa_1 = 6.35$)

$HCO_3^- \leftrightarrow CO_3^{2-} + H^+$ ($pKa_2 = 10.33$)

A release of sodium hydroxide into the aquatic environment from the use of NaOH could potentially increase the sodium concentration and the pH in the aquatic environment. Table 2 shows the concentration of sodium hydroxide needed to increase the pH to values of 9.0, 10.0, 11.0 and 12.0.

Table 2: Sodium Hydroxide Concentration (mg/L) Needed to Increase pH (DeGroot et al., 2002; taken from OECD, 2002b)

Buffer capacity*	Final pH			
	9.0	10.0	11.0	12.0
0 mg/L HCO_3 (distilled water)	0.4	4.0	40	400
20 mg/L HCO_3 (10^{th} percentile of 77 rivers)	1.0	8.2	51	413
106 mg/L HCO_3^- (mean value of 77 rivers)	3.5	26	97	468
195 mg/L HCO_3^- (90^{th} percentile of 77 rivers)	6.1	45	145	525

*The initial pH of a bicarbonate solution with a concentration of 20-195 mg/L was 8.25 to 8.35.

Na^+ and OH^- ions will not adsorb on the particulate matter or surfaces and will not accumulate in living tissues (OECD, 2002b).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Limited toxicity data exist for sodium hydroxide (NaOH). Depending on the concentration, solutions of NaOH are corrosive, irritating or non-irritating. These solutions cause direct effects to the skin, eyes, respiratory tract and gastrointestinal tract. Vapours from aqueous solutions of KOH can cause respiratory irritation. NaOH is not a skin sensitiser. There are no repeated dose, reproductive and developmental toxicity studies on sodium hydroxide.

B. Toxicokinetics/Metabolism

Sodium hydroxide dissociates completely in aqueous solutions to sodium (Na^+) and hydroxyl (OH^-) ions. Sodium is an essential nutrient involved in fluid and electrolyte balance and is required for normal cellular function (Ganong, 1995). Sodium is the major extracellular cation in the body; the total body content is tightly regulated (Ganong, 1995).

C. Acute Toxicity

There are no oral toxicity guideline studies on sodium hydroxide. An oral LD_{50} of a 1 to 10% solution of NaOH in rabbits was reported to be 325 mg/kg (expressed as 100% NaOH) (OECD, 2002a,b). Mortality was also observed when a 1% NaOH solution was dosed, but in this case, the applied volume was relatively high (24 mL per kg body weight) (OECD, 2002a,b).

Acute toxicity studies were not identified for the inhalation and dermal route.

D. Irritation

Animal studies have shown that an 8% NaOH solution is corrosive to the skin. In humans, 0.5 to 4% NaOH concentrations produced skin irritation; and, based on the results of two different human patch tests, a NaOH solution that is slightly less than 0.5% would be non-irritating to human skin (OECD, 2002a,b).

Results from animal eye irritation studies indicate that a 0.2-1.0% NaOH solution would be non-irritating, while 1.2 or > 2% NaOH solutions would be corrosive (OECD, 2002a,b).

E. Sensitisation

Male volunteers were exposed on the skin of their back to solutions of 0.063 to 1.0% NaOH in the induction phase of a human patch test. After 7 days the volunteers were challenged to a concentration of 0.125% NaOH. The irritant response correlated well with the concentration of NaOH, but an increased response was not observed when the previously patch tested sites were re-challenged. Based on this study, sodium hydroxide is not a skin sensitiser (OECD, 2002a,b; ECHA) [Kl. score = 2].

F. Repeated Dose Toxicity

No studies were identified for the oral and dermal route. An inhalation study was conducted in rats exposed to aerosols of solutions of NaOH ranging from 5% to 40%. Exposures were twice weekly (hours/day and total exposure days unspecified). All animals in the 40% solution group died within a month mostly from bronchopneumonia. At the lower concentrations, respiratory tract lesions were observed; an NOAEL was not identified (NIOSH, 1975).

G. Genotoxicity

In Vitro Studies

Several *in vitro* studies have been conducted on NaOH (OECD, 2002a,b; ECHA). Although these studies reported negative results, they are considered unreliable (Kl. score = 3) due to methodological or reporting deficiencies.

In Vivo Studies

Several *in vivo* studies have been conducted on NaOH (OECD, 2002a,b; ECHA). Although these studies reported negative results, they are considered unreliable (Kl. score = 3) due to methodological or reporting deficiencies.

H. Carcinogenicity

No studies were identified.

I. Reproductive Toxicity

No valid studies were identified regarding toxicity to reproduction in animals after oral, dermal or inhalation exposure to NaOH.

J. Developmental Toxicity

No valid studies were identified regarding developmental toxicity in animals after oral, dermal or inhalation exposure to NaOH (OECD, 2002a,b; ECHA).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Oral and dermal repeated dose, reproductive, and developmental toxicity studies have not been conducted on NaOH. A repeated dose toxicity study was conducted by the inhalation route, but the methodology and documentation preclude its use for deriving a toxicological reference value. These toxicity studies would have questionable usefulness because of the corrosive/irritating nature of NaOH, which would limit the amount absorbed. NaOH dissociates to sodium and hydroxyl ions in bodily fluids, and a significant amount of these ions are already ingested in foods. Furthermore, both ions are present in the body and are highly regulated by homeostatic mechanisms. Thus, a toxicological reference value was not derived for NaOH.

The Australian drinking water guideline values for sodium (180 ppm, aesthetic) and pH may be applicable (ADWG, 2021).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium hydroxide does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium hydroxide has low acute toxicity to aquatic organisms.

B. Aquatic Toxicity

The OECD-SIDS SIAR on NaOH states that while the toxicity of the NaOH has been assumed to be related to the hydroxyl anion, in general a pH change could influence the speciation of other chemicals and therefore increase and/or decrease toxicity of the substance.

There are no guideline studies on NaOH; the studies summarised below have Klimisch scores of 3 or 4.

Acute Fish

The 24-hour LC_{50} to *Carassius auratus* (goldfish) is 160 mg/L. At 100 mg/L, which was equivalent to a pH of 9.8, no mortality was observed. The 48-hour LC_{50} to *Leuciscus idus melanotus* is 189 mg/L. The 96-hour LC_{50} of *Gambusia affinis* (mosquitofish) is 125 mg/L. At 84 mg/L, no effects on the fish were observed. The pH was 9 at 100 mg/L.

Acute Invertebrate

The 48-hour LC_{50} is 40 mg/L for *Ceriodaphnia cf. dubia*. The toxicity threshold concentration of NaOH for *Daphnia magna* was reported to range from 40 to 240 mg/L.

Acute Algae

No studies were identified.

C. Terrestrial Toxicity

No studies were identified.

D. Calculation of PNEC

The OECD-SIDS SIAR on NaOH states the following regarding the aquatic toxicity studies on NaOH (OECD, 2002b):

> *"In many cases pH, buffer capacity and/or medium composition were not discussed in the publications, although this is essential information for toxicity tests with NaOH. This is the most important reason why most of the studies, mentioned above were considered invalid. Although valid acute ecotoxicity tests and chronic ecotoxicity tests with NaOH are not available, there is no need for additional testing with NaOH. A significant number of acute toxicity tests are available, and the results of the tests are more or less consistent. Altogether they give a sufficient indication of acute toxicity levels of sodium hydroxide."*
>
> *"Furthermore, acute toxicity data cannot be used to derive a PNEC or a PNEC added for sodium hydroxide. Aquatic ecosystems are characterised by an alkalinity/pH, and the organisms of the ecosystem are adapted to these specific natural conditions. Based on the natural alkalinity of waters, organisms will have different optimum pH conditions, ranging from poorly buffered waters with a pH of 6 or less to very hard waters with pH values up to 9. A lot of information is available about the relationship between pH and ecosystem structure and also natural variations in pH of aquatic ecosystems have been quantified and reported extensively in ecological publications and handbooks."*
>
> *"Normally a PNEC or a PNEC added has to be derived from the available ecotoxicity data. A PNEC added is a PNEC which is based on added concentrations of a chemical (added risk approach). Based on the available data it is not considered useful to derive a PNEC or a PNEC added for NaOH because:*
>
> - *The natural pH of aquatic ecosystems can vary significantly between aquatic ecosystems,*

- *Also, the sensitivity of the aquatic ecosystems to a change of the pH can vary significantly between aquatic ecosystems and*
- *The change in pH due to an anthropogenic NaOH addition is influenced significantly by the buffer capacity of the receiving water."*

"Although a PNEC or a PNEC added was not calculated for NaOH, there is a need to assess the environmental effect of a NaOH (alkaline) discharge. Based on the pH and buffer capacity of effluent and receiving water and the dilution factor of the effluent, the pH of the receiving water after the discharge can be calculated. Of course, the pH change can also be measured very easily via a laboratory experiment or by conducting field measurements. The change in pH should be compared with the natural variation in pH of the receiving water and based on this comparison it should be assessed if the pH change is acceptable."

Based on the information above, PNEC values for freshwater, sediment, and soil were not derived for sodium hydroxide.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Sodium hydroxide is an inorganic salt that dissociates completely to sodium and hydroxide ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both sodium and hydroxide ions are also ubiquitous and are present in most water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Sodium and hydroxide ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated. Thus, sodium hydroxide is not expected to bioaccumulate and does not meet the screening criteria for bioaccumulation.

No chronic toxicity data exist on sodium hydroxide; however, the acute EC_{50} values are > 1 mg/L in fish, invertebrates and algae. Thus, sodium hydroxide does not meet the screening criteria for toxicity.

The overall conclusion is that sodium hydroxide is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Metal Corrosive Category 1

Skin Corrosive, Category 1A

Eye Damage, Category 1

EU Concentration Limits:
≥ 5%: Skin Corrosive 1A
≥ 2 to <5%: Skin Corrosive 1B

≥ 0.5%to <2%: Skin Irritant Category 2
≥ 0.5% to <2%: Eye Irritant Category 2

In addition to the hazard statements corresponding the GHS classification for corrosive, the following non-GHS hazard statement is to be added to the SDS: AUH071: Corrosive to the Respiratory Tract.

B. Labelling

Danger

C. Pictograms

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Flush with plenty of fresh water for 15 minutes holding eyelids open, lifting eyelids occasionally to ensure complete removal of the product. Remove contacts, if present and easy to do. DO NOT allow rubbing of eyes or keeping eyes closed. Seek medical attention.

Skin Contact

Rinse with soap and plenty of water for several minutes. Remove contaminated clothing. Seek medical attention immediately.

Inhalation

Remove person to fresh air. Apply artificial respiration if not breathing. Seek medical attention.

Ingestion

Rinse mouth with water (only if the person is conscious), but do not administer fluids. Do NOT induce vomiting. Seek medical attention immediately.

B. Fire Fighting Information

Extinguishing Media

Carbon dioxide, water spray, foam, dry chemical.

Specific Exposure Hazards

Containers may explode when heated. May form explosive mixtures with strong acids. Hazardous combustion products may include the following materials: halogenated compounds, metal oxides/oxides, sodium monoxide.

Special Protective Equipment for Firefighters

Full protective clothing and approved self-contained breathing apparatus required for firefighting personnel.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment and avoid direct contact. Do not touch damaged containers or spilt material unless wearing appropriate protective clothing. Ventilate the area before entry.

Environmental Precautions

Prevent spills from entering storm drains or sewers and contact with soil.

Steps to be Taken if Material is Released or Spilt

Use an absorbent material to recover as much product as possible, then rinse the affected area with water to dilute the residue. Disposal of leftover product and used containers should be carried out in accordance with all local, state and federal regulations.

D. Storage and Handling

General Handling

Wear appropriate personal protective equipment. Avoid contact with eyes, skin or clothing. Avoid breathing mist, vapours or spray. Use only with adequate ventilation. Wash hands after use. Launder contaminated clothing.

Storage

Store away from acids. Keep container closed when not in use. Store in a cool well-ventilated area.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for sodium hydroxide in Australia is 2 mg/m^3 as a peak limitation, with a sensitisation notation. A peak limitation is defined by Safe Work Australia as a maximum or peak airborne concentration of a substance determined over the shortest analytically practicable period of time which does not exceed 15 minutes.

Engineering Controls

Good general ventilation should be used. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits.

Personal Protection Equipment

Respiratory Protection: Use a mask or approved air-purifying respirator with appropriate cartridge or canister in spray applications or in confined spaces.

Hand Protection: Wear impervious gloves to prevent skin contact and absorption of this material. Rubber or Neoprene gloves may afford adequate skin protection.

Skin Protection: Wear appropriate clothes (i.e., coveralls). Use non-slip footwear.

Eye Protection: Wear eye protection in situations where splash or thick mists are possible.

Other Precautions: Avoid contact with skin, eyes and clothing. When using, do not eat or drink. Wash hands thoroughly with soap and water before eating or drinking. Remove contaminated clothing and launder before reuse.

F. Transport Information

For sodium hydroxide solutions of > 5%:
Australian Dangerous Goods
UN1824, Corrosive liquid, (Sodium hydroxide solution)
Class 8
Packing Group: II

Lower concentrations of sodium hydroxide may require a different packing group or may not require any hazard code if the concentration of NaOH is low enough not to be considered a corrosive material.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

De Groot et al. (2002). The addition of sodium hydroxide to a solution with sodium bicarbonate to a fixed pH. Solvay Pharmaceuticals Int. Doc. No. 8320/47/01; cited in OECD, 2002a,b.

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

Ganong, W.F. (1995). Review of Medical Physiology, 17th Edition, Appleton & Lange, Norwalk, Connecticut, USA.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology 25:1-5.

Lide, D.R. (2009). Physical Constants of Inorganic Compounds. CRC Handbook of Chemistry & Physics, 89th Edition, CRC Press.

NIOSH. (1975). National Institute of Occupational Safety and Health: Criteria Document: Sodium Hydroxide p.46 (1975) DHEW Pub. NIOSH 76-105; cited in NICNAS IMAP assessment report for sodium hydroxide, https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1406#cas-A [redacted]

O'Neil, M.J. [Ed.]. (2006). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. P. 1485, Whitehouse Station, NJ: Merck and Co., Inc.

OECD. (2002a). IUCLID Data Set for Sodium hydroxide (CAS No. [redacted] UNEP Publications. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=DC48343F-5AEA-4850-9A17-0A89331E4320.

OECD. (2002b). Screening Information Dataset (SIDS) Initial Assessment Report for Sodium hydroxide (CAS No. [redacted] UNEP Publications. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=DC48343F-5AEA-4850-9A17-0A89331E4320.

UNEP. (1995). Water quality of world river basins. UNEP Environment Library No. 14, Nairobi, Kenya; cited in OECD, 2002a,b.

2-PROPENOIC ACID, POLYMER WITH SODIUM PHOSPHINATE (1:1), SODIUM SALT

This dossier on 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies pertinent to the risk assessment of 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt in coal seam gas extraction activities. The majority of information presented in this dossier is based on a surrogate 2-propenoic acid, polymer with sodium phosphinate (CAS No. [redacted] Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-Propenoic acid, polymer with sodium phosphinate (1:1), sodium salt

CAS RN: [redacted]

Molecular formula: $(C_3H_4O_2.H_3O_2\text{-}P.Na)_x$- x-Na

Molecular weight: Variable

Synonyms: 2-propenoic acid, polymer with sodium phosphinate, sodium salt; 2-propenoic acid polymer with sodium hypophosphite, sodium salt; 2-Propenoic acid, polymer with sodium hypophosphite, sodium salt

SMILES: Not applicable

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of 2-Propenoic acid, Polymer with Sodium Phosphinate (CAS No. [redacted])

Property	Value	Reference
Physical state at 20°C and 101.3 kPa	Colourless liquid	BWA, 2006
Melting Point	-1 to -3°C	BWA, 2006
Boiling Point	101 to 103°C	BWA, 2006
Specific Gravity	1.20 to 1.24	BWA, 2006
pH	3.5 to 4.5	BWA, 2006
Viscosity	75-200 mm^2/s @ 25°C	BWA, 2006
Water Solubility	Miscible	BWA, 2006

III. ENVIRONMENTAL FATE PROPERTIES

In an OECD 301E test, 2-propenoic acid, polymer with sodium phosphinate degraded 20% in 28 days, indicating that it is not readily biodegradable (BWA, 1999).

As a polymer, 2-propenoic acid, polymer with sodium phosphinate is not expected to bioaccumulate, because its molecular weight will limit its bioavailability.

IV. HUMAN HEALTH HAZARD ASSESSMENT

There is very limited information on 2-propenoic acid, polymer with sodium phosphinate.

A technical data sheet on Belsperse® 164 Dispersant (active ingredient: CAS No. [redacted] lists this product as having an acute oral LD_{50} value of > 5,000 mg/kg in rats. The product is non-irritating to the skin and eyes (BWA, 2006).

In a letter to the U.S. EPA, male and female rats dosed by oral gavage with a 40% solution of this polymer showed treatment-related signs of osteomalacia associated with hyperphosphaturia and calciuria by week 8 of a 90-day study (U.S. EPA, 2016a).

The U.S. EPA TSCATS database also has a brief summary of a 4-week rat oral gavage conducted on the product BELSPERSE 164 (CAS No. [redacted] At 5,000 mg/kg/day, there were adverse clinical signs, gross organ pathology and changes in blood biochemical parameters. The NOAEL was 2,000 mg/kg/day (U.S. EPA, 2016b).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicity information on 2-propenoic acid, polymer with sodium phosphinate is inadequate and/or unreliable for deriving toxicological reference and drinking water guidance values for this polymer.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

2-Propenoic acid, polymer with sodium phosphinate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

2-Propenoic acid, polymer with sodium phosphinate exhibits low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

<u>Acute Studies</u>

Table 2 lists the results of acute aquatic toxicity studies conducted on 2-propenoic acid, polymer with sodium phosphinate.

Table 2: Acute Aquatic Toxicity Studies on 2-Propenoic Acid, Polymer with Sodium Phosphinate (CAS No. [redacted])

Test Species	Endpoint	Results (mg/L)	Reference
Rainbow trout	96-hour LC_{50}	> 1,000	BWA, 2006
Zebra fish	96-hour LC_{50}	> 1,000	BWA, 2006
Daphnia	24-hour EC_{50}	320	BWA, 2006
Algae	72-hour EC_{50}	130	BWA, 2006

Chronic Studies

No studies were located.

C. Terrestrial Toxicity

No studies were located.

D. Calculation of PNEC

The PNEC calculations for 2-propenoic acid, polymer with sodium phosphinate follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (> 1,000 mg/L), *Daphnia* (> 320 mg/L) and algae (> 130 mg/L). No long-term studies on 2-propenoic acid, polymer with sodium phosphinate are available. On the basis of the short-term results from three trophic levels, an assessment factor of 1,000 has been applied to the lowest reported effect concentration of 130 mg/L for algae. The $PNEC_{water}$ is 0.13 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. The K_{ow} and K_{oc} have not been experimentally derived for 2-propenoic acid, polymer with sodium phosphinate; these values cannot estimate using QSAR models because of the high molecular weight of 2-propenoic acid, polymer with sodium phosphinate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$.

PNEC soil

There are no toxicity data for soil-dwelling organisms. The K_{ow} and K_{oc} have not been experimentally derived for 2-propenoic acid, polymer with sodium phosphinate; these values cannot be estimated using QSAR models because of the high molecular weight of 2-propenoic acid, polymer with sodium phosphinate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Based on the information for read-across substance 2-Propenoic acid, polymer with sodium phosphinate, 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt is not readily biodegradable. Thus, it meets the screening criteria for persistence.

Read-across substance 2-Propenoic acid, polymer with sodium phosphinate is a high molecular weight polymer that is not expected to be bioavailable to aquatic or terrestrial organisms. Thus, 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt it is not expected to bioaccumulate.

No chronic aquatic toxicity studies have been conducted on read-across substance 2-propenoic acid, polymer with sodium phosphinate. The acute E(L)C_{50} values are > 1 mg/L. Thus, 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt does not meet the screening criteria for toxicity.

The overall conclusion is that 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictogram

None.

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In the case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide, phosphorus oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing closed work clothing is recommended.

F. Transport Information

2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

BWA. (1999). BWA Water Additives. Belsperse® 164 Dispersant. General Product Information,

BWA. (2006). BWA Water Additives. Product Information for Belsperse 164 – High Performance Dispersant for Industrial Water Systems. 2006 BWA, V1010

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

U.S. EPA [EPA]. (2016a). U.S. Environmental Protection Agency (EPA) Toxic Substance Control Act Test Submissions (TSCATS) database. DCN 88900000038; accessed October 2016.

U.S. EPA [EPA]. (2016b). U.S. Environmental Protection Agency (EPA) Toxic Substance Control Act Test Submissions (TSCATS) database. DCN 88920001980; accessed October 2016.

GLUTARALDEHYDE

This dossier on glutaraldehyde presents the most critical studies pertinent to the risk assessment of glutaraldehyde in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from NICNAS (1994) and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Glutaraldehyde

CAS RN: [redacted]

Molecular formula: $C_7H_8O_2$

Molecular weight: 100.12 g/mol

Synonyms: Pentanedial; glutaral; glutaric dialdehyde; 1,3-diformylpropane; 1,5-pentanedial; glutaric aldehyde; glutaric acid dialdehyde; dioxopentane; glutardialdehyde; 1,5-pentanedione; Algicide®C

SMILES: C(CC=O)CC=O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-Chemical Properties of Glutaraldehyde

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa*	Sweetish smelling, clear water liquid	1	ECHA
Melting Point*	-33°C (pressure not provided)	1	ECHA
Boiling Point*	101.5°C @ 98.71 kPa	1	ECHA
Density*	1,130 kg/m^3 @ 20°C	1	ECHA
Vapour Pressure*	21 Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})*	-0.36 @ 23°C and pH 7	1	ECHA
Water Solubility*	Miscible @ 20°C	2	ECHA
Flash Point*	Not measurable	1	ECHA
Auto flammability*	395°C @ ~1,000hPa	1	ECHA
Viscosity*	12.75 mm^2/s (static) at 25°C	1	ECHA
Henry's Law Constant	0.011 Pa m^3/mol at 25°C [QSAR]	2	ECHA

*ca. 50% glutaraldehyde solution (in water)
1 ppm = 4.095 mg/m3
1 mg/m3 = 0.244 ppm

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Glutaraldehyde is considered readily biodegradable. It is also expected to have a low potential for bioaccumulation. The K_{oc} values for glutaraldehyde indicate that it will have low potential for adsorption to suspended solids and sediment in water and moderate adsorption to soil. Glutaraldehyde is not expected to undergo hydrolysis in the environment. Overall, glutaraldehyde shows limited persistence in the environment.

B. Partitioning

In an OECD TG 111 test (hydrolysis as a function of pH), glutaraldehyde was hydrolytically stable at pH 4 and pH 7 but decomposed at pH 9 (ECHA) [Kl. score = 2].

Photolytic degradation of glutaraldehyde occurred in water under sensitised conditions: the half-life was 18 days when equivalent to 36 days of natural sunlight (12 hours/day; sensitised acetone system); and 49 days when equivalent to 34 days of natural sunlight (12 hours/day; sensitised acetonitrile system). There was no photodegradation of glutaraldehyde under darkness or non-sensitised conditions (ECHA) [Kl. score = 2].

C. Biodegradation

Glutaraldehyde was considered readily biodegradable in an OECD 301A (DOC die away test). Degradation was 90-100% in 28 days (ECHA) [Kl. score = 1].

In a simulation test involving aerobic sewage treatment [activated sludge units] (OECD TG 303A), glutaraldehyde degraded 97% after 73 days based on DOC removal (ECHA) [Kl. score = 1].

In an aerobic aquatic metabolism test, [^{14}C]-glutaraldehyde had a half-life of 10.6 hours in the water/sediment system. A minor transformation product was glutaric acid: the maximum yield was 18.9 to 21.5% at 12 hours, which then declined rapidly to 10.1 to 11% by 24 hours; and was not observed at the end of the study period in the aqueous phase (ECHA) [Kl. score = 1].

In an anaerobic aquatic metabolism test, [^{14}C]-glutaraldehyde was rapidly metabolised with the first-order half-life being 7.7 hours. Glutaraldehyde was transformed to 5-hydroxypentanal (ca 37% of applied radioactivity) on day 1; after that, it declined to < 10%; it was not detected at all after 30 days. The second stable transformation product was 1,5-pentanediol (35% of radioactivity on Day 1), which accounted for 70% of the radioactivity at the end of the test. A minor transformation product was a compound formed via Aldol condensation, cyclisation and dehydration. This compound accounted for about 10-20% of total radioactivity from Day 1 onwards (ECHA) [Kl. score = 1].

In an aerobic soil metabolism test, the half-life of the degradation of [^{14}C]-glutaraldehyde was calculated to be 1.7 days, indicating rapid degradation in soil by microbial biotransformation. Degradation products were measured but not identified (ECHA) [Kl. score = 1].

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

D. Environmental Distribution

The organic carbon/water partition coefficients (K_{oc}) values were determined for sediment and four types of soil. The values are as follows: 120 for sediment; 210 for sandy loam; 500 for silty clay loam; 340 for silt loam; and 460 for loamy sand (ECHA; Leung, 2001) [KI. score = 1].

Based on these K_{oc} values, glutaraldehyde is considered to be moderately mobile in soil. If released to water, based on these K_{oc} values and its water solubility, it has moderate potential for adsorption to suspended solids or sediments.

E. Bioaccumulation

Glutaraldehyde is not expected to bioaccumulate. The measured log K_{ow} at pH 5, 7 and 9 are -0.41, -0.36 and -0.80, respectively (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Glutaraldehyde has moderate-to-high acute toxicity by the oral route, low-to-moderate toxicity by the dermal route, and moderate-to-high toxicity by the inhalation route. Acute inhalation exposure may cause respiratory irritation. Glutaraldehyde is corrosive to the skin and eyes; it is also a skin and respiratory sensitiser. Repeated oral exposures via drinking water to rats have resulted in general systemic toxicity, but no target organ effects. In contrast, the upper respiratory tract, particularly the nasal cavity, is the target organ in rodents from repeated inhalation exposure. Glutaraldehyde may exhibit weak genotoxic effects in some *in vitro* tests, whereas the *in vivo* studies consistently show no genotoxic activity. Glutaraldehyde is not a reproductive toxicant; developmental toxicity can occur at maternally toxic doses, but there is no teratogenicity.

B. Toxicokinetics

Dermal Absorption

[1,5-^{14}C]-glutaraldehyde was applied to the skin of male and female F344 rats. Doses were 0.75% and 7.5%: this corresponds to approximately 6.5 and 63 mg/kg for males; and approximately 8.7 and 102 mg/kg for females. The dermal absorption data are presented in Table 2. The results indicate that glutaraldehyde has a low rate of absorption by the dermal route (ECHA).

Table 2: Dermal Absorption Data in Rats on Glutaraldehyde (ECHA)

Sex	Absorption rate constant/hr		% of applied dose	
	Low Dose	High Dose	Low Dose	High Dose
Males	1.5	0.7	0.7	1.3
Females	1.8	0.9	0.3	2.1

An *in vitro* percutaneous absorption study was conducted on glutaraldehyde using excised skin from rats, rabbits, mice, guinea pigs and humans. The skin samples were placed in a flow-through skin penetration chamber, and [^{14}C]-glutaraldehyde was added at doses of 0.75% and 7.5%. The results are presented in Table 3. Glutaraldehyde did not penetrate any of the skin samples to a significant degree, suggesting that only minimal amounts of glutaraldehyde may be available for systemic

uptake and distribution after skin exposure. The results also show that skin absorption was greater for the animal species used in toxicity tests than human skin (ECHA; Frantz et al., 1993).

Table 3: *In vitro* Percutaneous Absorption (mg/cm^2) of Glutaraldehyde (ECHA; Frantz et al., 1993)

Species	Low Dose	High Dose
Animal*	0.006	0.08
Human	0.002	0.02

*Percutaneous absorption in rats, mice, guinea pigs, mice and rabbits were similar to each other and were reported as a single value.

C. Acute Toxicity

The oral LD_{50} values are: 123 to 820 mg/kg in rats; 100 to 352 mg/kg in mice; and 50 mg/kg in guinea pigs (NICNAS, 1994).

The dermal LD_{50} values are: 640 to 2,000 mg/kg in rabbits; > 2,500 mg/kg in rats; and > 4,500 mg/kg in mice (NICNAS, 1994).

The 4-hour inhalation LC_{50} values for glutaraldehyde are listed in Table 4:

Table 4: Acute inhalation LC_{50} values for Glutaraldehyde

Test Material	LC_{50} (males) [mg/L]	LC_{50} (females) [mg/L]	LC_{50} (both sexes) [mg/L]	Reference
50% aq. aerosol	0.52	0.45	-	OECD, 1995
25% aq. aerosol	-	-	0.8	OECD, 1995
50% aq. aerosol	0.35	0.28	-	OECD, 1995
5% soln. vapour	0.096	0.164	-	OECD, 1995

During the exposure period, the animals showed signs of eye and respiratory irritation, as indicated by laboured and audible breathing, and wetness and encrustation around the nose and eyes.

D. Irritation

Glutaraldehyde is corrosive to the skin and eyes of rabbits (NICNAS, 1994; ECHA). Signs of irritation occurred at a concentration of 2% for skin and 0.2% for eyes (NICNAS, 1994). In the acute inhalation studies, rats exposed to aerosols or vapours of glutaraldehyde showed signs of eye and respiratory irritation (OECD, 1995).

E. Sensitisation

Glutaraldehyde is a skin sensitiser to guinea pigs and humans. Information on the individual studies can be found in NICNAS (1994) and in the ECHA REACH database (ECHA).

Asthmatic symptoms, such as wheezing, coughing, chest tightness, breathing difficulties and non-specific hyper-responsiveness have been reported to occur in humans occupationally exposed to glutaraldehyde (NICNAS, 1994). It is unclear whether the asthma is an allergic hypersensitivity response or a result of the aggravation of pre-existing asthma due to the irritating properties of

glutaraldehyde. Nevertheless, glutaraldehyde should be considered a respiratory sensitiser, although one of low potency.

F. Repeated Dose Toxicity

Oral

Male and female Wistar rats were given in their drinking water 0, 100, 500, or 2,000 ppm glutaraldehyde for 90 days. The approximate daily intakes were 0, 3, 15 or 53 mg/kg/day for males, and 0, 4, 19 or 72 mg/kg/day for females. There were no signs of neurotoxicity at any dose level. There was slight impairment of food consumption in the 2,000 ppm animals, as well as slight impairment of body weight and body weight gain. Impaired water consumption was seen in the 100 and 500 ppm females. The NOAEL for males is 500 ppm (15 mg/kg/day). The NOAEL for females is 100 ppm (4 mg/kg/day) since the impaired water consumption in the 100 ppm females was considered a palatability problem and not an adverse effect (ECHA) [Kl. score = 1].

Male and female F344 rats were given in their drinking water 0, 50, 250 or 1,000 ppm glutaraldehyde for 13 weeks. Additional groups of animals were given in their drinking water 0 or 1,000 ppm glutaraldehyde for 13 weeks followed by a 4-week recovery period. The approximate daily intakes were 0, 5, 25 or 100 mg/kg/day for males; and 0, 7, 35 or 120 mg/kg/day for females. Water consumption was reduced in a dose-dependent manner in the $\geq$ 250 ppm males and 1,000 ppm females, which was attributed to an aversion to the taste and/or odour of glutaraldehyde in the water. There was also a reduction in food consumption in the 1,000 ppm animals with a parallel reduction in body weights. It is unclear whether the reduction in food consumption was related to the decreased water consumption. Urine volume was decreased with an increase in specific gravity, along with a slight increase in protein and ketone concentration, in the $\geq$ 250 ppm animals, which was probably related to the decreased water consumption. There were no treatment-related changes in the haematology parameters measured. Blood urea nitrogen was increased in a dose-related manner in the $\geq$ 250 ppm females at the 6-week time point, but not at the 13-week or 17-week time points. Relative kidney weights were increased in a dose-related manner in the $\geq$ 250 ppm males and females and increased absolute kidney weights in the females. Histopathological examination showed no treatment-related effects. The NOAEL is 50 ppm (5 and 7 mg/kg/day for males and females, respectively) based on dose-related increase in kidney weights at $\geq$ 250 ppm (ECHA) [Kl. score = 2].

Male and female Wistar rats were given in their drinking water 0, 100, 500 or 2,000 ppm glutaraldehyde for 12 months. The approximate daily intakes were: 0, 6.4, 30.5, or 116.6 mg/kg/day for males; and 0. 9.6, 46, or 153 mg/kg/day for females. There was no treatment-related mortality. At 2,000 ppm, treatment-related effects included respiratory sounds (both sexes), decrease in body weight (males), decrease in body weight gain (both sexes), decrease in food consumption (both sexes), reduced water consumption (both sexes), lesions within the glandular stomach (both sexes showed erosion/ulceration of the glandular stomach), increased incidence of clear cell foci in the liver (males) and a single case of slight diffuse squamous metaplasia in the epithelium of the larynx (male). At 500 ppm, water consumption was reduced in males which was considered to be a palatability (bad taste) problem and not an adverse effect. No effects were seen in the 100 ppm animals. The NOAEL for this study is 500 ppm, which corresponds to 30.5 and 46 mg/kg/day for males and females, respectively (ECHA) [Kl. score = 1].

Male and female Fischer 344 rats were given in their drinking water 0, 50, 250 or 1000 ppm glutaraldehyde for 104 weeks. The mean glutaraldehyde consumption was 0, 4, 17 and 64 mg/kg/day for males and 0, 6, 25 and 86 mg/kg/day for females. There were no treatment-related mortalities or clinical symptoms of toxicity. In the 250 and 1,000 ppm groups, there was reduction in

body weight and body weight gain; reduction in food and water consumption; increased statistically significant incidence of nucleated erythrocytes and of large monocytes; decreases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and glutamate dehydrogenase; dose-related decrease in urine volume accompanied by a dose-related increase in osmolality; changes in absolute and relative kidney weight; gastric irritation; increases in bone marrow hyperplasia; and increased incidence of renal tubular pigmentation. The decreased water consumption was considered to be due to the bad taste, smell and/or irritancy of the test substance in the drinking water; thus, it is of no toxicological relevance. As a result of reduced water intake, there are renal physiological adaptation, such as decreased urine, increased osmolality and changes in kidney weight. The haematological and clinical chemistry parameter changes were marginal and were considered to be of no toxicological relevance. The main haematological finding seen at the end of the study, which consisted of the appearance of nucleated erythrocytes and large monocytes in all treated groups (statistically significant for the ≥250 ppm males), was related to the incidence of large granular lymphocytic leukaemia (LGLL) in the spleen. The bone marrow hyperplasia and renal tubular pigmentation are related to the occurrence/incidence of LGLL and were considered by the authors of the study as being secondary to low-grade haemolytic anaemia in animals with LGLL. The NOAEL for this study is 50 ppm which corresponds to 4 and 6 mg/kg/day for males and females, respectively (Van Miller et al., 2002) [Kl. score = 2].

Inhalation

Male and female F344 rats were exposed by inhalation to 0, 0.0625, 0.125, 0.25, 0.5 or 1.0 ppm (0, 0.26, 0.5, 1, 2 or 4.1 mg/m^3) glutaraldehyde for 6.5 hours/day, 5 days/week for 13 weeks. The study focused on the respiratory tract, using histopathology and epithelial cell labelling index as end points. Histopathological lesions in the nasal passages and turbinates were seen at ≥ 0.25 ppm. Treatment-related effects were primarily the respiratory mucosa (nasal cavity and tips of the turbinates) and the olfactory epithelium (dorsal meatus). Hyperplasia, squamous metaplasia, olfactory degeneration, squamous exfoliation (accumulation of keratin, cell debris and bacteria in the lumen of the nasal vestibule) and focal erosions were reported for both sexes, and the severity and incidence of the findings increased with increasing concentration of glutaraldehyde. The NOAEL for this study is 0.125 ppm (Gross et al., 1994) [Kl. score = 1].

Male and female B6C3F$_1$ mice were exposed by inhalation to 0, 0.0625, 0.125, 0.25, 0.5 or 1.0 ppm (0, 0.26, 0.5, 1, 2 or 4.1 mg/m^3) glutaraldehyde for 6.5 hours/day, 5 days/week for 13 weeks. The study focused on the respiratory tract, using histopathology and epithelial cell labelling index as end points. Histopathologic lesions in the nasal passages and turbinates were seen at all exposure concentrations (≥ 0.0625 ppm). Treatment-related lesions were primarily the respiratory mucosa (nasal cavity and tips of the turbinates) and the olfactory epithelium (dorsal meatus). Hyperplasia, squamous metaplasia, olfactory degeneration, squamous exfoliation (accumulation of keratin, cell debris and bacteria in the lumen of the nasal vestibule) and focal erosions were reported for both sexes, and the severity and incidence of the findings increased with increasing test concentration. Furthermore, neutrophilic inflammation was seen at ≥ 0.062 ppm, and squamous metaplasia as well as necrosis were seen in the larynx at 1 ppm. The LOAEL for this study is 0.0625 ppm; a NOAEL was not established (Gross et al*.,* 1994) [Kl. score = 1].

Male and female B6C3F$_1$ mice were exposed by inhalation to 0 or 0.1 ppm (0 or 0.41 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for 52 and 78 weeks. Survival was similar between treated and control groups. Hyperplasia of the squamous epithelium lining of the dorsal wall of the nasal passages and the lateral aspect of the atrioturbinate was seen in a greater number of exposed females than in controls. Epidermal erosion and ulceration as well as squamous and inflammatory exfoliation were also seen in the nasal lumens. All of these changes were dependent on the length of

glutaraldehyde exposure. The authors concluded that, since the induced lesions occurred in the more anterior part of the nasal passages, that they were likely the result of an irritation mechanism (Zissu et al., 1998) [Kl. score = 2].

Male and female Fischer 344 rats were exposed by inhalation to 0, 0.25, 0.5, or 0.75 ppm (0, 1, 2, or 3.1 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for two years. Survival in the mid- and high-dose females was statistically significantly decreased compared to controls. Mean body weights of all exposed males and the mid- and high-dose females were generally less than those of the controls. Non-neoplastic lesions were limited primarily to the most anterior region of the nasal cavity. Effects included hyperplasia and inflammation of the squamous epithelium; hyperplasia, goblet cell hyperplasia, inflammation and squamous metaplasia of the respiratory epithelium; and hyaline degeneration of the olfactory epithelium. The LOAEL for this study is 0.25 ppm based on hyperplasia and inflammation of the squamous epithelium of the nose in both sexes. A NOAEL was not established (van Birgelen et al., 2000) [Kl. score = 2].

Male and female B6C3F$_1$ mice were exposed by inhalation to 0, 0.0625, 0.125 or 0.25 ppm (0, 0.26, 0.5 or 1 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for two years. Survival of the treated animals was similar to controls. Mean body weights of the high-dose females were generally lower than the controls. Non-neoplastic lesions were limited primarily to the anterior region of the nasal cavity; the effects were qualitatively similar to those seen in the rats (see accompanying summary on the two-year rat study by van Birgelen et al. [2000]). Squamous metaplasia of the respiratory epithelium was observed in both sexes of mice while female mice also had inflammation and hyaline degeneration of the respiratory epithelium. The incidence and severity grade (in parentheses) of the hyaline degeneration were: 16/50 (1.4), 35/49 (1.4), 32/50 (1.3) and 30/50 (1.1) for the 0, 0.0625, 0.125 and 0.25 ppm dose groups, respectively. The LOAEL for this study is 0.0625 ppm based on hyaline degeneration of the respiratory epithelium in female mice. A NOAEL was not established (van Birgelen et al., 2000) [Kl. score = 2].

Dermal

Applications of a 50% solution of glutaraldehyde was applied to the skin of male and female SD rats for 13 weeks. The doses were 0, 50, 100 and 150 mg/kg glutaraldehyde. At the application site, there were signs of irritation (scabs, desquamation and very slight or well-defined erythema). There was no treatment-related mortality, clinical signs, body weights, feed consumption and ophthalmoscopic effects. There were no changes in the haematology and clinical chemistry parameters that were considered to be biologically or toxicologically relevant. Organ weights were similar between treated and control animals. Histopathological examination showed treatment-related effects in the skin associated with chronic irritation; no other changes were noted that were considered to be treatment-related. The NOAEL for this study is 150 mg/kg, the highest dose tested (ECHA) [Kl. score = 1].

G. Genotoxicity

In Vitro Studies

Glutaraldehyde may exhibit weak genotoxic effects in some *in vitro* tests. The bacterial reverse mutation assays have been the most consistent. Variable results have been reported for the forward gene mutation tests; and for sister chromatid exchange (SCE), chromosomal aberration and Unscheduled DNA Synthesis (UDS) tests (Vergnes and Ballantyne, 2002).

In Vivo Studies

The *in vivo* studies conducted on glutaraldehyde are presented in Table 5. All the studies show that glutaraldehyde is not mutagenic or genotoxic.

Table 5: *In Vivo* Genotoxicity Studies on Glutaraldehyde

Test System	Results*	Klimisch Score	Reference
Rat bone marrow (chromosomal aberration)	-	1	ECHA
Rat bone marrow (chromosomal aberration)	-	2	ECHA
Mouse bone marrow (micronucleus)	-	1	ECHA
Rat bone marrow (chromosomal aberration)	-	2	ECHA
Rat germ cell cytogenetic assay (alkaline elution)	-	2	ECHA
Drosophila SLRL Test	-	2	ECHA
Rat liver UDS Assay	-	1	ECHA
Rat germ cell cytogenetic assay (alkaline elution)	-	2	ECHA
Mouse peripheral blood micronucleus study	-	2	Vernes and Ballantyne (2002)
Rat liver UDS Assay	-	2	Mirsalis *et al.* (1989)

* +, positive; -, negative

H. Carcinogenicity

Oral

Male and female Fischer 344 rats were given in their drinking water 0, 50, 250 or 1,000 ppm glutaraldehyde for 104 weeks. The mean glutaraldehyde consumption was 0, 4, 17 and 64 mg/kg/day for males and 0, 6, 25 and 86 mg/kg/day for females. Mortality rates were 25-30% and 19-23% for males and females, respectively, with no dose-related increase. The major cause of death in all dose groups including the controls was LGLL. There was an increased incidence of LGLL in the liver and spleen in all treated females ($\geq$ 50 ppm). The incidence of LGLL was not significantly increased in the treated males compared to the controls. No other treatment-related increased incidence of tumours was seen (Van Miller et al., 2002) [Kl. score = 2].

Male and female Wistar rats were given in their drinking water 0, 100, 500 or 2,000 ppm glutaraldehyde for two years. The mean daily intake of glutaraldehyde was as follows: 0, 6.1, 31.9 and 120.7 mg/kg/day for males; and 0, 10.5, 48.5 and 176.4 mg/kg/day for females. In the high-dose animals, there was mortality (2 males and 9 females) from asphyxia, and mean terminal body weights were significantly decreased compared to the controls. There were no treatment-related neoplastic effects (ECHA) [Kl. score = 1].

Inhalation

Male and female $B6C3F_1$ mice were exposed by inhalation to 0 or 0.1 ppm (0 or 0.4 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for 52 and 78 weeks. No exposure-related neoplastic lesions were observed in either males or females (Zissu et al., 1998) [Kl. score = 2].

Male and female Fischer 344 rats were exposed by inhalation to 0, 0.25, 0.5 or 0.75 ppm (0, 1, 2 or 3.1 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for two years. Survival in the mid- and high-dose females was statistically significantly decreased compared to controls. Survival of the treated males was similar to controls. No exposure-related neoplastic lesions were observed in either males or females (van Birgelen et al., 2000) [Kl. score = 2].

Male and female B6C3F$_1$ mice were exposed by inhalation to 0, 0.0625, 0.125 or 0.25 ppm (0, 0.26, 0.5 or 1 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for two years. Survival of the treated animals was similar to controls. No exposure-related neoplastic lesions were observed in either males or females (van Birgelen et al., 2000) [Kl. score = 2].

I. Reproductive Toxicity

A two-generation reproductive toxicity study was conducted in Wistar rats given 0, 100, 500 and 2,000 ppm glutaraldehyde in their drinking water. The approximately mean daily intake is 0, 12, 58 and 199 mg/kg/day for the parental males and females of the F_0 and F_1 generation during premating. There were no adverse effects on reproductive performance or fertility. Oestrous cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights, gross and histopathological findings of these organs were similar between treated and control groups. In the high-dose animals, there was decreased water and/or food consumption; and decreased body weights and/or reduced body weight gains during the premating periods in the F_0 and F_1 parental females during premating, gestation and/or lactation. The high-dose F_1 parental females also had increased the number of erosions/ulcers with microscopic erosion(s) or inflammatory oedema in the mucosa/submucosa of the glandular stomach. There were no adverse effects in the 500 ppm animals except for slight decreases in water consumption due to a palatability (bad taste) problem. Treatment-related signs of developmental toxicity were seen in the progeny of the high-dose F_0 and F_1 parental generation and included impairment in body weight and consequently in organ weights in the respective F_1 and F_2 pups. The NOAEL for reproductive toxicity is 2,000 ppm (199 mg/kg/day), the highest dose tested. The NOAEL for parental systemic toxicity is 500 ppm (58 mg/kg/day). The NOAEL for developmental toxicity is 500 ppm or 58 mg/kg/day (ECHA) [Kl. score = 1].

A two-generation reproductive toxicity study was conducted in Crj: CD(SD) rats given 0, 50, 250 and 1,000 ppm glutaraldehyde in their drinking water. Mean daily intake was not calculated. Parental body weights and body weight gains were significantly reduced at 1,000 ppm at some periods, particularly during pre-mating. Food consumption was significantly reduced at 1,000 ppm for the F_0 and F_1 parental animals during pre-mating and gestation, and F_1 females during lactation. Water consumption was reduced throughout the pre-mating period for the F_0 and F_1 250 and 1,000 ppm parental animals. There was no indication of adverse effects on reproductive performance or fertility at any dose level. For the F_1 1,000 ppm offspring, body weights were reduced from lactation days 21-28. The NOAEL for reproductive toxicity is 1,000 ppm, the highest dose tested. The NOAEL for parental systemic toxicity is 50 ppm. The NOAEL for developmental toxicity is 250 ppm (Neeper-Bradley and Ballantyne, 2000) [Kl. score = 2].

J. Developmental Toxicity

Pregnant Wistar rats were given in their drinking water 0, 50, 250 or 750 ppm (0, 5, 26 or 68 mg/kg) glutaraldehyde from GD 6 to 16. Water consumption was reduced in a dose-related manner in the $\geq$ 250 ppm dams, and was considered not to be a toxic response, but due to the palatability (bad taste) of the drinking test solution. No other maternal effects were seen in the study. There were no significant differences between treated and controls in the sex distribution, placental weights, foetal

weights, malformations or variations. The NOAEL for maternal and developmental toxicity in this study is 68 mg/kg/day, respectively (ECHA) [Kl. score = 1].

Pregnant Wistar rats were dosed by oral gavage with 0, 25, 50 or 100 mg/kg glutaraldehyde on GD 6 to 15. Mortality was significantly increased in the high-dose group (5/26); there were 2/21 deaths in the mid-dose group. Clinical signs (piloerection) occurred in all treated groups in a dose-dependent manner. Maternal body weight gain and feed consumption were significantly reduced in the high-dose dams, but not at the lower doses. The necropsy findings showed evidence of stomach irritation in almost all of the animals that died during the study and in 12/21 of the surviving dams in the high-dose group. The number of implantations per litter, resorptions and dead foetuses per litter, live foetuses per litter and incidence of post-implantation loss per litter was similar across all groups. The mean foetal body weights for male and female foetuses were significantly reduced in the high-dose group; this was attributed to the reduced food consumption of the dams during gestation rather than a direct effect of treatment. There was no evidence of a treatment-related teratogenic effect. The NOAEL for maternal and developmental toxicity is 50 mg/kg/day, respectively (Ema et al., 1992) [Kl. score = 2].

Pregnant Himalayan rabbits were dosed by oral gavage with 0, 5, 15 or 45 mg/kg glutaraldehyde on GD 7 to 19. In the high-dose group, 5/15 died on GD 9-11. Food consumption and body weight gain were also significantly reduced in the high-dose group. Clinical observations in 12/15 high-dose does included soft faces, diarrhoea and blood in the bedding. The mean gravid uterus weight was significantly reduced in the high-dose group. Post-implantation loss was greatly increased (94.3%) in the high-dose group: no viable foetuses in 9/15 of the high-dose does, only early resorptions; only one female gave four alive foetuses on the scheduled date. There were reduced placental and foetal body weights in the only four foetuses. No significant maternal or developmental effects were seen in the mid- and low-dose groups. The NOAEL for maternal and developmental toxicity in this study is 15 mg/kg/day (ECHA) [Kl. Score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for glutaraldehyde follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

The lowest NOAEL values from key toxicity studies on glutaraldehyde are listed in Table 6.

Table 6: Lowest NOAEL Values from Key Toxicity Studies on Glutaraldehyde by the Oral Route

Species/Sex	Study Duration	mg/kg/day	Endpoint	Reference
Rats, female	90/days	4	Decreased body weights, food and water consumption	ECHA
Rats, male	13-wk (drinking water)	5	Increased kidney weights	ECHA

Species/Sex	Study Duration	mg/kg/day	Endpoint	Reference
Rats, male	12-months (drinking water)	30.5	Clinical signs; decreased body weights and food consumption; increased clear cell foci in liver	ECHA
Rats, male	2-yr (drinking water)	4	Reduced body weight, body-weight gain, and food consumption	Van Miller *et al.* (2002)
Rats	2-generation (drinking water)	58	Systemic toxicity	ECHA
Rats	GD 6-16 (drinking water)	68	Developmental toxicity	ECHA
Rats	GD 6-15 (oral gavage)	50	Developmental toxicity	Ema *et al.* (1992)
Rabbits	GD 7-19 (oral gavage)	15	Developmental toxicity	ECHA

The lowest NOAEL from these studies is 4 mg/kg/day based on reduced body weights, body weight gain and feed consumption in male rats from the two-year drinking water study (Van Miller et al., 2002). The NOAEL of 4 mg/kg/day will be used for determining the oral Reference Dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 4/(10 x 10 x 1 x 1 x 1) = 4/100 = <u>0.04 mg/kg/day</u>

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD: Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2 L (ADWG, 2011)
Drinking water guidance value = (0.04 x 70 x 0.1)/2 = 0.14 mg/L

B. Cancer

Increased incidence of large granular cell lymphatic leukaemia (LGLL) was observed in all groups of male and female Fischer 344 rats given glutaraldehyde in their drinking water, including the controls (Van Miller *et al.,* 2002). For the males, the incidence of LGLL was not statistically significantly increased. However, for the females, the incidence of LGLL was significantly increased in all treated females (≥ 50 ppm). Inhalation exposure of Fischer 344 rats to glutaraldehyde did not result in an increased incidence of tumours, including LGLL.

LGLL, also known as mononuclear cell leukaemia, is an extremely common spontaneous neoplastic disease of the ageing F344 rat (Stromberg, 1985; Ward *et al.* 1990; Thomas et al., 2007). Consistent features are splenomegaly, anaemia, thrombocytopenia and leukemic infiltration of the spleen, liver, lung, and in an advanced stage, of several other organs. The incidence is variable but has been increasing progressively with time and can exceed 70% in controls in some studies. This compares with background incidence of less than 1% in other strains of commonly used laboratory rats (Haseman et al., 1998; Thomas et al., 2007). The incidence in F344 rats is modulated by a variety of factors not clearly related to carcinogenicity. Corn oil gavage, for example, has been shown consistently to reduce the incidence of MCL in male, but not female, controls (reviewed in Thomas et al., 2007).

The neoplastic mononuclear cells appear to be derived from large granular lymphocytes (LULs) (reviewed in Thomas et al., 2007). The tumour cell is of the NK type in most, if not all, cases. LGL leukaemia, although uncommon, does occur in humans. There are two types: T-LGL leukaemia which has a chronic course characterised by neutropenia, recurrent infections, splenomegaly and accompanying rheumatoid arthritis, and the much rarer NK-LGL leukaemia which has an acute course, more pronounced splenomegaly, and thrombocytopenia. The latter type appears to resemble more closely the disease in the F344 rat than the former. The aetiology of human LGL leukaemia is unknown. There is some evidence that viral infection may play a role but no evidence that a chemically-related increased of LGLL in the F344 rat is indicative of the potential to induce LGL leukaemia in humans.

To extrapolate results from an animal model that has a clear predisposition (high spontaneous rates) to a tumour type to humans, of which this is not the case, seems inappropriate if the mechanism(s) for LGLL formation in that strain is not understood. Although that rat strain may be useful for understanding the disease process in humans, it does not seem reasonable to use the results from that rat strain for risk assessment purposes. There should be confirmation of a putative leukemogenic effect in the F344 rat in another strain before any conclusions are made about the use of this tumour type for human health risk assessment purposes.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Glutaraldehyde does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Glutaraldehyde has a moderate acute toxicity concern to fish and invertebrates, but is highly toxic to algae. It is of low toxicity concern to terrestrial invertebrates and plants. To birds, glutaraldehyde is moderately toxic on an acute basis and slightly toxic on a subacute dietary basis.

B. Aquatic Toxicity

Acute Studies

Table 7 lists the results of acute aquatic toxicity studies conducted on glutaraldehyde.

Table 7: Acute Aquatic Toxicity Studies on Glutaraldehyde

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Bluegill sunfish	96-hr LC_{50}	13	2	ECHA
Oncorhynchus mykiss	96-hr LC_{50}	10	2	ECHA
Daphnia magna	48-hr LC_{50}	14.87	2	ECHA
Daphnia magna	48-hr LC_{50}	14	2	ECHA
Scenedesmus subspicatus	72-hr EC_{50}	0.375 (biomass) 0.6 (growth rate) 0.025 (NOEC)	1	ECHA
Scenedesmus subspicatus	72-hr EC_{50}	0.92 (growth rate) 0.61(biomass) 0.33 (NOEC)	2	ECHA; Leung, 2001
Scenedesmus subspicatus	72-hr EC_{50}	0.61 (growth rate)	2	ECHA

Chronic Studies

The chronic aquatic toxicity studies conducted on glutaraldehyde are listed in Table 8.

Table 8: Chronic Aquatic Toxicity Studies on Glutaraldehyde

Test Species	Endpoint	Results (mg/L)	Kl. score	Reference
Oncorhynchus mykiss	97/day (OECD 210)	LOEC = 5 NOEC = 1.6	1	ECHA
Daphnia magna	21/day	NOEC = 5	1	ECHA

C. Terrestrial Toxicity

Table 9 lists the results of toxicity studies conducted on glutaraldehyde with earthworms, soil microorganisms and birds.

Table 9: Terrestrial Toxicity Studies on Glutaraldehyde

Test Species (method)	Endpoint	Results	Kl. score	Reference
Earthworm *Eisenia fetida* (OECD 207)	14-d LC_{50}	> 500 mg/kg soil dw	1	ECHA
Soil microorganisms* (OECD 216)	28-d EC_{50} 28-d EC_{10}	360 mg/kg soil dw 11.5 mg/kg soil dw	1	ECHA
Soil microorganisms* (OECD 217)	28-d EC_{50} 28-d EC_{10}	> 593 mg/kg soil dw 1.5 mg/kg soil dw	1	ECHA
Mallard ducks	Single-dose (oral gavage) LC_{50}	206 mg/kg	2	ECHA
Mallard ducks	5-d (dietary) NOEC	> 2,500 ppm	1	ECHA

*organic carbon content of soil = 1.34% dry weight

Glutaraldehyde has also been evaluated in a terrestrial plants test: seedling emergence and seedling growth test (OECD TG 208). The test material contained 48.9% glutaraldehyde. The results are as follows:

Avena sativa (oats): 19/day EC_{50} value is > 1,000 mg/kg soil dry weight based on emergence rate, dry weight and shoot length. The NOECs for *Avena sativa* (oats) were $\geq$ 1,000 mg/kg dry weight on all three parameters tested.

Brassica napus (rapeseed): 19/day EC_{50} is > 1,000 mg/kg soil dry weight based on emergence rate and shoot length and 994 mg/kg soil dry weight based on dry weight. The NOECs were $\geq$ 1,000, 500 and 250 mg/kg soil dry weight for emergence rate, dry matter and shoot length, respectively.

Vicia sativa (vetch): 19/day EC_{50} is > 1,000 mg/kg soil dry weight based on emergence rate and shoot length, and 901 mg/kg soil dry weight based on dry weight. The NOECs were $\geq$ 1,000, 125 and 125 mg/kg soil dry weight for emergence rate, dry matter, and shoot length, respectively (ECHA) [Kl. score = 1].

D. Calculation of PNEC

The PNEC calculations for glutaraldehyde follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (10 mg/L), *Daphnia* (14 mg/L) and algae (0.375 mg/L). Results from chronic studies are also available for all three trophic levels, with the lowest NOEC being 0.025 mg/L for algae. On the basis that the data consists of short-term and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC of 0.025 mg/L for algae. The $PNEC_{water}$ is 0.0025 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.006 mg/kg wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (3.1/1280) \times 1000 \times 0.0025$
$= 0.006$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 4.8)/1000 \times 2400]$
$= 3.1\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{0c} \times f_{oc}$
$= 120 \times 0.04$
$= 4.8$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for glutaraldehyde in sediment is 120.
F_{oc} = fraction of organic carbon suspended sediment = 0.04 [default].

PNEC soil

Experimental results are available for three trophic level. An acute LC_{50} value is available for earthworms (> 500 mg/kg). Results from long-term studies are available for two trophic levels, with the lowest NOEC or EC_{10} being 1.5 mg/kg soil dry weight for soil organisms.

The EC_{10} value is corrected for bioavailability of glutaraldehyde in soil by normalising to the fraction organic carbon matter content (Fom) in the soil using the following equation:

$EC_{10(std)} = EC_{10(exp)} \times Fom_{soil(std)}/Fom_{soil(exp)}$

Where:
$Fom_{soil(std)}$ = 1% (default soil fraction organic matter)
$Fom_{soil(exp)}$ = 1.34% (see Table 9)
$EC_{10(std)}$ = 1.5 mg/kg x 1/1.34 = 1.12 mg/kg

On the basis that the data consists of one short-term result from one trophic level and two long-term results from two additional levels, an assessment factor of 50 has been applied to the lowest reported long-term EC_{10} of 1.12 mg/kg soil dry weight [corrected for organic carbon content] for soil organisms. The $PNEC_{soil}$ is 0.02 mg/kg soil dry weight.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Glutaraldehyde is readily biodegradable and thus does not meet the screening criteria for persistence.

The log K_{ow} for glutaraldehyde at different pH values ranges from -0.36 to -0.80. Thus, glutaraldehyde does not meet the screening criteria for bioaccumulation.

The lowest NOEC value from chronic aquatic toxicity studies is < 0.1 mg/L. Thus, glutaraldehyde meets the screening criteria for toxicity.

The overall conclusion is that glutaraldehyde is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity Category 3 [oral]

Acute Toxicity Category 2 [inhalation]

Skin Corrosion Category 1B

Eye Damage Category 1

Respiratory Sensitiser 1A

Skin Sensitiser 1A

STOT Single Exposure Category 3 [respiratory irritation]

Aquatic Acute Category 1

Aquatic Chronic Category 2

The appropriate hazard statements corresponding the GHS classifications are to be added to the SDS, including the non-GHS hazard statement “AUH071: Corrosive to the Respiratory Tract”.

B. Labelling

Danger

C. Pictograms

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

First aid information was obtained from the ECHA REACH database (ECHA).

Eye Contact

Wash immediately and continuously with flowing water for at least 30 minutes. Remove contact lenses after the first 5 minutes and continue washing. Obtain prompt medical consultation, preferably from an ophthalmologist. Eye wash fountain should be located in immediate work area.

Skin Contact

Take off contaminated clothing. Wash skin with soap and plenty of water for 15-20 minutes. Call a poison control centre or doctor for treatment advice. Wash clothing before reuse. Shoes and other leather items which cannot be decontaminated should be disposed of properly. Safety shower should be located in immediate work area.

Inhalation

Move person to fresh air. If a person is not breathing, call an emergency responder or ambulance, then give artificial respiration; if by mouth-to-mouth use rescuer protection (pocket mask, etc.). Call a poison control centre or doctor for treatment advice. If breathing is difficult, oxygen should be administered by qualified personnel.

Ingestion

If the person is fully alert and cooperative, have the person rinse mouth with plenty of water. In cases of ingestion have the person drink 4 to 10 ounces (120-300 mL) of water. Do not induce vomiting. Do not attempt mouth rinse if the person has respiratory distress, altered mental status, or nausea and vomiting. Call a physician and/or transport to an emergency facility immediately. See Note to Physician. Seek medical attention immediately.

Notes to Physician

Maintain adequate ventilation and oxygenation of the patient. May cause asthma-like (reactive airways) symptoms. Bronchodilators, expectorants, antitussives and corticosteroids may be of help. Glutaraldehyde may transiently worsen reversible airways obstruction including asthma or reactive airways disease. Chemical eye burns may require extended irrigation. Obtain prompt consultation, preferably from an ophthalmologist. If the burn is present, treat as any thermal burn, after decontamination. Due to irritant properties, swallowing may result in burns/ulceration of mouth,

stomach and lower gastrointestinal tract with subsequent stricture. Aspiration of vomitus may cause lung injury. Suggest endotracheal/oesophagal control if lavage is done. Probable mucosal damage may contraindicate the use of gastric lavage. Inhalation of vapours may result in skin sensitisation. In sensitised individuals, re-exposure to very small amounts of vapour, mist or liquid may cause a severe allergic skin reaction. No specific antidote. Treatment of exposure should be directed at the control of symptoms and the clinical condition of the patient. Have the Safety Data Sheet, and if available, the product container or label with you when calling a poison control centre or doctor, or going for treatment.

Medical Conditions Aggravated by Exposure

Excessive exposure may aggravate pre-existing asthma and other respiratory disorders (e.g., emphysema, bronchitis, reactive airways dysfunction syndrome).

Emergency Personnel Protection

First Aid responders should pay attention to self-protection and use the recommended protective clothing (chemical resistant gloves, splash protection). If the potential for exposure exists, refer to Section 8 of the Safety Data Sheet for specific personal protective equipment.

B. Fire Fighting Information

Firefighting information was obtained from the ECHA REACH database (ECHA).

Extinguishing Media

Use water fog, carbon dioxide, dry chemical or foam to extinguish combustible residues of this product

Specific Exposure Hazards

This material will not burn until the water has evaporated. Residue can burn. Some components of this product may decompose under fire conditions. The smoke may contain unidentified toxic and/or irritating compounds. Combustion products may include, and are not limited to, carbon monoxide and carbon dioxide.

Special Protective Equipment for Firefighters

Wear positive-pressure self-contained breathing apparatus (SCBA) and protective firefighting clothing (includes firefighting helmet, coat, trousers, boots and gloves). Avoid contact with this material during firefighting operations. If contact is likely, change to full chemical resistant firefighting clothing with self-contained breathing apparatus. If this is not available, wear full chemical resistant clothing with self-contained breathing apparatus and fight the fire from a remote location.

C. Accidental Release Measures

Information on accidental release measures was obtained from the ECHA REACH database (ECHA).

Personal Precautions

Use appropriate safety equipment. Evacuate area. Keep upwind of the spill. Ventilate area of leak or spill. Only trained and properly protected personnel must be involved in clean-up operations.

Environmental Precautions

Spills or discharge to natural waterways is likely to kill aquatic organisms. Prevent from entering into soil, ditches, sewers, waterways and/or groundwater.

Steps to be Taken if Material is Released or Spilt

Avoid making contact with spilt material; glutaraldehyde will be absorbed by most shoes. Always wear the correct protective equipment, consisting of splash-proof mono-goggles, or both safety glasses with side shields and a wraparound full-face shield, appropriate gloves and protective clothing. A self-contained breathing apparatus or respirator and absorbents may be necessary, depending on the size of the spill and the adequacy of ventilation.

Small spills: Wear the correct protective equipment and cover the liquid with absorbent material. Collect and seal the material and the dirt that has absorbed the spilt material in polyethylene bags and place in a drum for transit to an approved disposal site. Rinse away the remaining spilt material with water to reduce odour, and discharge the rinsate into a municipal or industrial sewer.

Large spills: In the case of nasal and respiratory irritation, vacate the room immediately. Personnel cleaning up should be trained and equipped with a self-contained breathing apparatus, or an officially approved or certified full-face respirator equipped with an organic vapour cartridge, gloves, and clothing impervious to glutaraldehyde, including rubber boots or shoe protection. Deactivate with sodium bisulphite (2-3 parts [by weight] per part of active substance glutaraldehyde), collect the neutralised liquid and place in a drum for transit to an approved disposal site.

D. Storage and Handling

Information on storage and handling was obtained from the ECHA REACH database (ECHA).

General Handling

Do not get in eyes, on skin, on clothing. Avoid breathing vapour. Do not swallow. Keep container closed. Use with adequate ventilation. Wear goggles, protective clothing and butyl or nitrile gloves. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

Other Handling Precautions

Do not spray or aerosolise the undiluted form of the product. Full personal protective equipment (including skin covering and full-face SCBA respirator) is required for dilutions or mixtures of the product used in a spray application.

Storage

Do not store in: Aluminium. Carbon steel. Copper. Mild steel. Iron. Shelf life: Use within 12 Months.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for glutaraldehyde in Australia is 0.1 ppm (0.41 mg/m^3) as a peak limitation, with a sensitisation notation. A peak limitation is defined by Safe Work Australia as a maximum or peak airborne concentration of a substance determined over the shortest analytically practicable period of time which does not exceed 15 minutes.

The information below on exposure controls and personal protection was obtained from the Halliburton Safety Data Sheet (SDS) on ALDACIDE® G ANTIMICROBIAL (revision date: 11-Dec-2014).

Engineering Controls

Use in a well-ventilated area. Local exhaust ventilation should be used in areas without good cross ventilation. If vapours are strong enough to be irritating to the nose or eyes, the TLV is probably being exceeded, and special ventilation or respiratory protection may be required.

Personal Protection Equipment

Respiratory Protection: If engineering controls and work practices cannot keep exposure below occupational exposure limits or if exposure is unknown, wear a NIOSH-certified, European Standard EN 149, AS/NZS 1715:2009, or equivalent respirator when using this product. Selection of and instruction on using all personal protective equipment, including respirators, should be performed by an Industrial Hygienist or other qualified professional. Full Facepiece Respirator with Organic vapour cartridge with particulate pre-filter.

Hand Protection: Chemical-resistant protective gloves (EN 374). Suitable materials for longer, direct contact (recommended: protection index 6, corresponding to > 480-minute permeation time as per EN 374): Butyl rubber gloves. (>= 0.7 mm thickness). This information is based on literature references and on information provided by glove manufacturers or is derived by analogy with similar substances. Please note that in practice the working life of chemical-resistant protective gloves may be considerably shorter than the permeation time determined in accordance with EN 374 as a result of the many influencing factors (e.g., temperature). If signs of wear and tear are noticed, then the gloves should be replaced. Manufacturer's directions for use should be observed because of the great diversity of types.

Skin Protection: Butyl coated apron or clothing.

Eye protection: Splash proof chemical mono-goggles or safety glasses with side shield in conjunction with a face shield. Do NOT wear contact lenses.

Other Precautions: Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

For aqueous glutaraldehyde solutions at a concentration that is corrosive (i.e., 30% and higher):

Australia Dangerous Goods

UN3265, Corrosive Liquid, Acidic, Organic, N.O.S. (Contains Glutaraldehyde)

Class 8

Packing Group III

Environmentally Hazardous Substance

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state, and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII.REFERENCES

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

Ema, M., Itami, T., and Kawasaki, H. (1992). Teratological assessment of glutaraldehyde in rats by gastric intubation. Toxicol. Lett. 63: 147-153.

enHealth Human Risk Assessment (HHRA). (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Frantz, S.W., Beskitt, J.L., Tallant, M.J., Futrell, J.W., and Ballantyne, B. (1993). Glutaraldehyde: species comparisons of in vitro skin penetrations. J. Toxicol.-Cut. & Ocular Toxicol. 12: 349-361.

Gross, E.A., Mellick, P.W., Kari, F.W., Miller, F.J., and Morgan, K.T. (1994). Histopathology and cell replication responses in the respiratory tract of rats and mice exposed by inhalation to glutaraldehyde for up to 13 weeks. Fundam. Appl. Toxicol. 23: 348-362.

Haseman, J.K., Hailey, J.R., and Morris, R.W. (1998). Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F_1 mice in two-year carcinogenicity studies: A National Toxicology Program update. Toxicol. Pathol. 26: 428-441.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology 25:1-5.

Leung, H.W. (2001). Ecotoxicology of glutaraldehyde: review of environmental fate and effects studies. Ecotoxicol. Environ. Safety 49: 26-39.

Mirsalis, J.S., Tyson, C.K., Steinmetz, K.L., Loh, E.K., Hamilton, C.M., Bakke, J.P., and Spalding, J.W. (1989). Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in vivo treatment: testing of 24 compounds. Environ. Mol. Mutagen. 14: 155-164.

Neeper-Bradley, T.L., and Ballantyne, B. (2000). Two-generation reproduction study by dosing with glutaraldehyde in the drinking water of CD rats. J. Toxicol. Environ. Health A 61: 107-129.

NICNAS. (1994). Glutaraldehyde – Full Public Report. National Industrial Chemicals Notification and Assessment Scheme (NICNAS), AGPS, Canberra, Australia.

OECD. (1995). OECD-SIDS document on Glutaraldehyde, CAS No. [redacted] UNEP Publications. Accessed at: http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=b13f2e48-0425-4a8a-b7b8-c04cfaab06e8

Stromberg, P.C. (1985). Large granular lymphocyte leukaemia in F344 rats: Model for human T lymphoma, a malignant histiocytosis and T-cell chronic lymphocytic leukaemia. Am. J. Pathol. 119: 517-519.

Thomas, J., Haseman, J.K., Goodman, J.I., Ward, J.M., Loughran, Jr., T.P., and Spencer, P.J. (2007). A review of large granular lymphocytic leukaemia in Fischer 344 rats as an intial step toward evaluating the implication of the endpoint to human cancer risk assessment. Toxicol. Sci. 99: 3-19.

van Birgelen, A.P.J.M., Chou, B.J., Renne, R.A., Grumbein, S.L., Roycroft, J.H., Hailey, J.R., and Bucher, J.R. (2000). Effects of glutaraldehyde in a 2-year inhalation study in rats and mice. Toxicol. Sci. 55: 195-205.

Van Miller, J.P., Hermansky, S.J., Losco, P.E., and Ballantyne, B. (2002). Chronic toxicity and oncogenicity study with glutaraldehyde dosed in the drinking water of Fischer 344 rats. Toxicol. 175: 177-189.

Vergnes, J.S., and Ballantyne, B. (2002). Genetic toxicology studies with glutaraldehyde. J. Appl. Toxicol. 22: 45-60.

Ward, J.M., Rehm, S., and Reynolds, C.W. (1990). Tumours of the haematopoietic system. In: Pathology of Tumours in Laboratory Animals, Vol. 1, Second Edition (Turusov, V.S., and Mohr, U., Eds.), pp. 625-657, International Agency for Research on Cancer, Lyon, France.

Zissu, D., Bonnet, P., and Binet, S. (1998). Histopathological study in B6C3F1 mice chronically exposed by inhalation to glutaraldehyde. Toxicol. Lett. 95: 131-139.

HYDROCHLORIC ACID

This dossier on hydrochloric acid presents the most critical studies pertinent to the risk assessment of hydrochloric acid in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from OECD-SIDS documents (OECD, 2002a,b) and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

NICNAS has assessed hydrochloric acid in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to the environment.

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Chlorane

CAS RN: [redacted]

Molecular formula: HCl

Molecular weight: 36.46 g/mol

Synonyms: Hydrochloric acid; HCl; chlorane; hydrogen chloride; muriatic acid; chlorohydric acid

SMILES: Cl

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of hydrochloric acid

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Colourless to slightly yellow gas of fuming liquid with pungent, irritating odour.	2	ECHA
Melting Point	-114.22°C	2	ECHA
Boiling Point	-85°C	4	ECHA
Density	1.639 kg/m^3 @ 0°C (gas) 1190 kg/m^3 @ 15°C (liquid)	4	ECHA
Vapour Pressure	4,104 kPa 4,723 kPa @ 25°C	4	ECHA
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	Very soluble	4	ECHA
Viscosity	1.7 × 10^{-6} m^{2}s @ 20°C	1	ECHA

Hydrochloric acid can exist in a gaseous phase at room temperature and pressure. Hydrochloric acid is also very soluble in water and is a strong acid that dissociates completely in water to hydrogen (H^+) and chloride (Cl^-) ions.

III. ENVIRONMENTAL FATE PROPERTIES

Due to its high water solubility, hydrochloric acid will be found predominantly in the aquatic environment where it dissociates completely to hydrogen (H^+) and chloride (Cl^-) ions. Both ions are ubiquitous in the environment (UNEP, 1995).

The addition of hydrochloric acid to an aquatic ecosystem may decrease the pH depending on the buffer capacity of the receiving water. In general, the buffer capacity is regulated by the equilibria between CO_2, HCO_3^- and CO_3^{2-}:

$$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+ \ (pKa_1 = 6.35)$$
$$HCO_3^- \leftrightarrow CO_3^{2-} + H^+ \ (pKa_2 = 10.33)$$

A release of hydrochloric acid into the aquatic environment from the use of HCl could potentially increase the chloride concentration and decrease the pH in the aquatic environment. Table 2 shows the amount of hydrochloric acid that would need to be added to bicarbonate solutions to obtain pH values of 6.0 and 4.0. The UNEP (1995) study reported that the 10th percentile, mean and the 90th percentile of bicarbonate concentrations in 77 rivers in North America, South America, Asia, Africa, Europe and Oceania were 20, 106 and 195 mg/L, respectively. The data show that the decrease in pH depends on the buffer capacity (bicarbonate concentration) of the receiving water. The calculated values in Table 2 were confirmed experimentally.

Table 2: Buffer capacity to maintain the pH based on bicarbonate concentration from UNEP monitoring data (de Groot and van Dijk, 2002; taken from OECD, 2002b)

Initial concentration of HCO_3^-	Final pH	Concentration of HCl required to obtain the final pH value
		Calculated (mg/L)
20 mg/L HCO_3^- (10th percentile 77 rivers)	6.0	8.28
	4.0	11.9
106 mg/L HCO_3^- (mean value of 77 rivers)	6.0	43.9
	4.0	63.2
195 mg/L HCO_3^- (90th percentile 77 rivers)	6.0	80.7
	4.0	116.3

H^+ and Cl^- ions will not adsorb on the particulate matter or surfaces and will not accumulate in living tissues (OECD, 2002a,b).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Hydrochloric acid is a corrosive liquid. Depending on the concentration, aqueous solutions of hydrochloric acid (HCl) are either corrosive, irritating or non-irritating to the skin, eyes and gastrointestinal tract. Vapours from aqueous solutions of HCl can cause respiratory irritation. HCl is not a skin sensitiser. Subchronic inhalation studies show localised irritation to the upper respiratory tract of rats and mice, but no systemic toxicity. No repeated dose toxicity studies have been

conducted by the oral route. Positive findings have been reported in some *in vitro* genotoxicity studies, which are considered to be the result of the pH change in the test system. A lifetime inhalation study showed no carcinogenicity in rats exposed to HCl. No adequate reproductive or developmental studies have been conducted on HCl.

B. Acute Toxicity

The oral LD_{50} values in rats were reported to be 238 to 277 mg/kg and 700 mg/kg (OECD, 2002a,b) [Kl. scores = 2 and 4, respectively].

The lethal dose by dermal exposure is > 5,010 mg/kg for rabbits (OECD 2002a,b) [Kl.score=4].

The LC_{50} values in rats for HCl gas are 40,989 and 4,701 ppm for 5 and 30 minutes, respectively (ECHA) [Kl.score=2]. The LC_{50} values in rats for HCl aerosol are 31,008 and 5,666 ppm (45.6 and 8.3 mg/L) for 5 and 30 minutes, respectively (ECHA) [Kl.score=2].

C. Irritation

Application of a 37% aqueous solution of HCl for 1 or 4 hours was corrosive to the skin of rabbits (OECD, 2002a,b) [Kl.score=2]. Application of 0.5 mL of a 17% solution of aqueous solution of HCl for 4 hours was corrosive to the skin of rabbits (OECD, 2002a,b) [Kl.score=3]. Moderate skin irritation was observed in rabbits following an application of 0.5 mL of a 3.3% aqueous solution of HCl for five days; no irritation was observed with 0.5 mL of a 1% aqueous solution (OECD, 2002a,b) [Kl.score=2]. In humans, an aqueous solution of 4% of HCl was slightly irritating, while a 10% solution was sufficiently irritating to be classified as a skin irritant (OECD, 2002a,b).

Instillation of 0.1 mL of a 10% aqueous solution of HCl to the eyes of rabbits resulted in severe eye irritation (ECHA) [Kl.score=2]. Instillation of 0.1 mL of a 5% solution of HCl produced corneal opacity, iridial lesions, conjunctival redness and chemosis in 3/3 animals at 1 hour and at day one post-instillation. There was no recovery in any animal and the study was terminated on day two (ECHA) [Kl.score=1].

D. Sensitisation

Hydrochloric acid was not a skin sensitiser in a guinea pig maximisation test (ECHA) [Kl.score=2].

E. Repeated Dose Toxicity

<u>Oral</u>

No adequate studies were located.

<u>Inhalation</u>

Male and female SD rats and F344 rats were exposed by inhalation to 0, 10, 20 or 50 ppm 6 hours/day, 5 days/week for up to 90 days. Clinical signs were mainly indicative of the irritant/corrosive nature of HCl. Body weights were significantly decreased in the 50 ppm male F344 rats. There were no treatment-related effects on the haematology or clinical chemistry parameters or urinalysis. At study termination, heart, kidney and testes weights were increased in the 100 and/or 50 ppm groups; these changes were considered to be mainly related to the treatment-

related effect on body weight. Histopathological examination showed minimal to mild rhinitis in the ≥ 20 ppm dose groups of both strains of rats (both sexes). The NOAELs for systemic toxicity and localised irritation (site-of-contact) are 20 and 10 ppm, respectively (ECHA) [Kl.score=1].

Male and female $B6C3F_1$ mice were exposed by inhalation to 0, 10, 20 or 50 ppm HCl, 6 hours/day, 5 days/week for up to 90 days. Clinical signs were mainly indicative of the irritant/corrosive nature of HCl. Body weights were significantly decreased in the 50 ppm groups. At study termination, absolute liver weights were decreased in the 50 ppm males. Histopathologic examination showed only eosinophilic globules in the nasal epithelium in the 50 ppm animals. The NOAEL for this study is 20 ppm (ECHA) [Kl.score=1].

Male SD rats were exposed by inhalation to 0 or 10 ppm HCl 6 hours/day, 5 days/week for 128 weeks. Survival and body weights were similar between treated and control groups. There was a higher incidence of hyperplasia of the larynx compared to control, but no serious irritating effects of the nasal epithelium (ECHA) [Kl.score=2].

Dermal

No studies were located.

F. Genotoxicity

In vitro Studies

Table 3 presents the *in vitro* genotoxicity studies on hydrochloric acid.

Table 3: *In vitro* genotoxicity studies on hydrochloric acid

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	+	2	ECHA
Chromosomal aberration (CHO cells)	+	+	2	ECHA
Saccharomyces cerevisiae (mitotic recombination	-	-	2	ECHA
E. coli W3110 (pol A+) and P3078 (pol A-) repair assay	-	-	2	ECHA

* +, positive; -, negative

In the mouse lymphoma assay, the mutant frequency increased as the pH was lowered to 6.5 to 6.0 (from increased HCl) in the presence of metabolic activation. A decrease in pH from the addition of HCl to the medium also resulted in clastogenic effects to CHO cells in the absence or presence of metabolic activation. The positive findings in these two studies are considered to be the result of the pH change in the test media.

In vivo Studies

No adequate studies were located.

G. Carcinogenicity

Oral

No studies were located.

Inhalation

Male SD rats were exposed by inhalation to 0 or 10 ppm HCl 6 hours/day, 5 days/week for 128 weeks. Survival and body weights were similar between treated and control groups. There was a higher incidence of hyperplasia of the larynx compared to control, but no serious irritating effects of the nasal epithelium. There was no increased incidence of tumours in the HCl-treated rats compared with controls (ECHA) [Kl.score=2].

H. Reproductive Toxicity

No studies were located.

I. Developmental Toxicity

No adequate studies were located.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Repeated dose, reproductive and developmental toxicity studies by the oral route have not been conducted on hydrochloric acid. These toxicity studies would have questionable usefulness because of the corrosive/irritating nature of hydrochloric acid, which would limit the amount of absorbed HCl. Hydrochloric acid dissociates to hydrogen and chloride ions in bodily fluids, and a significant amount of these ions are already ingested in foods. Furthermore, both ions are present in the body and are highly regulated by homeostatic mechanisms. Thus, an oral toxicological reference and drinking water guidance values were not derived from hydrochloric acid.

The Australian drinking water guideline values for pH (6.5 to 8.5) and chloride (250 ppm, aesthetics) may be applicable (ADWG, 2011).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Hydrochloric acid does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The hazard of hydrochloric acid for aquatic organisms is caused by the hydrogen ion (H^+). The toxicity values in terms of mg/L are not relevant because of the varying buffering capacity of different test systems and different aquatic ecosystems.

B. Aquatic Toxicity

Acute Studies

The acute aquatic toxicity studies on hydrochloric acid are listed in Table 4.

Table 4: Acute aquatic toxicity studies on hydrochloric acid

Test Species	Endpoint	Results	Klimisch Score	Reference
Lepomis macrochirus	96-hour LC_{50}	pH 3.25 – 3.5 (20 mg/L)	2	ECHA; OECD 2002a,b
Daphnia magna	48-hour EC_{50}	pH 4.92 (0.45 mg/L)	1	ECHA
Chlorella vulgaris	72-hour EC_{50} 72-hour EC_{10}	pH 4.7 [growth rate] (0.73 mg/L) PH 4.7 (0.364 mg/L)	1	ECHA

Chronic Studies

No chronic studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

PNEC values[1] were not derived for hydrochloric acid because factors such as the buffer capacity, the natural pH and the fluctuation of the pH are very specific for a certain ecosystem.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (IChEMS, 2022; ECHA, 2023).

Hydrochloric acid is an inorganic salt that dissociates completely to hydrogen and chloride ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both hydrogen and

[1] An aquatic PNEC (mg/L) has been derived as part of the chemical assessment conducted under National Industrial Chemicals Notification and Assessment Scheme (NICNAS). However, the chronic aquatic toxicity data set used to derive the PNEC value was not available for review.

chloride ions are also ubiquitous and are present in water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Hydrogen and chloride ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated. Thus, hydrochloric acid is not expected to bioaccumulate.

No chronic toxicity data exist on hydrochloric acid. The acute EC_{50} values are > 1 mg/L in fish, < 1 mg/L for invertebrates and algae. Thus, hydrochloric acid meets the screening criteria for toxicity.

The overall conclusion is that hydrochloric acid is a PBT substance based on toxicity to invertebrates and algae.

IX. CLASSIFICATION AND LABELLING

A. Classification

For HCl concentrations of >25%:

- Metal Corrosive Category 1
- Skin Corrosive 1B
- STOT SE Category 3 [Respiratory irritant]

In addition to the hazard statements corresponding to the GHS classification for corrosive, the following non-GHS hazard statement is to be added to the SDS: AUH071: Corrosive to the Respiratory Tract.

B. Labelling

<u>Danger</u>

According to the classification provided by companies to ECHA in REACH registrations this substance causes severe skin burns and eye damage, is toxic if inhaled, may damage fertility or the unborn child, causes serious eye damage, may cause damage to organs through prolonged or repeated exposure, may be corrosive to metals and may cause respiratory irritation.

C. Pictogram

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of the body with soap and fresh water. Get medical attention immediately.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the aid of a pocket mask equipped with a one-way valve or another proper respiratory medical device. Give artificial respiration if the victim is not breathing. Get medical attention immediately.

Ingestion

Rinse mouth and lips with plenty of water if a person is conscious. Do not induce vomiting. Do not use mouth-to-mouth method if the victim ingested the substance. Obtain medical attention immediately if ingested.

Notes to Physician

Treat as corrosive due to pH of the material. All treatments should be based on observed signs and symptoms of distress in the patient.

B. Firefighting Information

Extinguishing Media

Use dry chemical, carbon dioxide, water spray or fog, or foam.

Specific Exposure Hazards

Containers may explode when heated. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following materials: halogenated compounds, may release dangerous gases (chlorine).

Special Protective Equipment for Firefighters

Structural firefighters' protective clothing provides limited protection in fire situations only; it is not effective in spill situations where direct contact with the substance is possible. Wear chemical protective clothing that is specifically recommended by the manufacturer. It may provide little or no thermal protection. Wear positive pressure self-contained breathing apparatus (SCBA). Move containers from the fire area if you can do it without risk.

C. Accidental Release Measures

Personal Precautions

Ventilate enclosed areas. Do not walk through spilt material. Do not touch damaged containers or spilt material unless wearing appropriate protective clothing. Wear appropriate personal protective equipment, avoid direct contact. Do not breath mist, vapours or spray. Do not get in eyes, on skin or on clothing.

Environmental Precautions

Prevent entry into waterways, sewers, basements or confined areas.

Steps to be Taken if Material is Released or Spilt

ELIMINATE all ignition sources (no smoking, flares, sparks or flames in immediate area). As an immediate precautionary measure, isolate spill or leak area for at least 50 meters in all directions. Keep unauthorised personnel away. Stay upwind. Keep out of low areas. Do not get water inside container.

D. Storage and Handling

General Handling

Handle and open container with care. Use only with adequate ventilation. Keep away from heat. Use caution when combining with water. DO NOT add water to corrosive liquid; ALWAYS add corrosive liquid to water while stirring to prevent the release of heat, steam and fumes. Wear appropriate personal protective equipment, and avoid direct contact. Do not breath mist, vapours or spray. Do not get in eyes, on skin or on clothing. Do not ingest. Wash thoroughly with soap and water after handling and before eating, drinking or using tobacco.

Storage

Keep contain tightly closed. Store in a cool, dry, well-ventilated place. Keep away from incompatible materials. Keep from direct sunlight. Separate from alkalis. Do not store above 49°C/120°F.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for hydrochloric acid in Australia is 5 ppm (7.5 mg/m^3 as a peak limitation, with a sensitisation notation). A peak limitation is defined by Safe Work Australia as a

maximum or peak airborne concentration of a substance determined over the shortest analytically practicable period of time that does not exceed 15 minutes.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. Use a properly fitted, air-purifying or air-fed respirator complying with an approved standard if a risk assessment indicates this is necessary. Respirator selection is based on known or anticipated exposure levels, the hazard of the product and the safe working limits of the selected respirator.

Hand Protection: Chemical-resistant, impervious gloves complying with an approved standard should be worn at all times when handling chemical products if a risk assessment indicates this is necessary. Considering the parameters specified by the glove manufacturer, check during use that the gloves are still retaining their protective properties. It should be noted that the time to breakthrough for any glove material may be different for different glove manufacturers. In the case of mixtures, consisting of several substances, the protection time of the gloves cannot be accurately estimated.

Skin Protection: Personal protective equipment for the body should be selected based on the task being performed and the risks involved and should be approved by a specialist before handling hydrochloric acid.

Eye Protection: Wear chemical splash goggles and face shield.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Australian Dangerous Goods

UN 1789 (HYDROCHLORIC ACID)

Class: 8

Packing Group: II or III

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

Australian Drinking Water Guidelines [ADWG]. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council. Updated September 2022. https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines

de Groot, W.A., & van Dijk, N.R.M. (2002). Addition of hydrochloric acid to a solution with sodium bicarbonate to a fixed pH. Solvay Pharmaceuticals, Study No. A SOL.S.027; cited in OECD 2002a and 2002b.

European Chemicals Agency [ECHA]. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances.

European Chemicals Agency [ECHA]. (2023). Chapter R.11: vPvB assessment. In *Guidance on information requirements and chemical safety assessment*. Version 4.0. https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Industrial Chemicals Environmental Management Standard [IChEMS]. (2022). Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals. https://www.dcceew.gov.au/sites/default/files/documents/australian-pbt-criteria.pdf

Klimisch, H.J., Andreae, M., & Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol., 25*, 1–5.

Organisation for Economic Co-operation and Development [OECD]. (2002a). IUCLID Data Set for Hydrogen chloride (CAS No. [redacted] UNEP Publications.

Organisation for Economic Co-operation and Development [OECD]. (2002b). Screening Information Dataset (SIDS) Initial Assessment Report for Hydrogen chloride (CAS No. [redacted] UNEP Publications.

UN Environment Programme [UNEP]. (1995). Water quality of world river basins. UNEP Environment Library No. 14, Nairobi, Kenya; cited in OECD, 2002a and 2002b.

SODIUM CHLORIDE

This dossier on sodium chloride presents the most critical studies pertinent to the risk assessment of sodium chloride in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. CHEMICAL NAME AND IDENTIFICATION

Chemical Name (IUPAC): sodium; chloride

CAS RN: [redacted]

Molecular formula: NaCl

Molecular weight: 58.44 g/mol

Synonyms: Halite, Salt, Table salt, Saline, Rock salt, Common salt, Dendritis, Purex'

SMILES: [Cl-].[Cl-].[Ca+2]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Sodium Chloride

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White crystaline solid	-	ECHA
Melting Point	801 °C @ 101.3 kPa	-	ECHA
Boiling Point	The study does not need to be conducted, because NaCl is a solid which melts above 300°C.	1	ECHA
Density	2163 kg/m^3 @ 20 °C	1	ECHA
Vapour Pressure	The study does not need to be conducted, because NaCl is a solid which melts above 300°C.	1	ECHA
Partition Coefficient (log K_{ow})	The study does not need to be conducted, because NaCl is inorganic.	1	ECHA
Water Solubility	317 g/L @ 20°C	2	ECHA
Dissociation Constant (pKa)	Not applicable, NaCl is an electrovalent substance.	-	ECHA

III. ENVIRONMENTAL FATE SUMMARY

Sodium chloride (NaCl) dissociates completely in aqueous solutions to sodium (Na^+) and chloride (Cl^-) ions. Sodium chloride and its dissociated ions are ubiquitous in the environment.

The transport and/or leaching of sodium (Na^+) and chloride (Cl^-) ions is affected by clay minerals (type and content), pH, and organic matter. Similar to potassium, sodium ions are less mobile and less prone to leaching than anions in soil, such as chloride and nitrate (NO_3^-). Chloride binds only weakly to soil particles, and therefore follows water movement (DoEE, 2017; OECD, 2001).

Chloride (Cl^-) ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated (OECD, 2001). Neither sodium chloride nor its dissociated ions are expected to bioaccumulate.

Release to surface waters under the assessed circumstances is expected to have limited long-term environmental effects as these salts are ubiquitous and are present in most water, soil and sediment, therefore organisms are adapted to a level of exposure. The magnitude of the acute effect for a receiving aquatic environment would depend on the released concentrations as well as the degree of adaptation of species present to these naturally occurring ions and salts (DoEE, 2017).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Historically, sodium chloride (as a major ingredient in edible salt) has been commonly used in cooking as a condiment and food preservative. Sodium is an electrolyte that regulates the amount of water in your body and also plays a part in nerve impulses and muscle contractions. When depleted in the body, sodium must be replaced in order to maintain intracellular osmolarity, nerve condition, muscle contraction and normal renal function. Sodium chloride is used to treat or prevent sodium loss caused by dehydration, excessive sweating or other causes.

The NHMRC has established dietary guidelines for the intake of sodium per day (adult) as less than 2,000 mg sodium per day (NHMRC, 2007 updated 2017). Sodium chloride is categorised under GRAS (Generally Recognised as Safe) by the FDA (U.S. Food and Drug Administration) and the average daily levels of sodium intake for adults range from 2 to 5 grams. A technical report by WHO and the Food and Agriculture Organization (FAO) recommended the consumption of less than 5 grams sodium chloride (or 2 grams sodium) per day as a population nutrient intake goal, while ensuring that the salt is iodised (WHO, 2007).

NICNAS has assessed sodium chloride in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to human health or the environment[1] .

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

Sodium chloride has low acute toxicity by the oral, dermal or inhalation route. It is not a skin irritant or a skin sensitiser. Long-term studies in rats fed sodium chloride showed elevated blood pressure. It is not a carcinogen and nor a developmental toxicant.

B. Acute Toxicity

Oral

The acute oral LD_{50} values of sodium chloride in rats is greater than 3,550 mg/kg with fiducial limits of 3,040 – 4,140 mg/kg (ECHA) [KI scores = 2].

Dermal

A dermal toxicity study was conducted in rabbits and the LD_{50} value was greater than 10,000 mg/kg and hence not classified according to EU Annex VI (ECHA) [KI scores = 2].

Inhalation

An acute inhalation toxicity study was conducted at a dose of 42 mg/L administered as an aerosol of a 20% aqueous solution to male rats and the results of the study indicated that the LC_{50} of sodium chloride was greater than 42 mg/L (42,000 mg/m^3) and hence not classified (ECHA) [KI scores = 2].

C. Irritation

Skin

When in contact with the intact skin, sodium chloride causes no response, either in undiluted form or in solution. Sodium chloride is considered to be slightly to not irritating to the skin (ECHA) [KI score = 2].

Eye

No adequate or reliable studies are available.

D. Sensitisation

Sodium chloride is not considered to be a skin sensitiser (ECHA).

E. Repeated Dose Toxicity

Oral

The estimated fatal dose of sodium chloride is approximately 0.75 to 3.00 g/kg (HSDB - Hazard Substance Data Bank - 750 to 3000 mg/kg). The lowest toxic dose (TDLo) for an adult man with normal blood pressure is 8,200 mg/kg (Patty's Handbook of Toxicology). High oral sodium chloride intake is associated with increased risk of hypertension; however, this is a well studied field in humans and additional animal testing data would not add value. Based on the studies, sodium chloride is not classified for any repeated dose effects.

A two-year feeding study was conducted to investigate the impact of sodium chloride on rats. Animals received a chronic administration at doses of 4% sodium chloride over a period

of 2 years which induces elevated blood pressure in the rats. The LOAEL from this key study identified a dose level of < 4% via the diet and the calculated LOAEL was 2,533 mg/kg/day (ECHA).

Dermal

No adequate or reliable studies are available.

Inhalation

No adequate or reliable studies are available.

F. Genotoxicity

No adequate or reliable studies are available.

G. Carcinogenicity

Sodium chloride is not classified as a carcinogen (ECHA). Sodium chloride is not listed with IARC.

H. Reproductive Toxicity

No adequate or reliable studies are available.

I. Developmental Toxicity

Sodium chloride is not classified as a developmental toxicant (ECHA).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The Australian drinking water guideline value for chloride ions is 250 mg/L based on aesthetics (ADWG, 2011).

The Australian drinking water guideline value for sodium ions is 180 mg/L based on aesthetics (ADWG, 2011).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium chloride does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL EFFECTS SUMMARY

A. Summary

Sodium chloride is of low acute toxicity concern to aquatic organisms, in part because of the effect of pH changes from the dissociated hydrogen ion.

B. Aquatic Toxicity

Acute Studies

The 96-hour LC_{50} value of 5,840 mg/L for sodium chloride was determined in a continuous flow-through exposure system with bluegill sunfish (*Lepomis macrochirus*) (ECHA) [KI score =1].

The EC_{50} 48-hour (immobilisation, *Daphnia magna*) was determined to be 1,900 mg/L (ECHA) [KI score = 2].

The EC_{50} of NaCl at 96 hours to *Lemna* was determined for comparison and found to be 6,870 mg/L (6.87 g/L) (ECHA) [KI score = 1].

Chronic Studies

The 33-day NOEC value of 252 mg/L for sodium chloride was determined in a continuous flow-through exposure system with early life stage fathead minnows (*Pimephales promelas*) (ECHA) [KI score = 2].

A 21-day NOEC (reproduction, *Daphnia pulex*) was determined to be 314 mg/L (ECHA) [KI score = 2].

C. Terrestrial Toxicity

The mean 14-day LC_{50} for three experiments conducted with the earthworm, *E. fetida* was 3,296 mg NaCl/kg soil dw. The 10-week NOEC (based on mortality) was 3,507 mg NaCl/kg soil for the earthworm, *E. fetida* (ECHA) [KI score = 2].

In a 7-day exposure study with red fescue grass, the EC_{50} for germination was 500.8 mg NaCl/kg soil dw. In a 7-day exposure study with Kentucky bluegrass, the NOEC for stem growth was 243 mg NaCl/kg soil dw (ECHA) [KI score = 2].

The 12-hour LD_{50} for wild house sparrows was approximately 3,000 - 3,500 mg/kg NaCl (ECHA) [KI score = 2].

D. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Sodium chloride is an inorganic mineral. Thus, biodegradation is not applicable to this substance. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to sodium chloride.

Bioaccumulation in fish is not expected given the inorganic nature of the substance. Thus, sodium chloride does not meet the screening criteria for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on sodium chloride are greater than 0.1 mg/L. The E(L)C_{50} values from the acute aquatic toxicity studies on sodium chloride are > 1 mg/L. Thus, sodium chloride, does not meet the criteria for toxicity.

The overall conclusion is that sodium chloride is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not Classified

B. Labelling

No signal word.

C. Pictogram

None

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Keep product and empty container away from heat and sources of ignition. May emit toxic fumes of chloride and sodium oxide (above 1,413°C). Depending on conditions, decomposition products may include hydrogen chloride gas.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Prevent from entering sewers, waterways, or low areas.

Steps to be Taken if Material is Released or Spilled

Soak up with inert absorbent material.

D. Storage And Handling

General Handling

Keep product and empty container away from heat and sources of ignition. Ensure adequate ventilation, especially in confined areas.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for choline chloride.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Sodium chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment and Energy [DoEE]. (2017). Environmental risks associated with surface handling of chemicals used in coal seam gas extraction in Australia, Project report prepared by the Chemicals and Biotechnology Assessments Section (CBAS), in the Chemicals and Waste Branch of the Department of the Environment and Energy as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

HSBD. Hazardous Substances Data Bank. https://pubchem.ncbi.nlm.nih.gov/source/hsdb/6368

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

NHMRC. (2007). Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes, Version 1.2 updated September 2017. National Health and Medical Research Council. Department of Health and Ageing. Australian Government.

OECD. (2001). Screening Information Assessment Report (SIAR) for Potassium chloride (CAS No. [redacted] UNEP Publications. Available at: https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?id=68BF142A-D550-432C-8C48-13883944BA1D.

Patty's Toxicology, 6 Volume Set, 6th Edition. Volume 3: 375. July 2012.

WHO. (2007) Reducing salt intake in populations: report of a WHO forum and technical meeting. https://www.who.int/dietphysicalactivity/Salt_Report_VC_april07.pdf. Accessed 28 Apr 2020

DIETHYLENE GLYCOL

This dossier on diethylene glycol presents the most critical studies pertinent to the risk assessment of diethylene glycol in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

NICNAS has assessed diethylene glycol in an Inventory Multi-tiered Assessment and Prioritisation (IMAP) Tier 1 assessment and concluded that it poses no unreasonable risk to the environment[1] .

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-(2-hydroxyethoxy)ethan-1-ol

CAS RN: [redacted]

Molecular formula: $C_4H_{10}O_3$ or $(CH_2CH_2OH)_2O$

Molecular weight: 106.12 g/mol

Synonyms: Diethylene glycol; 2,2'-oxydiethanol; diglycol; bis(2-hydroxyethyl) ether; 2-hydroxyethyl ether; 2,2'-oxybisethanol; 2-(2-hydroxyethoxy)ethanol; ethanol, 2,2'-oxybis-; 2-(2-hydroxyethoxy)ethan-1-ol; glycol ethyl ether; ethylene diglycol

SMILES: C(COCCO)O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of diethylene glycol

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	A colourless viscous liquid	2	ECHA
Melting point	-6.5°C @ 101.3 kPa	2	ECHA
Boiling point	244.9°C @ 101.3 kPa	2	ECHA
Density	1,118 kg/m^3 @ 20°C	2	ECHA
Vapour pressure	0.008 hPa @ 25°	2	ECHA
Partition coefficient (log K_{ow})	-1.98 (calculated)	2	ECHA
Water solubility	1,000 g/L @ 20°C	2	ECHA
Flash point	138°C	2	ECHA
Auto flammability	372°C	2	ECHA

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]%2C+

Property	Value	Klimisch Score	Reference
Viscosity	30 mPa s (dynamic) @ 25°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

The substance is readily biodegradable, is unlikely to bioaccumulate, nor is it likely to adsorb or desorb to soil or sediment to a great extent.

B. Biodegradation

Diethylene glycol is readily biodegradable. In an OECD 301B test, there was 70-80% and 90-100% degradation after 28 days, as determined by CO_2 evolution and DOC removal respectively (ECHA) [Kl.score=2].

In an OECD 301A test, there was 90-100% degradation after 28 days, although the 10-day window was missed (ECHA) [Kl.score=1]. In a modified MITI I test (OECD 301C), there was up to 92% degradation after 28 days (ECHA) [Kl.score=2].

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

No experimental data are available for diethylene glycol. Using KOCWIN in EPI Suite™ (USEPA, 2017), the estimated K_{oc} value from the molecular connectivity index (MCI) and log K_{oc} are 1 and -0.08 L/kg, respectively (ECHA) [Kl Score = 2]. Based on these K_{oc} values, if released to soil, diethylene glycol is expected to not adsorb to soil and have a very high mobility. If released to water, based on the K_{oc} value and its water solubility, it is also not expected to adsorb to suspended solids and sediment.

D. Bioaccumulation

The calculated log K_{ow} for diethylene glycol is -1.98 (Verschueren, 1983). Diethylene glycol has low potential to bioaccumulate. In a 3-day bioaccumulation fish study with *Leuciscus idus melanotus*, the BCF was determined to be 100 (Freitag et al., 1985) [Kl score = 2].

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The substance exhibits low oral acute toxicity. It is not a significant skin or eye irritant, nor is it considered to be a skin sensitiser. No dermal or inhalation repeat dose studies were available but oral repeat does studies suggest moderate urinary dysfunction with oxalate formation in rats. The substance is not genotoxic, carcinogenic nor developmentally toxic.

B. Acute Toxicity

The oral LD_{50}'s in rats is 19,600 mg/kg (Lenk et al., 1989; ECHA) [Kl.score=2] and 16,500 mg/kg (Laug et al., 1939; ECHA) [Kl.score=2].

No deaths were reported in rats exposed to a saturated vapour for 6 hours (OECD, 2007) [Kl score = 2]. No deaths were also reported in male and female Aplk:APfSD (Wistar-derived) rats exposed to 5,080 mg/m^3 diethylene glycol aerosol (MMAD = 2.83 µm, GSD = 2.05) for 4 hours (OECD, 2007) [Kl.score=2].

The dermal LD_{50} in rabbits was reported to be 12,500 mg/kg (OECD, 2007) [Kl score = 2]. The dermal LD_{50} in rabbits was reported to be 13,300 mg/kg (ECHA) [Kl.score=4].

C. Irritation

When applied to the skin of rabbits for 24 hours under occlusive conditions, diethylene glycol was essentially non-irritating with a PII score of 0.04 (Guillot et al., 1982, ECHA) [Kl.score=2]. In a human repeated irritation patch test, diethylene glycol was minimally irritating to the skin (OECD, 2007) [Kl.score=2].

Diethylene glycol was not considered a skin irritant in an *in vitro* reconstructed human epidermis test (ECHA) [Kl.score=1].

Instillation of 0.1 mL diethylene glycol into the eyes of rabbits produced minor, transient irritation; no corneal lesions were observed (OECD, 2007) [Kl score = 2]. When instilled into the eyes of rabbits, the ocular irritancy was 11.67 based on a modified Kay Calandra scale of 0 to 110 (Guillot et al., 1982, ECHA) [Kl.score=2].

D. Sensitisation

Diethylene glycol was not a skin sensitiser to guinea pigs in a maximisation test (OECD, 2007; ECHA) [Kl.score=1]. Diethylene glycol was not a skin sensitiser in a human repeat irritation patch test (OECD, 2007; ECHA) [Kl.score=4].

E. Repeated Dose Toxicity

Oral

Male and female Wistar rats were given 0, 0.085, 0.17, 0.4 and 2.0% diethylene glycol in their diet for 225 days. The corresponding average daily intakes were 0, 51, 105, 234 and 1,194 mg/kg/day for males, and 0, 64, 126, 292 and 1462 mg/kg/day for females. In the 0.4% and 2% groups, there were oxalate crystalluria and mild defects of renal function (increased urine volume), as measured by concentration tests. The only finding in the 0.17% group was a 13.2% increase in urinary oxalate excretion in males; no effects were observed in the 0.085% group. The NOAEL and NOEL for this study was 0.17% (approximately 105 mg/kg/day) and 0.085% (approximately 51 mg/kg/day), respectively (ECHA) [Kl score = 2].

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on diethylene glycol are shown in Table 2.

Table 2: *In vitro* genotoxicity studies on diethylene glycol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	OECD (2007), ECHA
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	ECHA
Chromosomal aberration (CHO cells)	-	-	2	OECD (2007), ECHA
Sister chromatid exchange (CHO cells)	-	-	2	OECD (2007), ECHA

*+, positive; -, negative

In Vivo Studies

Micronuclei were not increased in the bone marrow of NMRI mice given a single intraperitoneal injection of 0, 500, 1,000 or 2,000 mg/kg diethylene glycol (ECHA) [KI score = 1].

G. Carcinogenicity

Oral

Male and female F344 rats were given 0, 1.25 or 2.5% diethylene glycol (97% purity) in their drinking water for two years. The daily intake was estimated to be 0, 1,210 and 2,630 mg/kg/day for males and 0, 1,160 and 2,550 mg/kg/day for females. Mortality was increased in the 2.5% males; drinking water consumption was increased in the 2.5% males and females. There were no significant differences in the incidence of tumours between treated and control animals (Hiasa et al., 1990; ECHA) [KI score = 2].

Male Osborne-Mendel rats were given 0, 1, 2 or 4% diethylene glycol in their feed for two years. During the first 26 weeks of the study, weight gain was significantly reduced at all dose levels. After the first year, the growth of rats fed the 4% diets was significantly reduced relative to the controls. There were no significant differences in food consumption at any treatment level. Mortality in rats fed the 4% diet was significantly higher than the control group; all animals were found dead before the end of the study (most dying during the last 12 months), compared with 7/12 control deaths. The incidence of bladder stones and bladder tumours increased with diethylene glycol exposure, with 0, 0, 6 and 5 bladder tumours observed in the control, 1, 2 and 4% DEG groups, respectively. Bladder stones were observed in 0, 2, 7 and 11 rats in the control, 1, 2 and 4% groups, respectively. In all but one case, bladder stones were present when bladder tumours were observed, suggesting that chronic irritation was a factor in the production of bladder tumours. The severity and incidence of signs of kidney damage (hydronephrosis, hydroureter, focal tubular atrophy, hyalin cast formation, glomerular atrophy) increased in a treatment-related manner, with gross kidney lesions observed in 1/12, 3/12 and 8/12 of the rats in the low-, mid- and high-dose groups, respectively. Liver damage observed histologically also increased with the level of diethylene glycol exposure. It

cannot be ruled out that this older study, which showed a significant increase in bladder stones and bladder tumours, may have been influenced by the presence of ethylene glycol as an impurity (Fitzhugh and Nelson, 1946) [KI score = 3].

Male and female rats were given 0, 2 or 4% diethylene glycol (containing 0.031% ethylene glycol) in their feed for two years. Rats were either just weaned, 2 months old or 12 months old at the initiation of the exposure. The dietary concentration of diethylene glycol was adjusted for the food consumption and body weight of each group. For 4% diet, the dosage in weanlings was 5,400 mg/kg/day for the first 28 days, approximately 3,700 mg/kg/day during the next two-week period, gradually declined to about 2,000 mg/kg/day over the next three months and remained at that level for the rest of the study. A study average of 2,300 mg/kg/day for weanlings fed 4% in the diet was calculated from data provided by the authors. None of the 12-month old male rats included in the study survived, whereas all the females in that group survived to termination of the study. Although weanling rats developed more bladder stones than the other groups, the difference was insignificant. The yearling rats developed their bladder stones somewhat earlier. The yearling rats in the 4% groups had the highest stone formation (8 out of 20 rats) and had the only bladder tumour in this dose group; the rat with the bladder tumour also had bladder stones. No bladder stones or tumours were observed in rats of any age in the control or in the 2% groups. The bladder tumours associated with the stones were considered to be the result of mechanical irritation, and diethylene glycol was not considered to be a primary rat carcinogen. The LOAEL and NOAEL for this study were dietary concentrations of 4% and 2% (approximately 2,300 and 1,200 mg/kg), respectively. It cannot be ruled out that this older study, which showed a significant increase in bladder stones and bladder tumours, may have been influenced by the presence of ethylene glycol as an impurity (Weil et al., 1965) [KI score = 3].

H. Reproductive Toxicity

In a two-generation study, male and female rats were dosed by oral gavage with 1 mL/100 g body weight of a 20% aqueous solution of diethylene glycol (approximately 2 mL/kg/day) for 8 weeks. A control group was given daily oral gavage doses of 1 mL/100 g body weight distilled water. Five of the treated females were dosed with diethylene glycol until parturition, the other five until the pups were weaned. Treatment of the P-generation with diethylene glycol for 12 weeks did not impair reproduction. The test animals and the controls became pregnant at almost the same time, litter size averaged 8-10 young, and the young exhibited similar, uniform development. Growth and onset of oestrus were not affected by treatment. The endocrine glands investigated showed no differences from the controls with regard to weight and fine structure. The receptiveness and litter size of the untreated F_1 generation were the same as those of the P-generation, and the F_2 generation was normal with regard to weight gain, onset of sexual maturity and weight as well as histology of the organs examined. The NOAEL for this study was calculated to be 2,200 mg/kg/day (Wegener, 1953; ECHA) [KI score = 2].

A continuous breeding protocol (RACB) was used to study the reproductive toxicity of diethylene glycol in mice. Male and female CD-1 mice were administered in their drinking water 0, 0.35, 1.75 or 3.5% diethylene glycol. Mice were exposed for 7 days prior to mating, 98 days during cohabitation of breeding pairs and a further 23 days after segregation of each pair.

Breeding study: The mice given 1.75% or 3.5% diethylene glycol consumed significantly more drinking water than did the controls. Based on water consumption and body weight data, the 0, 0.35, 1.75 and 3.5% dose groups were equivalent to average daily intakes of 0, 612, 3,062 or 6,125 mg/kg/day, respectively. There was no treatment-related mortality. In the 3.5% dose group, there was significant decreases in the number of litters produced per pair, number of live pups per litter,

proportion of pups born alive, and the absolute and adjusted pup weights. A significant dose-related trend for reduced absolute pup weights was also observed. Exposure to the 3.55 dose group also resulted in a significant increase in the cumulative days to litter and fewer breeding pairs were able to produce litters: 82%, 76%, and 59% of the pairs exposed to 3.5% in the diet produced the third, fourth or fifth litters, respectively, whereas 97-100% of the control group produced litters.

Crossover mating: The mating index and the fertility of the 3.5% dosed males or females were unaffected compared with the control mice. However, live pup weight was decreased in the highest-dose group, in which a 9% difference was observed for the offspring of the control males and the treated females. At the end of this test the parental animals (F0 of breeding study) were necropsied. For the male mice there were no significant differences in the body or organ weights, either absolute or adjusted for body weight. Analysis of the cauda epididymal contents of F0 males at necropsy indicated that there were no effects of diethylene glycol in the highest-doses group on the sperm concentration or the percentage of motile or abnormal sperm. The mean body weight of the 3.5% dosed F0 females was significantly decreased relative to the control females. The magnitude of this decrease was approximately 7%. These animals also exhibited significantly decreased absolute liver and pituitary weights, but their organ-to body weight ratios were not different from controls. There were no significant treatment-related gross or histopathological lesions in the organs examined from the male and female F0 mice (Williams et al., 1990) [Kl score = 2].

I. Developmental Toxicity

Time-pregnant CD rats were dosed by oral gavage with 0, 1,118, 4,472 or 8,944 mg/kg on gestational days 6-15. In the high-dose females, there were reduced body weight gain, reduced food consumption, increased water consumption, increased liver and kidney weights and histopathological changes in the kidney. The mid-dose females exhibited only increased water consumption. There were no treatment-related effects on corpora lutea or implantations. Foetal body weights were reduced in the high-dose animals. Total or individual external or visceral variations were similar between treated and control groups; however, individual skeletal variations were significantly increased in the mid- and high- dose groups. The pattern of delayed ossification was considered consistent with reduced foetal body weight. Malformations were similar between treated and control groups. The maternal and developmental NOELs for this study were 1,118 mg/kg/day (Ballantyne and Snellings, 2005) [Kl score = 2].

Time-pregnant CD-1 mice were dosed by oral gavage with 0, 559, 2,795 or 11,180 mg/kg/day during gestational days 6-15. In the high-dose females, there was mortality, clinical signs, and increased water consumption; only increased water consumption was observed in the mid-dose females. Foetal body weights were significantly reduced in the high-dose animals. There were no increases in variations or malformations between treated and control animals. The maternal and developmental NOELs were 559 and 2,795 mg/kg/day, respectively (Ballantyne and Snellings, 2005) [Kl score = 2].

Groups of 15 pregnant Himalayan rabbits were administered oral (gavage) doses of 0, 100, 400 or 1,000 mg/kg DEG on gestational days 7-19. No maternal toxicity was observed at any of the DEG doses administered. The foetal and litter incidence of skeletal, soft tissue and external anomalies or variations were comparable to those of the control and/or historical control groups. The authors set the maternal and developmental toxicity NOEL at greater than 1,000 mg/kg (Hellwig et al., 1995) [Kl score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for diethylene glycol follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The lowest NOAEL reported in the repeat dose toxicity study is 105 mg/kg/day based on the 225-day rat dietary study. Although, there was a 13.2% increase in oxalate excretion at this dose level, this was considered a biomarker and not an indicator of toxicity. At 0.4% (the LOAEL), there were oxalate crystalluria and mild defects of renal function (increased urine volume), as measured by concentration tests. The NOAEL of 105 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / ($UF_A \times UF_H \times UF_L \times UF_{Sub} \times U_{FD}$)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 105/(10 × 10 × 1 × 1 × 1) = 105/100 = 1.0 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) × (human weight) × (proportion of intake from water) / (volume of water consumed) × (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) × (human weight) × (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (1.05 × 70 × 0.1)/2 = 3.7 mg/L

B. Cancer

A two-year study of in rats showed no carcinogenic effects when diethylene glycol was administered in drinking water (Hiasa et al., 1990). In older studies, bladder tumours were observed in rats given diethylene glycol in feed; the tumours are considered to be the result of physical irritation from the bladder stones that also were noted in the same animals (Fitzhugh & Nelson, 1946; Weil et al.,

1965). It cannot be ruled out that these older studies, which showed a significant increase in bladder stones and bladder tumours, may have been influenced by the presence of ethylene glycol as an impurity. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Diethylene glycol does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The substance is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on diethylene glycol.

Table 3: Acute aquatic toxicity studies on diethylene glycol

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Pimephales promelas	96-hour LC_{50}	75,200	2	ECHA
Oncorhynchus mykiss	96-hour LC_5	66,000	2	ECHA
Daphnia magna	24-hour EC_{50}	>10,000	2	ECHA
Daphnia magna	48-hour EC_{50}	65,980	2	ECHA
Daphnia magna	48-hour EC_{50}	62,630	2	ECHA

Chronic Studies

In ECHA, the aquatic toxicity of the 'ethylene glycol and higher glycols' (mono-, di-, tri-, tetra- and pentaethylene glycol) is evaluated in a read-across approach. Data on all three trophic levels (fish, *daphnia*, algae) are available to describe the aquatic toxicity of the glycol read-across members. Due to the fact, that not for each single substance data for all required endpoints are available, a weight of evidence approach is used, which includes additional information based on QSAR calculation with the EpiWin-Program ECOSAR v1.11. Measured data, as well as estimated data, demonstrate that all glycols within the read-across are not harmful to aquatic organisms. No adverse effects on aquatic organisms occurred up to concentrations above 100 mg/L (ECHA).

No data for fish was available for diethylene glycol. However, chronic studies for fish are available for ethylene glycol (CAS No.: [redacted] The 7-day NOEC for the fathead minnow (*Pimephales promelas*) was determined to be 15,380 mg/L based on the weight of the test organisms (ECHA) [Kl.score=2].

No data for invertebrates was available for diethylene glycol. However, three studies were conducted with Dapnids (*Ceriodaphnia dubia* or *Daphnia magna*) for ethylene glycol (CAS-No.: [redacted] or triethylene glycol (CAS No.: [redacted] The study with ethylene glycol was conducted according to USEPA guideline 600/4-89/001 with *Ceriodaphnia dubia* as test species. The 7-day NOEC for reproduction was determined to be 8,590 mg/L ethylene glycol (nominal). Two studies measured the effect of triethylene glycol on the reproduction of *Daphnia magna*. One study was conducted according to the national standard ASTM (E 47.01, Draft No. 1, "Draft proposed standard practice for conducting renewal life cycle toxicity tests with Daphnia magna"). In this test the Daphnids were exposed to triethylene glycol for 21 days. Based on reproduction the reported NOEC is > 15,000 mg/L triethylene glycol (nominal) (ECHA) [Kl Score = 2].

Data for algae was available for diethylene glycol. The 8-day TGK to algae *Scenedesmus quadricauda* was determined to be 2,700 mg/L for diethylene glycol (ECHA) [Kl score = 2].

From the QSAR calculations it can be expected for diethylene glycol that algae are slightly more sensitive (ChV = 1,200 mg/L) than invertebrates (ChV = 1,891 mg/L) or fishes (ChV = 7,694 mg/L) (ECHA) [Kl Score = 2].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for diethylene glycol follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C50 values are available for fish (66,000 mg/L), and Daphnia (> 10,000 mg/L). Results from a chronic algae study is available on diethylene glycol (2,700 mg/L). On the basis that the data consists of short-term results from two trophic levels and a long-term result from one trophic level, an assessment factor of 100 has been applied to the lowest reported value, which is the chronic value for algae. The $PNEC_{water}$ is 27 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 17.3 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.89/1280) \times 1000 \times 27$
$= 17.3$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.04/1000 \times 2400]$
$= 0.89\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg)

BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$

$= 1 \times 0.04$

$= 0.04$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for diethylene glycol based on the molecular connectivity index (MCI) is 1 L/kg (USEPA, 2017).

F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.36 mg/kg soil dry weight.

The calculations are as follows:

$PNECsoil = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$

$= (0.02/1500) \times 1000 \times 27$

$= 0.36$ mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)

BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$

$= 1 \times 0.02$

$= 0.02$ m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for diethylene glycol based on the molecular connectivity index (MCI) is 1 L/kg (USEPA, 2017).

f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (IChEMS, 2022; ECHA, 2023).

Diethylene glycol has been shown to be readily biodegradable; thus, it does not meet the screening criteria for persistence.

The calculated log K_{ow} is -1.98, and the experimental BCF is 100. Thus, diethylene glycol does not meet the screening criteria for bioaccumulation.

The lowest chronic toxicity value for diethylene glycol is > 0.1 mg/L. Thus, diethylene glycol does not meet the criteria for toxicity.

Therefore, diethylene glycol is not a PBT substance.

IX. CLASSIFICATION AND LABELING (ABSTRACTED FROM PUBCHEM)

A. Classification

Irritant

B. Labelling

Danger

C. Pictogram

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS) (ABSTRACTED FROM PUBCHEM)

A. First Aid

Eye Contact

First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control centre. Do not put any ointments, oils or medication in the victim's eyes without specific instructions from a physician. IMMEDIATELY transport the victim after flushing eyes to a hospital even if no symptoms (such as redness or irritation) develop.\

Skin Contact

IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently wash all affected skin areas thoroughly with soap and water. If symptoms such as redness or irritation develop, IMMEDIATELY call a physician and be prepared to transport the victim to a hospital for treatment.

Inhalation

IMMEDIATELY leave the contaminated area; take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital. Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used; if not available, use a level of protection greater than or equal to that advised under Protective Clothing.

Ingestion

DO NOT INDUCE VOMITING. If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control centre. Be prepared to transport the victim to a hospital if advised by a physician. If the victim is convulsing or unconscious,

do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY transport the victim to a hospital.

Notes to Physician (abstracted from PubChem)

The patient should be resuscitated with isotonic crystalloidal fluids, and acidosis should be corrected. Early treatment with a competitive ADH inhibitor (e.g., 4-methylpyrazole or ethanol), hemodialysis and supportive care offer the best hope for patient recovery.

Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand-valve resuscitator, bag-valve-mask device or pocket mask, as trained. Perform CPR as necessary. Immediately flush contaminated eyes with gently flowing water. Do not induce vomiting. If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature.

Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if necessary. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary oedema and treat if necessary. Monitor for shock and treat if necessary. Anticipate seizures and treat if necessary. For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with 0.9% saline (NS) during transport. Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of water for dilution if the patient can swallow, has a strong gag reflex and does not drool. Administer activated charcoal.

Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary oedema or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag-valve-mask device may be beneficial. Consider drug therapy for pulmonary oedema. Monitor cardiac rhythm and treat arrhythmias if necessary. Start IV administration of D5W /SRP: "To keep open", minimal flow rate. Use 0.9% saline (NS) lactated Ringer's (LR) if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Consider vasopressors if patient is hypotensive with a normal fluid volume. Watch for signs of fluid overload. Treat seizures with diazepam or lorazepam. Use proparacaine hydrochloride to assist eye irrigation.

Medical Conditions Aggravated by Exposure

Respiratory conditions (asthma, etc.)

Emergency Personnel Protection

Wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. During a fire, irritating and highly toxic gases may be generated by thermal decomposition or combustion. Use water spray to keep fire-exposed containers cool.

B. Fire Fighting Information (abstracted from Comet Chemical SDS 2013)

Extinguishing Media

Use powder, alcohol-resistant foam, water spray, carbon dioxide.

Specific Exposure Hazards

Combustible when exposed to heat or flame; can react with oxidising materials.

Special Protective Equipment for Firefighters

Firefighters must use standard protective equipment including flame retardant coat, helmet with face shield, gloves, rubber boots, and in enclosed spaces, SCBA. Firefighters should wear proper protective equipment and self-contained breathing apparatus with full face piece operated in positive pressure mode. Move containers from fire area if safe to do so. Water spray may be useful in cooling equipment exposed to heat and flame.

C. Accidental Release Measures

Personal Precautions

Restrict access to area until completion of clean-up. Ensure clean-up is conducted by trained personnel only. All persons dealing with clean-up should wear the appropriate protective equipment including self-contained breathing apparatus.

Environmental Precautions

Ventilate the area. Stop spill or leak at source if safely possible. Dike for water control. Contain and absorb spilled liquid with non-combustible, inert absorbent material (e.g., sand), then place absorbent material into a container for later disposal.

Steps to be Taken if Material is Released or Spilled

Absorb spill with inert material (e.g., vermiculite, sand or earth), then place in suitable container. Clean up spills immediately, observing precautions in the Protective Equipment section. Provide ventilation.

D. Storage and Handling

General Handling

Wear protective gloves/clothing and eye/face protection. Use with adequate ventilation. Do not ingest. Do not breathe mist or vapour. Avoid contact with eyes, skin and clothing. Wash with soap and water after handling. Keep away from extreme heat and flame. Keep away from acids and other incompatibles. Keep containers tightly closed when not in use.

Other Handling Precautions

Wash thoroughly after handling. Use with adequate ventilation. Avoid breathing vapours from heated material. Avoid contact with eyes, skin and clothing. Keep container tightly closed. Wash clothing before reuse. Avoid breathing spray or mist.

Storage

Store in a cool, dry, well-ventilated area. Store away from areas of excessive heat, open flames, sparks and other possible sources of ignition. Keep away from incompatibles. Storage area should be

clearly identified, clear of obstruction and accessible only to trained and authorised personnel. Inspect periodically for damage or leaks.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for diethylene glycol.

Engineering Controls

Good general ventilation should be used. Localised ventilation should be used where vapours, mist or aerosols may be generated.

Personal Protection Equipment

Respiratory Protection: Wear an approved respirator with dust/mist pre-filters if any exposure to dust or mist is possible.

Hand Protection: Wear appropriate chemical-resistant gloves.

Skin Protection: Wear protective clothing to minimise skin contact.

Eye Protection: Wear chemical splash goggles and face shield.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Diethylene glycol is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

Australian Drinking Water Guidelines [ADWG]. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council. Updated September 2022. https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines

Ballantyne, B., & Snellings, W.M. (2005). Developmental toxicity study with diethylene glycol by gavage to CD rats and CD-1 mice. *Food Chem. Toxicol., 43*, 1637–1646.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra. https://www.dcceew.gov.au/water/coal-and-coal-seam-gas/national-assessment-chemicals/consultation-risk-assessment-guidance-manual

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. ECHA REACH database: http://echa.euroa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2023). Chapter R.11: vPvB assessment. In *Guidance on information requirements and chemical safety assessment*. Version 4.0. https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Fitzhugh, O.G., & Nelson, A. (1946). Comparison of the chronic toxicity of triethylene glycol with that of diethylene glycol. *J. Ind. Hyg. Tox., 25*, 40–43.

Freitag, D., Ballhorn, L., Geyer, H., & Korte, F. (1985). Environmental hazard profile of organic chemicals. An experimental method for the assessment of the behavior of organic chemicals in the ecosphere by means of simple laboratory tests with 14C labeled chemicals. *Chemosphere, 14*, 1589–1616.

Guillot, J. P., Martini, M. C., Giauffret, J. Y., Gonnet, J. F., & Guyot, J. Y. (1982). Safety evaluation of some humectants and moisturizers used in cosmetic formulations. *Int. J. Cosmetic Sci., 4*, 67–80.

Hellwig, J., Klimisch, H. J., & Jäckh, R. (1995). Investigation of the prenatal toxicity of orally administered diethylene glycol in rabbits. *Fundam. Appl. Toxicol., 28*, 27–33.

Hiasa, Y., Kitahori, Y., Morimoto, J., Konishi, W., & Ohshima, M. (1990). Absence of carcinogenic or promoting effects of diethylene glycol on renal tumourigenesis in rats. *J. Toxicol. Pathol., 3*, 97–104.

Industrial Chemicals Environmental Management Standard [IChEMS]. (2022). Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals. https://www.dcceew.gov.au/sites/default/files/documents/australian-pbt-criteria.pdf

Klimisch, H. J., Andreae, M., & Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol., 25*, 1–5.

Laug, E., Calvery, H. O., Morris, H. J., & Woodward, G. (1939). The toxicology of some glycols and derivatives. *J. Ind. Hyg. Toxicol., 21*, 173–201.

Lenk, W., Löhr, D., & Sonnenbichler, J. (1989). Pharmacokinetics and biotransformation of diethylene glycol and ethylene glycol in the rat. *Xenobiotica, 19*, 961–979.

Organisation for Economic Co-operation and Development [OECD]. (2007). SIDS Dossier on the HPV Chemical Diethylene Glycol (CAS No. [redacted]).

Pubchem. https://pubchem.ncbi.nlm.nih.gov/compound/DI_Hydroxyethyl_ether#section=InChI Accessed January 2022.

U.S. Environmental Protection Agency [EPA]. (2017). EPISuite™ v. 4.11. Office of Pollution Prevention and Toxics and Syracuse Research Corporation. https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

Verschueren, K. (1983). *Handbook of environmental data on organic chemicals*. 2nd Edition. Van Nostrand: 1,310

Wegener, H. (1953). The reproductive capacity of rats after the action of diethylene glycol. *Arch. Exper. Path. u. Pharmakol., 220*, 414–417.

Weil, C. S., Carpenter, C. and Smyth, H. F. (1965). Urinary bladder response to diethylene glycol. *Arch. Environ. Health, 77*, 569–581.

Williams, J., Reel, J., George, J., and Lamb, IV, J. (1990). Reproductive effects of diethylene glycol and diethylene glycol monoethyl ether in Swiss CD-1 mice assessed by a continuous breeding protocol. *Fundam. App. Toxicol., 74*, 622–635.

POTASSIUM CHLORIDE

This dossier on potassium chloride presents the most critical studies pertinent to the risk assessment of potassium chloride in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained primarily from the OECD-SIDS documents on potassium chloride (OECD, 2001a,b) and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Potassium chloride

CAS RN: [redacted]

Molecular formula: KCl

Molecular weight: 74.55 g/mol

Synonyms: Potassium chloride

SMILES: [Cl-] [K+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Potassium Chloride

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid; white crystals	2	ECHA
Melting Point	770°C @ 101.3 kPa	1	ECHA
Boiling Point	1,407°C (pressure not provided)	2	OECD, 2001a,b
Density	1984 kg/m^3	2	ECHA
Vapour Pressure	5.73 hPa @ 906°C	2	OECD, 2001a,b
Partition Coefficient (log Kow)	-	-	-
Water Solubility	255 g/L @ 25°C	2	Lide, 2009; ECHA

III. ENVIRONMENTAL FATE PROPERTIES

Potassium chloride (KCl) dissociates completely in aqueous solutions to potassium (K^+) and chloride (Cl^-) ions. Potassium chloride and its dissociated ions are ubiquitous in the environment.

The transport and/or leaching of potassium (K^+) and chloride (Cl^-) ions is affected by clay minerals (type and content), pH and organic matter. Potassium ions are less mobile and less prone to leaching than anions in soil, such as chloride and nitrate (NO_3^-). Chloride binds only weakly to soil particles, and therefore follows water movement (OECD, 2001b).

Potassium (K^+) and chloride (Cl^-) ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated (OECD, 2001b; Ganong, 1995). Neither potassium chloride nor its dissociated ions are expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Potassium chloride has low acute toxicity by the oral route. It is not a skin or eye irritant. Long-term studies in rats fed potassium chloride showed no systemic toxicity or carcinogenic effects. Potassium chloride has shown some genotoxic effects in *in vitro* assays; these occurred at high concentrations of potassium chloride and is thought to be due to a disruption of the osmotic balance of the cells. No *in vivo* genotoxicity studies have been conducted on potassium chloride. There were no developmental effects in pregnant female rats and mice given potassium chloride in their diet.

B. Toxicokinetics and Metabolism

Potassium chloride dissociates completely in aqueous solutions to potassium (K^+) and chloride (Cl^-) ions. Potassium is an essential nutrient: it has a number of critical roles, one of which is that it is the principal cation involved in maintaining the osmotic balance of bodily fluids (Ganong, 1995). Both potassium and chloride ions are involved in regulating the acid-base balance of the body (Ganong, 1995).

C. Acute Toxicity

The oral LD_{50} in rats was reported to be 3,020 mg/kg (Boyd and Shanas, 1961) [Kl score = 2].

No acute toxicity studies by the dermal or inhalation route were identified.

D. Irritation

Potassium chloride did not produce an irritant response in an *in vitro* skin irritation (OECD TG 439) test (ECHA) [Kl score = 1].

Potassium chloride did not produce an irritant response in an *in vitro* eye irritation test (ECHA) [Kl score = 2].

E. Sensitisation

No studies were identified.

F. Repeated Dose Toxicity

<u>Oral</u>

Male F344/Slc rats were given 0, 0.25, 1, 5 or 5% potassium chloride in their feed for two years. The mean daily intake was calculated to be 0, 110, 450 or 1,820 mg/kg/day, respectively. At the end of the study, survival rates were 48%, 64%, 58% and 84% in the respective dose groups. Nephritis was predominant in all groups, including the controls. The only treatment-related effect was gastritis (inflammation of the stomach lining). The incidence of gastritis and ulcers were 6%, 18%, 18% and 30% in the 0, 110, 450 and 1,820 mg/kg/day groups, respectively. The gastritis was thought to be indicative of a localised effect due to the irritating nature of the test material. The NOAEL for

systemic effects is 1,820 mg/kg/day, the highest dose tested (Imai et al., 1968; OECD 2001a,b) [Kl score = 2].

Male and female Wistar rats were fed diets containing 0 or 3% potassium chloride over a total period of 30 months. Due to the reduction of feed intake, the mean test substance intake and mean body weight decreased in time. The mean daily intake of potassium chloride was not calculated. There was hypertrophy of the zona glomerulosa in the adrenals (24/50 treated rats versus 4/50 in controls); and cystitis in the urinary bladder (males: 3/59; females 3/50) and single epithelial hyperplasia of the bladder (males 3/50; females 2/50) (Lina and Kuijpers, 2004) [Kl score = 2].

Inhalation

No studies were identified.

Dermal

No studies were identified.

G. Genotoxicity

In Vitro Studies

Potassium chloride was not mutagenic to *Salmonella typhimurium* strains TA100, TA 1535, TA 1537 and TA 98 strains in an *in vitro* bacterial mutation assay in the absence or presence of metabolic activation (Mortelmans et al., 1986).

Potassium chloride was weakly mutagenic in two separate L5178Y mouse lymphoma assays (Myhr and Caspary,1988; Mitchell et al., 1988). It was mutagenic at 4,000 and 5,000 μg/mL in the presence of metabolic activation in one study, and mutagenic at 7,000 μg/mL in the absence of metabolic activation. The authors stated that these responses are due to high salt concentrations which affect the ionic balance and osmotic pressure of the medium, inducing mutations in cells surviving the treatment.

Potassium chloride induced a significant increase in chromosomal aberrations in Chinese Hamster lung fibroblasts (V79) cells only at the highest test dose (12,000 μg/mL) in the absence of a metabolic activation system. Measurements of the osmotic pressure of the medium showed a two-fold increase at this test compound concentration when compared to the normal medium (530 mOsmol/kg versus 253 mOsmol/kg) (OECD, 2001b).

There are two other reports on the effect of potassium chloride on the formation of chromosome aberrations in Chinese hamster ovary cells (CHO). In these studies potassium chloride concentrations of 75 and 80 mM (approximately 5,500 and 6,000 μg/mL) resulted in 19% and 28% aberrant cells, respectively. An increased number of chromosome aberrations was observed with potassium chloride concentrations that reduced cell survival of 40% or more. The increases in mutagenicity and chromosome aberrations observed in these studies have been considered to be related to cytotoxicity resulting from the high potassium chloride concentrations used (Brusick, 1988).

The reported mutagenic effect of potassium chloride most probably results from a disruption of the osmotic balance of cells with a subsequent interference with chromosomal stability. This may result in the clastogenic effects (DNA breakage and chromosome structural instability) due to K^+ effects on sequestering of Mg^{++} ions required for normal maintenance of chromatin integrity (OECD, 2001b).

In Vivo Studies

No studies have been identified.

H. Carcinogenicity

Oral

F344/Slc male rats were given 0, 110, 450 or 1,820 mg/kg/day potassium chloride in feed for two years. At the end of the study, survival rates were 48%, 64%, 58% and 84% in the 0, 110, 45 and 1,820 mg/kg/day groups. There was no increased incidence of tumours that were considered to be treatment-related (Imai et al., 1968) [Kl score = 2].

Male and female Wistar rats were fed diets containing 0 or 3% potassium chloride over a total period of 30 months. There were no treatment-related differences in tumour response among the groups (Lina and Kuijpers, 2004) [Kl score = 2].

Inhalation

No studies were identified.

Dermal

No studies were identified.

I. Reproductive Toxicity

No studies were identified.

J. Developmental Toxicity

Pregnant Wistar rats were given doses of 3.1 to 310 mg/kg potassium chloride by oral gavage during gestation days 5 through 15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 310 mg/kg/day, the highest dose tested (FDRL, 1975) [Kl score = 2].

Pregnant CD-1 mice were given doses of 2.35 to 235 mg/kg potassium chloride by oral gavage during gestation Days 5 through 15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 235 mg/kg/day, the highest dose tested (FDRL, 1975) [Kl score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for potassium chloride follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

Two chronic rat feeding studies have been conducted on potassium chloride: only the study by Imai et al. (19686 was conducted with multiple doses and provided mean daily intake values. In this study, the only treatment-related effects were associated with chronic irritation in the gastrointestinal tract (gastritis and ulcers), a localised effect due to the irritating properties of the test material. No systemic toxicity was observed at any of the doses tested. The NOAEL for systemic toxicity in this study is 1,820 mg/kg/day, the highest dose tested. The NOAEL of 1,820 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subacute to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 4(10 x 10 x 1 x 1 x 1) = 1,820/100 = 18 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD:

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (18 x 70 x 0.1)/2 = 63 mg/L

Australian Drinking Water Guidelines

The Australian drinking water guideline value for chloride is 250 mg/L based on aesthetics (ADWG, 2011).

B. Cancer

Potassium chloride was not carcinogenic to rats in two chronic feeding studies. Therefore, no cancer reference value was derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Potassium chloride does not exhibit the following physico-chemical properties:

- Flammability
- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Potassium chloride is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

The results of the acute toxicity studies conducted on potassium chloride are presented in Table 2.

Table 2: Acute Aquatic Toxicity Studies on Potassium Chloride

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	880	2	Mount et al., 1997; ECHA
Daphnia magna	48-hour EC_{50}	660	2	Mount et al., 1997; ECHA
Ceriodaphnia dubia	48-hour EC_{50}	630	2	Mount et al., 1997; ECHA
Scenedesmus subspicatus	72-hour EC_{50}	> 100* (growth rate)	1	ECHA

*NOEC = > 100 mg/L

Chronic Studies

In a fish early-life-stage test with the fathead minnow (*Pimephales promelas*), the 7-day NOEC was 500 mg/L (ECHA).

C. Terrestrial Toxicity

No studies were identified.

D. Calculation of PNEC

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (820 mg/L), *Daphnia* (660 mg/L) and algae (> 100 mg/L). Although a chronic study was conducted on fish that fulfils the requirements in the OECD TG 210, it is not considered adequate for deriving a PNEC because of the short duration of the test. On the basis of the short-term results from three trophic levels, an assessment factor of 100 has been applied to the lowest reported effect concentration of 100 mg/L for algae. The $PNEC_{water}$ is 1.0 mg/L.

PNEC sediment

No reliable experimental toxicity data on sediment organisms are available. Potassium chloride dissociates completely in water with its environmental distribution is dominated by its high water solubility. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as potassium chloride. Therefore, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. Based on its properties, no adsorption of potassium chloride to sediment is to be expected, and the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No reliable experimental toxicity data on terrestrial organisms are available. The environmental distribution of potassium chloride is dominated by its water solubility. Sorption of potassium chloride should probably be regarded as a reversible situation, *i.e.*, the substance is not tightly nor permanently bound. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as potassium chloride. Therefore, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, potassium chloride is not expected to significantly adsorb to soil, and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Potassium chloride is an inorganic salt that dissociates completely to potassium and chloride ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both potassium and chloride ions are also ubiquitous and are present in most water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Potassium and chloride ions are essential to all living organisms, and their intracellular, and extracellular concentrations are actively regulated. Therefore, potassium chloride is not expected to bioaccumulate.

There are no adequate chronic aquatic toxicity studies available on potassium chloride. The acute $E(L)C_{50}$ values for potassium chloride are > 1 mg/L in fish, invertebrates and algae. Therefore, potassium chloride does not meet the screening criteria for toxicity.

The overall conclusion is that potassium chloride is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictograms

None.

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

Immediately flush eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. If symptoms persist, seek medical attention.

Skin Contact

Wash with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Do not induce vomiting. Rinse mouth with water and then drink a small amount of water. Get medical attention. Never give anything by mouth to an unconscious person.

B. Firefighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: potassium oxides, hydrogen chloride, chlorine gas.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Avoid creating and breathing dust.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage and Handling

General Handling

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls/Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for potassium chloride.

Engineering Controls

Use in a well-ventilated area.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Potassium chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Boyd, E.M., and Shanas, M.N. (1961). The acute oral toxicity of potassium chloride. Arch. Int. Pharmacodyn. Ther. 133: 275-283.

Brusick, D. (1988). Genotoxic effects in cultured mammalian cells produced by low pH treatment conditions and increased ion concentrations. Environ. Mutag. 8: 879-886.

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment (HHRA). (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

FDRL. (1975). Teratological evaluation of FDA 73-78 (KCl) in mice and rats. Final report prepared under DHEW. Contract No. FDA 223-74-2176 by Food and Drug Research Laboratories Inc. Waverly, New York.

Ganong, W.F. (1995). Review of Medical Physiology, 17th Edition, Appleton & Lange, Norwalk, Connecticut, USA.

Imai, S., Morimoto, J., Sekiya, N., Shima, M., Kiyozuka, Y., Nakamori, K., Tsubura, Y. (1986). Chronic toxicity test of KCl and NaCl in F344/Scl rats. J. Nara Med. Ass. 37:115-127 [in Japanese]; cited in OECD 2001a,b.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Lide, D.R. (2009). Physical Constants of Inorganic Compounds. CRC Handbook of Chemistry & Physics, 89th Edition, CRC Press.

Lina, B.A.R., and Kuijpers, M.H.M. (2004). Toxicity and carcinogenicity of acidogenic or alkalogenic diets in rats; effects of feeding NH_4Cl, $KHCO_3$ or KCl. Food Chem. Toxicol. 42: 135-153.

Mitchell, A.D., Rudd, C.J., Caspary, W.J. (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Intralaboratory results for sixty-three coded chemicals tested at SRI international. Env. Molecular Mutagenesis 12(13):37-101.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E. (1986). Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Env. Mutagenesis 8(7):1-119.

Mount, D.R., Gulley, D.D., Hockett, J.R., Garrison, T.D., and Evans, J.M. (1997). Statistical models to predict the toxicity of major ions to *Ceriodaphnia dubia, Daphnia magna* and *Pimephales promelas* (fathead minnows). Environ. Toxicol. Chem. 16: 2009-2019.

Myhr, B.C., Caspary, W.J. (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Intralaboratory results for sixty-three coded chemicals tested at Litton Bionetics, Inc. Env. Molecular Mutagenesis. 12(13):103-194.

OECD. (2001a). IUCLID Data Set for Potassium chloride (CAS No. [redacted] UNEP Publications. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=68BF142A-D550-432C-8C48-13883944BA1D.

OECD. (2001b). Screening Information Assessment Report (SIAR) for Potassium chloride (CAS No. [redacted] UNEP Publications. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=68BF142A-D550-432C-8C48-13883944BA1D.

Appendix C.3 January 2022 Risk Dossiers

2-PROPENAMID (IMPURITY)

This dossier on 2-Propenamid (impurity) (2PA) (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): prop-2-enamide

CAS RN: [redacted]

Molecular formula: C_3H_5NO

Molecular weight: 71.08 g/mol

Synonyms: 2-Propenamide; Acrylamide; Acrylamide solution 50%; EUROAMD

SMILES: C=CC(=O)N

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of 2PA

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Crystalline White solid	1	ECHA
Melting Point	84.5°C at 101.3 kPa	1	ECHA
Boiling Point	Not applicable as substance is solid	1	ECHA
Density	1130 kg/m³ at 30°C	2	ECHA
Vapour Pressure	Not applicable as substance is solid	1	ECHA
Partition Coefficient (log K_{ow})	-0.9 at 20°C	1	ECHA
Water Solubility	2,155 g/L at 30°C	1	ECHA
Flash Point	Not applicable as substance is solid	1	ECHA
Auto flammability	Not applicable as substance is solid	1	ECHA
Viscosity	Not applicable as substance is solid	1	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

2-Propenamid is expected to biodegrade and is not expected to sorb substantially to soils or sediments based on the low log K_{ow} and K_{oc} values. In addition, 2-propenamid is not expected to bioaccumulate.

B. Biodegradation

2PA was found to degrade approximately 100% in 28 days in the OECD Closed Bottle Test (301D) (ECHA) [KI Score = 1].

C. Environmental Distribution

No data available (ECHA). However, K_{oc} values of 3.554 L/kg (K_{ow} method) and 5.694 L/kg (MCI method) were estimated using USEPA EPI Suite™ KOCWIN v2.00 module. The estimated log K_{oc} values equal 0.551 and 0.755 for the K_{ow} and MCI methods, respectively [KI Score = 2]. Based on these estimated values, the substance is not expected to sorb substantially to soils or sediments.

D. Bioaccumulation

No experimental data were available for bioaccumulation or bioconcentration of 2PA. However, the log bioaccumulation factor (BAF) determined from regression-based calculations were performed using EPI Suite BCFBAF v3.01. Based on a log K_{ow} of -0.67, the log BAF according to the Arnot-Gobas method for assessing bioaccumulation at the upper trophic level was determined to be -0.047 [KI Score = 2]. The relatively low log BAF suggests 2PA will not bioaccumulate to any substantial degree.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of 2PA is low by the oral, inhalation and dermal routes. It is not irritating to the eyes or skin and is not a skin sensitiser. Repeated exposures of 2PA to rats in a chronic drinking water study exhibited neurotoxicity and carcinogenicity. *In vitro* and *in vivo* studies provide strong evidence that 2PA does not react directly with DNA. It has no reported reproductive or developmental effects.

B. Acute Toxicity

<u>Oral</u>

An EU Method B.1 (Acute Toxicity Oral) study was performed on Sprague-Dawley rats exposed to 2PA. Under the experimental conditions, the oral LD_{50} in rats of acrylamide in aqueous solution at 50% was 354 mg/kg in female rats with 95% confidence interval limits of 305-458 mg/kg. Toxicity was comparable in males. In accordance with the ethic and scientific recommendations concerning the LD_{50} a more precise determination was not conducted. Based on the results of this study, it can be concluded that the acute oral LD_{50} of acrylamide in rats is 177 mg/kg (ECHA) [KI score =1].

Inhalation

An OECD Guideline 433 draft (Acute Inhalation Toxicity: Fixed Concentration Procedure) was employed to estimate the acute inhalation toxicity of 2PA to an unspecified strain of male rat. The results of this test indicate that the 50.7% solution of acrylamide is practically non-toxic by the inhalation route with a LC_0 (60 mins) of 12 mg/L (ECHA) [KI score =2].

Dermal

An OECD Guideline 402 – Acute Dermal Toxicity was employed to estimate the acute dermal toxicity of 2PA to a non-specified strain of rabbit. Rabbits were occlusively dosed at 200, 795, 1,580 and 3,160 mg/kg of 50.7% aqueous acrylamide solution. Solution was applied to unabraided skin. The acute dermal LD_{50} for acrylamide was determined to be 1,141 mg acrylamide/kg bw (ECHA) [KI Score=1].

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was conducted to determine the skin irritation potential of 2PA using New Zealand White rabbits. Shaved areas of three male animals were treated with 0.5 g per animal of the test article prepared as a paste with 0.086 g of water. A semi-occlusive patch was overwrapped with a gauze binder and secured with tape for an exposure period of 4 hours. Post dosing, excess test article which had not penetrated was wiped away with a gauze pad moistened with water. Animals were observed for 1, 24, 48 and 72 hours after the removal of the bandage. Scoring was conducted according to the scale published in the OECD Guideline (No. 404 – 1992).

Neither erythema nor oedema was observed at any time. It can be concluded from the results obtained under the experimental conditions employed that acrylamide is not irritating to skin (ECHA) [KI score = 1].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) primary eye irritation study was performed using 2PA. Three male New Zealand White rabbits received 0.1 mL of undiluted solution in one eye. The other eye remained untreated. The exposure period was 24 hours. Reactions were scored at 1, 24, 48 and 72 hours and at 7, 14 and 21 days post-application to evaluate reversibility of the lesions.

Maximum conjunctivae, chemosis, iris and corneal opacity scores were 2, 2, 1 and 2.3, respectively, which were found to be fully reversible up to 21 days post exposure.

There were no deaths or remarkable body weight changes during the study period. Under the study conditions, 2PA is considered to cause irritation to the eye (ECHA) [KI score = 1].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) study (i.e., Buehler test) was performed on Pirbright-Hartley guinea pigs. Systemic toxic symptoms after application were not observed at any time during the study. Body weight development was positive and within normal ranges. No erythema nor oedema was observed at any point after the challenge application

in the control group. There were apparently no skin reactions in control animals but 85% of test animals gave a positive response. On the basis of these results, acrylamide should be considered a skin sensitiser in animals (ECHA) [Kl score = 1].

E. Repeated Dose Toxicity

Oral

An OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) was performed using Fischer 344 rats. 2PA was administered orally in drinking water for a period of two years. Dosing levels were given at 0.0, 0.01, 0.1, 0.5 and 2.0 mg/kg/day.

The rats were generally observed twice daily during the work week for overt signs of toxicity or changes in demeanour. These observations included the animals' movement within the cage, the availability of food and water, wastage of feed and the response to the opening and closing of the cage. Routine monitoring on weekends and holidays was limited to the removal of dead animals and animal husbandry procedures required to ensure the availability of food and water.

Parameters monitored during the study included mortality, body weight, food consumption, water consumption, clinical observations, haematology, clinical chemistry, urinalysis, organ weights, gross and histopathology. All rats were examined approximately monthly after the first month for palpable masses. Individual body weights were recorded monthly from all rats.

Overall, ingestion of 2PA induced neurotoxicity in F344 rats at doses ranging from 0.01-2.0 mg/kg/day. Testicular atrophy was observed in rats at elevated doses. The No Observed Adverse Effect Level (NOAEL) was determined to be 0.5 mg/kg in both sexes of rats (ECHA) [Kl Score = 1].

Inhalation

No data were available.

Dermal

No data were available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on 2PA based are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on 2PA

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) (Bacterial Reverse Mutation Assay)	-	-	2	ECHA

*+, positive; -, negative.

In Vivo Studies

Acrylamide has been extensively tested in a wide variety of *in vitro* and *in vivo* assays for detection of genetic effects. There is no compelling evidence that acrylamide induces point mutations or interacts with DNA *in vivo* to form DNA adducts. In contrast to point mutation and DNA damage assays, acrylamide induces a variety of chromosomal effects in bone marrow, but studies in spermatogonia are conflicting. Dominant lethal assays have generally produced positive results with acrylamide, which could be explained by chromosomal effects such as deletions. These studies, taken together, provide very strong evidence that acrylamide does not react directly with DNA (ECHA) [KI Score = 4].

G. Carcinogenicity

Oral

An OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) was performed using Fischer 344 rats. 2PA was administered orally in drinking water for a period of two years. Dosing levels were given at 0.0, 0.01, 0.1, 0.5 and 2.0 mg/kg/day.

Overall, ingestion of 2PA induced benign thyroid, mammary gland and tunica vaginalis tumours. The NOAEL was determined to be 0.5 mg/kg in both sexes of rats (ECHA) [KI Score = 1].

Despite National Toxicology Program conclusions that long-term dosing studies using 2PA provide clear evidence of carcinogenicity in rats, the cited study results provided in this dossier are equivocal relative to cancer responses. When evaluating a human relevance table, none of these tumors appear relevant to humans. Humans have substantially different mammary gland physiology from rodents and the tunica vaginalis tumors appear specific for the F344 rat. Only the thyroid may have significance (ECHA).

It should be noted that according to National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2002) acrylamide meets the National Occupational Health and Safety Commission (NOHSC) Approved Criteria (NOHSC, 1999) for classification as a Category 2 carcinogen (Risk Phrase R45 – May cause cancer).

Inhalation

No studies are available.

Dermal

No studies are available.

H. Reproductive Toxicity

Oral

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed on male and female Fischer 344 rats. 2PA was administered orally in drinking water at 0, 0.5, 2.0 or 5.0 mg/kg/day.

Long-term exposure to 2PA in the drinking water, over two generations in Fischer 344 rats, resulted in parental toxicity (reduced bodyweight, clinical signs of toxicity, histologic evidence of axonal swelling and/or degeneration in peripheral nerves) at 5.0 mg/kg/day, accompanied by prenatal lethality. Exposure to 2.0 mg/kg/day resulted in similar but lesser adult toxicity but no prenatal lethality. Exposure to 2.0 mg/kg/day resulted in no change to reproductive parameters in either generation except for reduced body weights and weight gain in F0 males in the pre-breed exposure period and reduced body weight and weight gain in F0 females late in the pre-breed exposure period. The only significant reproductive event induced by 2PA was decreased litter size as a result of dominant lethal mutations.

The NOAEL for all generations was determined to be 2 mg/kg/day (ECHA) [Kl Score = 1].

I. Developmental Toxicity

An OECD Guideline 414 (Prenatal Developmental Toxicity Study) was performed on Sprague-Dawley rats. Animals were dosed daily via oral gavage at 0, 2.5, 7.5 and 15 mg/kg.

Maternal Effects

There were no maternal mortalities and no clear clinical signs of toxicity. When corrected for gravid uterine weight, maternal body weight gain was decreased amongst animals receiving 7.5 and 15 mg/kg/day. The NOAEL for maternal toxicity was determined to be 2.5 mg/kg bw/day.

Developmental Effects

There were no apparent effects on embryo/foetal viability, growth or malformations. There was a slight, but not statistically significant, increase in the incidence of skeletal variations. The most frequently observed variation was the presence of a rudimentary extra lumbar rib. This finding is considered likely to be an indirect consequence of maternal toxicity or stress and is of limited toxicological importance. The NOAEL for developmental effects was determined to be 15 mg/kg bw/day (ECHA) [Kl score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for 2PA follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

Based on health considerations, the concentration of acrylamide in drinking water should not exceed 0.0002 mg/L according to Australian Drinking Water Guidelines Version 3.4. The guideline value for acrylamide of 0.0002 mg/L is based on a consideration of health effects in relation to the limit of determination for analysis using commonly available techniques.

Based on strict health related factors, a health-based derivation was determined as 0.0007 mg/L according to Australian Drinking Water Guidelines Version 3.4. A safety factor of 1,000 is used for the results of an animal study as a basis for human exposure (10 for interspecies variations, 10 for intraspecies variations and 10 for a less than lifetime study). An additional factor of 10 for carcinogenicity was not applied as tumours occur at doses above those that cause neurotoxic effects. The use of this safety factor was recommended by the NHMRC Standing Committee on Toxicity.

B. Cancer

An oral cancer slope factor for 2PA of 5×10^{-1} per mg/kg/day has been developed by USEPA and presented in the Integrated Risk Information System (IRIS) based on thyroid tumours and tunica vaginalis mesotheliomas (USEPA). Health based values will not be derived based on the noted slope factor since NICNAS has determined that the above noted drinking water guidance value is protective of both non-cancer and cancer effects.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

2PA does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

2PA has low acute and chronic aquatic toxicity.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on 2PA.

Table 3: Acute Aquatic Toxicity Studies on 2PA[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Onchorhyncus mykiss	96-hour LC_{50}	180	1	ECHA
Daphnia magna	48-hour EC_{50}	60	1	ECHA

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pseudokirchneriella subcapitata	72-hour EC_{50}	33 (growth inhibition) 50 (growth rate inhibition)	2	ECHA

Chronic Studies

Fish: A 28-day study was conducted to determine the toxicity of acrylamide monomer to carp (*Cyprinus carpio*). Fish were exposed to 2PA at concentrations of 0, 0.05, 0.5 and 5 mg/L. The NOEC was determined to be 5 mg/L (ECHA) [KI Score = 2].

Invertebrates: No freshwater invertebrate chronic toxicity data were available (ECHA) [KI Score = 1].

C. Terrestrial Toxicity

No data were available.

D. Calculation of PNEC

The PNEC calculations for 2PA follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (180mg/L), Daphnia (60 mg/L), and algae (33 mg/L). NOEC values from long-term studies are available for fish (5 mg/L). On the basis that the data consists of short-term studies for three trophic levels and long-term studies from one trophic level, an assessment factor of 100 has been applied to the lowest reported NOEC value of 5 mg/L. Therefore, the $PNEC_{water}$ is 0.05 mg/L.

PNEC sediment

2PA is expected to degrade rapidly in the environment. Moreover, based on the low K_{ow} and K_{oc} values, the substance is not expected to bind substantially to sediment. Therefore, a PNEC for sediment has not been calculated.

PNEC soil

2PA is expected to degrade rapidly in the environment. Moreover, based on the low K_{ow} and K_{oc} values, the substance is not expected to bind substantially to soil. Therefore, a PNEC for soil has not been calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

2PA is an organic substance that has been determined to be readily biodegradable. Thus, it does not meet the screening criteria for persistence.

The relatively low log BAF (-0.047) suggests 2PA will not bioaccumulate to any substantial degree. Therefore, 2PA does not meet the screening criterion for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on 2-PA are > 0.1 mg/L. The acute $E(L)C_{50}$ values from the acute aquatic toxicity studies on 2-PA are > 1 mg/L. Thus, 2-PA does not meet the criteria for toxicity.

Based on PBT assessment guidance cited above, 2PA is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Oral – Acute Tox. 3: H301: Toxic if swallowed.

Dermal – Acute Tox. 4: H312: Harmful in contact with skin.

Inhalation – Acute Tox. 4: H332: Harmful if inhaled.

Skin corrosion / irritation – Skin Irrit. 2: H315: Causes skin irritation.

Serious eye damage / eye irritation – Eye Irrit. 2: H319: Causes serious eye irritation.

Skin sensitisation – Skin Sens. 1: H317: May cause an allergic skin reaction.

Reproductive toxicity: H361: Suspected of damaging fertility or the unborn child.

Germ cell mutagenicity: H340: May cause genetic defects.

Carcinogenicity: H350: May cause cancer.

Specific target organ toxicity: STOT Rep. Exp. 1: H372: Causes damage to organs.

B. Signal word

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if

ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standards for 2-PA in Australia is 0.03 mg/m^3 as am 8-hour time weighted average (TWA). There is also a skin notation indicating that absorption through the skin may be significant source of exposure.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN number: 2074 (Solid)

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECETOC. (2000). European Centre for Ecotoxicology and Toxicology of Chemicals The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and the Related Food Web. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Technical Report No. 68, Brussels.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

NICNAS. (2002). Acrylamide Priority existing Chemical Assessment Report No. 23.

NOHSC (National Occupational Health and Safety Commission). (1999). List of Designated Hazardous Substances [NOHSC:10005(1999)]. Sydney, NOHSC.

USEPA. The Integrated Risk Information System (IRIS). www.epa.gov/iris.

2-PROPENOIC ACID, POLYMER WITH SODIUM PHOSPHINATE (1:1), SODIUM SALT

This dossier on 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies pertinent to the risk assessment of 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt in coal seam gas extraction activities. The majority of information presented in this dossier is based on a surrogate 2-propenoic acid, polymer with sodium phosphinate (CAS No. [redacted] Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-Propenoic acid, polymer with sodium phosphinate (1:1), sodium salt

CAS RN: [redacted]

Molecular formula: $(C_3H_4O_2.H_3O_2\text{-}P.Na)_x$- x-Na

Molecular weight: Variable

Synonyms: 2-propenoic acid, polymer with sodium phosphinate, sodium salt; 2-propenoic acid polymer with sodium hypophosphite, sodium salt; 2-Propenoic acid, polymer with sodium hypophosphite, sodium salt

SMILES: Not applicable

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of 2-Propenoic acid, Polymer with Sodium Phosphinate (CAS No. [redacted])

Property	Value	Reference
Physical state at 20°C and 101.3 kPa	Colourless liquid	BWA, 2006
Melting Point	-1 to -3°C	BWA, 2006
Boiling Point	101 to 103°C	BWA, 2006
Specific Gravity	1.20 to 1.24	BWA, 2006
pH	3.5 to 4.5	BWA, 2006
Viscosity	75-200 mm^2/s @ 25°C	BWA, 2006
Water Solubility	Miscible	BWA, 2006

III. ENVIRONMENTAL FATE PROPERTIES

In an OECD 301E test, 2-propenoic acid, polymer with sodium phosphinate degraded 20% in 28 days, indicating that it is not readily biodegradable (BWA, 1999).

As a polymer, 2-propenoic acid, polymer with sodium phosphinate is not expected to bioaccumulate, because its molecular weight will limit its bioavailability.

IV. HUMAN HEALTH HAZARD ASSESSMENT

There is very limited information on 2-propenoic acid, polymer with sodium phosphinate.

A technical data sheet on Belsperse® 164 Dispersant (active ingredient: CAS No. [redacted] lists this product as having an acute oral LD_{50} value of > 5,000 mg/kg in rats. The product is non-irritating to the skin and eyes (BWA, 2006).

In a letter to the U.S. EPA, male and female rats dosed by oral gavage with a 40% solution of this polymer showed treatment-related signs of osteomalacia associated with hyperphosphaturia and calciuria by week 8 of a 90-day study (U.S. EPA, 2016a).

The U.S. EPA TSCATS database also has a brief summary of a 4-week rat oral gavage conducted on the product BELSPERSE 164 (CAS No. [redacted] At 5,000 mg/kg/day, there were adverse clinical signs, gross organ pathology and changes in blood biochemical parameters. The NOAEL was 2,000 mg/kg/day (U.S. EPA, 2016b).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicity information on 2-propenoic acid, polymer with sodium phosphinate is inadequate and/or unreliable for deriving toxicological reference and drinking water guidance values for this polymer.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

2-Propenoic acid, polymer with sodium phosphinate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

2-Propenoic acid, polymer with sodium phosphinate exhibits low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

<u>Acute Studies</u>

Table 2 lists the results of acute aquatic toxicity studies conducted on 2-propenoic acid, polymer with sodium phosphinate.

Table 2: Acute Aquatic Toxicity Studies on 2-Propenoic Acid, Polymer with Sodium Phosphinate (CAS No. [redacted])

Test Species	Endpoint	Results (mg/L)	Reference
Rainbow trout	96-hour LC_{50}	> 1,000	BWA, 2006
Zebra fish	96-hour LC_{50}	> 1,000	BWA, 2006
Daphnia	24-hour EC_{50}	320	BWA, 2006
Algae	72-hour EC_{50}	130	BWA, 2006

Chronic Studies

No studies were located.

C. Terrestrial Toxicity

No studies were located.

D. Calculation of PNEC

The PNEC calculations for 2-propenoic acid, polymer with sodium phosphinate follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (> 1,000 mg/L), *Daphnia* (> 320 mg/L) and algae (> 130 mg/L). No long-term studies on 2-propenoic acid, polymer with sodium phosphinate are available. On the basis of the short-term results from three trophic levels, an assessment factor of 1,000 has been applied to the lowest reported effect concentration of 130 mg/L for algae. The $PNEC_{water}$ is 0.13 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. The K_{ow} and K_{oc} have not been experimentally derived for 2-propenoic acid, polymer with sodium phosphinate; these values cannot estimate using QSAR models because of the high molecular weight of 2-propenoic acid, polymer with sodium phosphinate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$.

PNEC soil

There are no toxicity data for soil-dwelling organisms. The K_{ow} and K_{oc} have not been experimentally derived for 2-propenoic acid, polymer with sodium phosphinate; these values cannot be estimated using QSAR models because of the high molecular weight of 2-propenoic acid, polymer with sodium phosphinate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Based on the information for read-across substance 2-Propenoic acid, polymer with sodium phosphinate, 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt is not readily biodegradable. Thus, it meets the screening criteria for persistence.

Read-across substance 2-Propenoic acid, polymer with sodium phosphinate is a high molecular weight polymer that is not expected to be bioavailable to aquatic or terrestrial organisms. Thus, 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt it is not expected to bioaccumulate.

No chronic aquatic toxicity studies have been conducted on read-across substance 2-propenoic acid, polymer with sodium phosphinate. The acute E(L)C_{50} values are > 1 mg/L. Thus, 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt does not meet the screening criteria for toxicity.

The overall conclusion is that 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictogram

None.

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In the case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide, phosphorus oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for 2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing closed work clothing is recommended.

F. Transport Information

2-propenoic acid, polymer with sodium phosphinate (1:1), sodium salt is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

BWA. (1999). BWA Water Additives. Belsperse® 164 Dispersant. General Product Information,

BWA. (2006). BWA Water Additives. Product Information for Belsperse 164 – High Performance Dispersant for Industrial Water Systems. 2006 BWA, V1010

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

U.S. EPA [EPA]. (2016a). U.S. Environmental Protection Agency (EPA) Toxic Substance Control Act Test Submissions (TSCATS) database. DCN 88900000038; accessed October 2016.

U.S. EPA [EPA]. (2016b). U.S. Environmental Protection Agency (EPA) Toxic Substance Control Act Test Submissions (TSCATS) database. DCN 88920001980; accessed October 2016.

ACRYLAMIDE, 2-ACRYLAMIDO-2-METHYLPROPANESULFONIC ACID, SODIUM SALT POLYMER (CAS RN [redacted])
POLYMER OF 2-ACRYLAMIDO-2-METHYLPROPANESULFONIC ACID SODIUM SALT AND METHYL ACRYLATE (CAS RN [redacted]

This group contains an acrylamide, 2-acrylamido-2-methylpropanesulfonic acid, sodium salt polymer (CAS RN [redacted] and polymer of 2-acrylamido-2-methylpropanesulfonic acid sodium salt and methyl acrylate (CAS RN [redacted] They are expected to have similar environmental concerns and have consequently been assessed as a group. Information provided in this dossier is based on data for the monomer sodium acryloyldimethyltaurate (CAS RN [redacted]

This dossier presents the most critical studies pertinent to the risk assessment of these substances in their use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): acrylamide, 2-acrylamido-2-methylpropanesulfonic acid, sodium salt polymer

CAS RN: [redacted]

Molecular formula: (C7-H13-N-O4-S.C3-H5-N-O.Na)x-

Molecular weight: 302.32 g/mol (monomer); Based on the type and intended use, the molecular weight of the polymer would likely range from 1,000 to > 1,000,000 g/mol (CIR, 2017).

Synonyms: 1-Propanesulfonic acid, 2-methyl-2-((1-oxo-2-propen-1-yl)amino)-, sodium salt (1:1), polymer with 2-propenamide

SMILES: Not applicable

Chemical Name (IUPAC): Polymer of 2-acrylamido-2-methylpropanesulfonic acid sodium salt and methyl acrylate

CAS RN: [redacted]

Molecular formula: (C7-H13-N-O4-S.C4-H6-O2.Na)x-

Molecular weight: 315.3202 g/mol (monomer); Based on the type and intended use, the molecular weight of the polymer would likely range from 1,000 to > 1,000,000 g/mol (CIR, 2017).

Synonyms: 2-Propenoic acid, 2-methyl-, polymer with 2-methyl-2-((1-oxo-2-propenyl)amino)-1-propanesulfonic acid monosodium salt

SMILES: Not applicable

Chemical Name (IUPAC): sodium;2-methyl-2-(prop-2-enoylamino)propane-1-sulfonate

CAS RN: [redacted]

Molecular formula: $C_7H_{12}NNaO_4S$

Molecular weight: 229.23 g/mol

Synonyms: 1-Propanesulfonic acid, 2-methyl-2-[(1-oxo-2-propenyl)amino]-, monosodium salt

SMILES: CC(C)(CS(=O)(=O)[O-])NC(=O)C=C.[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

NICNAS has assessed polymer of 2-acrylamido-2-methylpropanesulfonic acid sodium salt and methyl acrylate in an IMAP Tier 1 assessment and considers it a polymer of low concern, and concluded that it poses no unreasonable risk to human health and the environment[1].

Physical and chemical properties were not available for either polymer: acrylamide, 2-acrylamido-2-methylpropanesulfonic acid, sodium salt polymer (CAS RN [redacted] or polymer of 2-acrylamido-2-methylpropanesulfonic acid sodium salt and methyl acrylate (CAS RN [redacted] Available information for the monomer is provided in Table 1.

Table 1: Overview of the Physico-chemical Properties of Sodium Acryloyldimethyltaurate (CAS RN [redacted]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Light amber liquid @ 25°C with a faint organic odour	1	ECHA
Melting Point	-25°C @ 101.3 kPa	1	ECHA
Boiling Point	110°C @ 101.3 kPa	2	ECHA
Density	1200 - 1300 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	7.4 x 10^{-9} Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})	-4.34 (temperature and pH not specified)	2	ECHA
Water Solubility	1000 g/L @ 25°C	2	ECHA
Flash Point	No data available	-	-
Auto flammability	No data available	-	-
Viscosity	0.6 mm^2/s @ 20°C	2	ECHA

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

Property	Value	Klimisch score	Reference
Dissociation constant	No data available	-	-

III. ENVIRONMENTAL FATE PROPERTIES

No data is available for the polymers and limited studies are available for the monomer (sodium acryloyldimethyltaurate). The polymers are not expected to be readily biodegradable. The physico-chemical properties of the polymers would preclude it from undergoing significant biodegradation (Guiney et al., 1997). Biodegradation is limited due to the very high molecular weight and the low water solubility of the polymers. In addition, sodium acryloyldimethyltaurate was evaluated in a 44-day biodegradation in water study . This substance showed low biodegradation with a rate of less than 10% after 44 days (ECHA). [Kl. Score = 1]

Acryloyldimethyltaurate polymers are large (2000 µm; >1000 to >1,000,000 g/mol) molecules (CIR, 2017). Anionic polymers of this type will likely bind tightly to organic matter found within soils and sediments (Guiney et al., 1997). However, the polymers are not expected to bioaccumulate because of their poor water solubility and high molecular weight.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Sodium acryloyldimethyltaurate has low acute toxicity by the oral and dermal routes. It is not a skin or eye irritant; and, it is not a skin sensitiser. No systemic toxic effects were observed in repeated dose subchronic oral toxicity studies. Sodium acryloyldimethyltaurate is not genotoxic and is not a developmental toxicant.

B. Acute Toxicity

<u>Oral</u>

An OECD Guideline 401 (Acute Oral Toxicity) was performed. The study was conducted to determine the acute oral toxicity of sodium acryloyldimethyltaurate in Sprague-Dawley rats. Groups of 10 fasted animals (5 males and 5 females per dose except for 5 males only at the highest dose) were administered 0, 500, 1000, 2000, 4000, and 8000 mg/kg of the test substance via the oral route. The animals were observed for 14 days after dosing and then sacrificed and subjected to gross pathological examination. No unusual clinical or behavioural signs were observed in animals receiving dosages ranging from 1000-8000 mg/kg. Animals receiving 16000 mg/kg appeared ruffled and lethargic within 3-4 hours of test material administration. All animals appeared normal by day 5. No unscheduled deaths were recorded and gross examination revealed no pathological findings. There were no effects in the rat at the highest dose of 16,000 mg/kg. This is considered to be the No Observed Adverse Effect Level (NOAEL) (ECHA) [Kl. score =1].

The results from an OECD Guideline study (425) in rats showed that the LD_{50} > 5,000 mg/kg (> 1,200 mg/kg bw/day) for sodium acryloyldimethyltaurate (CIR, 2017).

Inhalation

No data was available.

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) was performed using New Zealand White rabbits. Under the conditions of the test, The LD_{50} of the test substance (OS 114454) was found to be greater than 2000 mg/kg (based on active ingredient, 4000 mg/kg based on test substance) when administered once for 24 hours to the clipped, intact skin of male and female albino rabbits. In addition, 2000 mg/kg was found to be a No-Observable-Effect Level (NOEL) for systemic toxicity under the conditions of this study. (ECHA) [Kl Score=1].

The results from an OECD Guideline (402) study in rats showed that the dermal LD_{50} for sodium acryloyldimethyltaurate is > 5,000 mg/kg (1,200 mg/kg bw/day) (CIR, 2017).

C. Irritation

Skin

Sodium acryloyldimethyltaurate was determined to be a minimal dermal irritant to rabbits by the USEPA (OPPTS 870.2500, Acute Dermal Irritation) and a dermal non-irritant based on OECD Guideline 404 (ECHA). [KI Score = 1].

Eye

Sodium acryloyldimethyltaurate was determined to be slightly irritating to the eye based on an OECD 405 study (CIR, 2017). In a USEPA OPPTS 870.2400 (Acute Eye Irritation) test, sodium acryloyldimethyltaurate was determined to be not irritating to the eye (ECHA). [KI Score = 1].

D. Sensitisation

There was no evidence that sodium acryloyldimethyltaurate was sensitising to human (HRIPT test) or rats (OECD Guideline 406 study) (CIR, 2017).

An EU Method B.6 (Skin Sensitisation) study (i.e., guinea pig maximisation test) was performed on Dunkin-Hartley guinea pigs. Under the conditions of this study, the test substance (OS 114454) did not produce evidence of skin sensitisation (delayed contact hypersensitivity) in nine of the ten test animals. The remaining animal gave an inconclusive response. The test substance was considered to be non-sensitising (ECHA). [Kl. Score = 1].

E. Repeated Dose Toxicity

Oral

In an OECD Guideline (407) study, sodium acryloyldimethyltaurate was exposed to Sprague Dawley rats via oral gavage for 28 days at doses of 50, 150, 400 and 1000 mg/kg bw/day. No significant toxicity was observed at any dose level. The NOEL was determined to be 1,000 mg/kg bw/day (ECHA). [KI Score = 1].

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on sodium acryloyldimethyltaurate are presented in Table 2. In general, the substance did not produce a significant increase in the number of revertants, with and without metabolic activation in any test strain (ECHA). [Kl. Score = 1]..

Table 2: *In Vitro* Genotoxicity Studies on sodium acryloyldimethyltaurate

Test System1	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) (Bacterial Reverse Mutation Assay)	-	-	1	CIR, 2017
Ames test, S. typhimurium (TA98, TA100, TA1535 and TA 1537) and E. coli (WP2uvrA)	-	-	-	CIR, 2017
OECD Guideline 473 (In Vitro mammalian chromosome aberration test) Chinese hamster ovary cells	-	+	1	ECHA
OECD Guideline 476 (Chinese hamster ovary cells)	-	-	1	ECHA

*+, positive; -, negative.

In Vivo Studies

An OECD Guideline 475 (Mammalian Bone Marrow Chromosome Abberation Test) study was conducted using Sprague Dawley rats exposed via oral gavage to sodium acryloyldimethyltaurate. The test material was non-clastogenic in rat bone marrow cells under the conditions of the assay (ECHA). [Kl. Score = 1]...

G. Carcinogenicity

Oral

No studies are available.

Inhalation

No studies are available.

Dermal

No studies are available.

H. Reproductive Toxicity

Oral

An OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) was performed using male and female Sprague-Dawley rats. Dosing preparations were administered orally, by gavage, as a single dose daily to F0 males and females beginning two weeks prior to mating. The F0 males were dosed for approximately seven weeks, including two weeks prior to mating, during mating and post-mating. The F0 females were dosed throughout the study, including two weeks prior to mating, during mating, during gestation, and following parturition. Individual doses were adjusted based on the most recent body weight data. Both F0 males and females were dosed up to and including the day prior to scheduled euthanasia.

Oral administration of OS#132086 at dosage levels of 100, 500 and 1000 mg/kg/day had no effect on F0 survival, growth, mating behavior, copulation, fertility, precoital intervals, gestation lengths, corpora lutea counts, implantation counts, mean live litter size, prelpost-implantation loss, gross necropsy findings or organ weights (testes and epididymides). Histopathological examination of the testes, ovaries and epididymides from control and high-dose rats did not reveal any test article-related microscopic changes. No test article-related effects were observed in the F1 offspring with respect to survival, clinical observations, body weights or gross necropsy findings. In addition, there were no indications of test article-related developmental effects in the F1 pups at any dosage level tested. Based on the results, a dosage level of 1000 mg/kg bw/day was considered a NOEL for this reproduction and developmental screening study in rats (ECHA). [Kl. Score = 1].

I. Developmental Toxicity

No studies are available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for sodium acryloyldimethyltaurate follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The developmental toxicity NOAEL of 1,000 mg/kg bw/day was determined for a test substance that contained sodium acryloyldimethyltaurate. This value is equivalent to the NOAEL determined from a repeated dose oral toxicity study for sodium acryloyldimethyltaurate (also 1,000 mg/kg bw/day). This NOAEL will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 10
UF_D (database uncertainty) = 1
Oral RfD = 1000/(10 x 10 x 1 x 1 x 10 x 1) = 1000/1000 = 1 mg/kg/day.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (1 x 70 x 0.1)/2 = 3.5 mg/L

B. Cancer

Sodium acryloyldimethyltaurate is not considered a carcinogen. Thus, a cancer reference value will not be calculated for this substance.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium acryloyldimethyltaurate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium acryloyldimethyltaurate exhibits low toxicity to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on sodium acryloyldimethyltaurate.

Table 3: Acute Aquatic Toxicity Studies on Sodium Acryloyldimethyltaurate

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Lepomis macrochirus (Bluegill)	96-hour LC_{50}	1000	1	ECHA
Daphnia magna	48-hour EC_0	1000	1	ECHA

Chronic Studies

Sodium acryloyldimethyltaurate has been evaluated for its toxicity towards the fresh water alga *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) in an Alga growth inhibition test according to OECD 201 under GLP requirements. The exposure duration was 96 hours under static conditions. The NOEC growth rate determined from the study was 2000 mg/L (ECHA) [Kl. Score = 1].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for sodium acryloyldimethyltaurate follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (1,000 mg/L) and *Daphnia* (1,000 mg/L). Results from chronic studies are also available for one trophic level (algae), with a NOEC of 2,000 mg/L. On the basis that the data consists of short-term studies for two trophic levels and long-term studies from one trophic level, an assessment factor of 100 has been applied to the lowest reported EC_{50} value of 1,000 mg/L for Lepomis macrochirus. Therefore, the $PNEC_{water}$ is 10 mg/L.

This value is more conservative than a PNEC derived using chronic data from the algae study (i.e., 20 mg/L).

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. The K_{ow} and K_{oc} have not been experimentally derived for sodium acryloyldimethyltaurate; these values cannot be reliably estimated using QSAR models. For example, estimated K_{oc} values using USEPA's EPISUITE vary between 10 L/K (MCI method) and 0.03155 L/kg (K_{ow} method). Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$.

PNEC soil

There are no toxicity data for soil-dwelling organisms. The K_{ow} and K_{oc} have not been experimentally derived for sodium acryloyldimethyltaurate; these values cannot be reliably estimated using QSAR models. For example, estimated K_{oc} values using USEPA's EPISUITE

vary between 10 L/K (MCI method) and 0.03155 L/kg (K_{ow} method). Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Based on the information for read-across substance sodium acryloyldimethyltaurate, the polymers in this groups are not readily biodegradable. Thus, they meet the screening criteria for persistence.

The polymers in this group are not expected to bioaccumulate because of their poor water solubility and high molecular weight. Therefore, these polymers do not meet the screening criterion for bioaccumulation.

The chronic toxicity data on read-across substance sodium acryloyldimethyltaurate show NOECs of > 0.1 mg/L. Acute $E(L)C_{50}$ values are also greater than 1 mg/L. Thus, the polymers in this group do not meet the screening criteria for toxicity.

The overall conclusion is that acrylamide, 2-acrylamido-2-methylpropanesulfonic acid, sodium salt polymer and polymer of 2-acrylamido-2-methylpropanesulfonic acid sodium salt and methyl acrylate are not PBT substances.

IX. CLASSIFICATION AND LABELLING

A. Classification

Irritation-Skin: H315 Causes skin irritation.

Aquatic Tox. H413: May cause long lasting harmful effects to aquatic life.

B. Signal word

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Please refer to the product SDS for additional information and for confirmation of the information provided herein.

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for acrylamide, 2-acrylamido-2-methylpropanesulfonic acid, sodium salt polymer or polymer of 2-acrylamido-2-methylpropanesulfonic acid sodium salt and methyl acrylate.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be an effective type of air-purifying respirator: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN number: none

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

CIR. (2017). Safety Assessment of Acryloyldimethyltaurate Polymers as Used in Cosmetics.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECETOC. (2000). European Centre for Ecotoxicology and Toxicology of Chemicals The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and the Related Food Web. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Technical Report No. 68, Brussels.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Guiney, P. D., McLaughlin, J. E., Hamilton, J. D., and Reinert, K. H. (1997). Dispersion Polymers. In: Ecological Assessment of Polymers Strategies for Product Stewardship and Regulatory Programs (Hamilton, J.D. and Sutcliffe, R. eds.), pp. 147-165, Van Nostrand Reinhold.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

AMMONIUM SULFATE

This dossier on ammonium sulfate (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): diazanium sulfate

CAS RN: [redacted]

Molecular formula: $H_8N_2O_4S$

Molecular weight: 132.14 g/mol

Synonyms: ammonium sulfate, diammonium sulfate, sulfuric acid diammonium salt, mascagnite

SMILES: [NH4+].[NH4+].[O-]S(=O)(=O)[O-]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of Ammonium Sulfate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	solid	2	ECHA
Melting Point	> 280°C (pressure not provided)	2	ECHA
Boiling Point	Not applicable as substance is solid	1	ECHA
Density	1770 kg/m^3 @ 25°C	2	ECHA
Vapour Pressure	0 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-5.1 @ 25°C	2	ECHA
Water Solubility	767 g/L @ 25°C	2	ECHA
Flash Point	Not applicable as substance is solid	1	ECHA
Auto flammability	Not applicable as substance is solid	1	ECHA
Viscosity	Not applicable as substance is solid	1	ECHA
Dissociation constant (pKa)	9.25 @ 25°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Ammonium sulfate dissociates in aqueous media to the ammonium ion (NH_4^+) and sulfate anion (SO_4^{2-}). Ammonium sulfate is an inorganic ionic substance that is not expected to adsorb or bioaccumulate. Ammonium sulfate is hydrophilic, and it has high mobility in the soil.

B. Biodegradation

Given the fact the ammonium sulfate is an inorganic substance, biodegradation testing is not applicable.

C. Environmental Distribution

Ammonium sulfate is water soluble so it is mainly expected to partition to aqueous phase. Based on its log K_{ow}, it is not expected to adsorb substantially to the soil phase.

D. Bioaccumulation

No experimental data were available for bioaccumulation or bioconcentration of ammonium sulfate. Based on the high water solubility and the ionic nature, ammonium sulfate is not expected to adsorb or bioaccumulate to a significant extent. In addition, due to the log K_{ow} of –5.1 bioaccumulation is not expected (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Ammonium sulfate exhibits low acute toxicity by the oral, inhalation and dermal routes. It is not irritating to the skin and eyes; and it is not a skin sensitiser. In repeated dose toxicity studies, dose-related changes were not observed in rats given ammonium sulfate in feed for 52-weeks. Ammonium sulfate is not genotoxic and is not carcinogenic. No reproductive or developmental effects were observed in read-across studies.

B. Acute Toxicity

<u>Oral</u>

In an OECD Guideline (401) study, Gassner rats were exposed to ammonium sulfate via oral gavage. The LD_{50} was determined to be 4,250 mg/kg bw/day in male and female rats (ECHA) [KI score = 2].

In an OECD Guideline (423 Acute Oral Toxicity) study Wistar rats were exposed to ammonium sulfate via oral gavage. The LD_{50} in rats was determined to be > 2000 mg/kg bw/day (ECHA) [KI score = 2].

<u>Inhalation</u>

In an OECD Guideline 433 (Acute Inhalation Toxicity: Fixed Concentration Procedure) study Sprague-Dawley rats were exposed to ammonium sulfate via nose only aerosol inhalation.

The resulting LC_0 was determined to be 3.5 mg/m^3 after 4 hours of exposure (ECHA) [KI score = 2].

Dermal

In an OECD Guideline 434 (Acute Dermal Toxicity) study Wistar rats were exposed to ammonium sulfate via open coverage. The LD50 for this study was determined to be > 2000 mg/kg bw/day (ECHA) [KI score = 2].

C. Irritation

Skin

Vienna White rabbits were exposed to ammonium sulfate for up to 20 hours and they were observed for 8 days. There were no signs of clinical toxicity, so ammonium sulfate is not considered irritating to the skin (ECHA) [KI score = 2].

Eye

Ammonium sulfate was placed on the eyes of Vienna White rabbits without rinsing for 8 days. All of the observed effects were considered reversible, so this substance is not considered an eye irritant (ECHA) [KI score 2].

D. Sensitisation

A guinea pig maximisation test was used to determine if ammonium sulfate is a skin sensitiser. The animals did not show any signs of toxicity throughout the study period. [KI. score = 1]. Ammonium sulfate is not sensitising to the skin of guinea pigs (ECHA) [KI score = 1].

E. Repeated Dose Toxicity

Oral

In an OECD 453 (Combined Chronic Toxicity/Carcinogenicity) study Fischer 344 rats were continuously exposed to ammonium sulfate via their feed for 52weeks.

In the chronic study, groups of 10 rats/sex were fed a diet containing the test substance (purity not given) at concentrations of 0, 0.1, 0.6, or 3% for 1 year. These concentrations corresponded to average daily intakes of 0, 42, 256, and 1527 mg/kg bw/day for males and 0, 48, 284, and 1490 mg/kg bw/day for females, respectively.

No mortality was found in any groups throughout the treatment period. No test substance-related change in the body weights was found. Absolute and relative kidney weights were increased at the high dose level for both sexes. Absolute spleen weights were decreased and relative liver weights were increased in high dose males. No dose-related changes were found in the other organs.

The NOAEL for females was determined to be 284 mg/kg bw/day and the NOAEL for males was determined to be 256 mg/kg bw/day (ECHA) [KI score = 1].

Inhalation

Rats were exposed via whole body inhalation of ammonium sulfate for 8 hours a day over a 14-day treatment period. The NOEC was determined to be 300 mg/m^3 (ECHA) [KI score = 2].

Dermal

No data were available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on ammonium sulfate based are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Ammonium Sulfate

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) S. typhimurium TA 1535, TA 1537, TA 98 and TA 100	-	-	2	ECHA
OECD Guidline 476 (In vitro Mammalian Cell Gene Mutation Test) Chinese hamster lung fibroblasts (V79)	-	-	1	ECHA
OECD Guidline 473 (In vitro Mammalian Chromosome Aberration Test) human lymphocytes	-	-	2	ECHA

*+, positive; -, negative.

In Vivo Studies

An *in vivo* mammalian somatic cell study also known as the cytogenicity/erythrocyte micronucleus cell test was conducted using ddY mice exposed to ammonium sulfate. The results showed that ammonium sulfate is not genotoxic to mice as there were no adverse effects observed (ECHA) [KI score = 2].

G. Carcinogenicity

Oral

A chronic oral toxicity and carcinogenicity study was conducted in rats, similar to the requirements of OECD TG 453. For investigation of the carcinogenic potential, groups of 50 rats/sex were fed a diet containing the test substance (purity not given) at concentrations of 0, 1.5, or 3% for 2 years. These concentrations corresponded to average daily intakes of 0, 564.1, and 1288.2 mg/kg bw/day for males and 0, 4649.9, and 1371.4 mg/kg bw/day for females respectively.

No macroscopic changes were recorded by gross pathology, except for massive nodular or focal lesions suggesting neoplastic changes. At histopathological examination, non-neoplastic and neoplastic lesions were noted in the control and treatment groups, with no significant inter-group difference in their incidences or severity.

The authors concluded that the no observed adverse effect level of ammonium sulfate was the 0.6% diet, which is equivalent to 256 and 284 mg/kg bw/d in males and females, respectively, and the compound is noncarcinogenic under the conditions of the study. There was no evidence of a long-term carcinogenic activity of the test substance.

Data on purity of the test substance are lacking; however, since no adverse effects were observed, this is not considered to affect the evaluation of the carcinogenic potential of ammonium sulfate in an adverse manner (ECHA) [Kl. Score = 1].

Inhalation

No studies are available.

Dermal

No studies are available.

H. Reproductive Toxicity

Oral

Read across of data for ammonium phosphate (7783-28-0) was conducted to screen for the reproductive and developmental toxicity effects of ammonium sulfate. A one generation reproductive toxicity study was conducted using Sprague Dawley rats exposed via oral gavage. The NOAEL for reproductive toxicity was determined to be 1500 mg/kg bw/day (ECHA) [KI score = 1].

I. Developmental Toxicity

An OECD Guideline 422 (Combined Repeated Dose Toxicity) study was conducted using Sprague Dawley rats exposed via oral gavage to a read across substance, ammonium phosphate (7783-28-0), for two weeks. A NOAEL could not be established for maternal toxicity based on inflammatory/degenerative stomach changes recorded during histopathological examination. The foetal NOAEL was determined to be 1,500 mg/kg bw/day (ECHA) [Kl. Score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for ammonium sulfate follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

Oral

The NOAEL from a rat 52-week oral feeding study was reported to be 256 mg/kg bw/day for males based on the actual dose received. This NOAEL will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 256/(10 x 10 x 1 x 1 x 1) = 256/100 = 2.56 mg/kg/day.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (2.56 x 70 x 0.1)/2 = 8.96 mg/L

B. Cancer

Ammonium sulfate is not considered a carcinogen. Thus, a cancer reference value will not be calculated for this substance.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Ammonium does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Ammonium sulfate is of low acute concern to aquatic life. Algae is more tolerant than fish or invertebrates.

B. Aquatic Toxicity

In aqueous solution, ammonium salts are completely dissociated into NH_4^+ and a corresponding anion. This equilibrium depends on temperature, pH and ionic strength of the water in the environment. Un-ionized NH_3 species exists in the aquatic environments and the fraction ($NH_3/(NH_3 + NH_4^+)$) steeply increases with elevated pH value or temperature. It is well known that toxicity to aquatic organisms has been attributed to un-ionized ammonia (NH_3) species, and NH_4^+ species is considered to be non- or significantly less-toxic (Emerson et al., 1975 in ECHA). However, recent developments in assessing ammonia toxicity clearly show that in contrast to earlier assumptions where un-ionized ammonia was considered to be the toxic component, both the uncharged and charged molecule are toxic. Therefore, a joint toxicity model has been proposed, with ammonia causing most toxicity at high pH values and ammonium ion also contributing to toxicity at lower pH values (U.S. EPA 1999, OECD 2007 in ECHA).

It is generally accepted, that the principal toxic component of ammonium salts such as ammonium chloride or -sulphate is ammonia, rather than the corresponding anion (see also: OECD 2004, SIDS ammonium chloride or OECD 2007 ammonium sulphate). Therefore, toxicity values for ammonium salts (such as: ammonium -sulphates, phosphates, carbonates, chlorides or nitrates), where the major toxic component is ammonia, can be considered as equivalent, therefore read-across to those substances is possible. Consequently, the aquatic toxicity data compiled for ammonium sulfate comprises the total topic of ammonia toxicity. Species mean chronic values (SMCV) as described in ECHA were considered as relevant endpoints.

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on ammonium sulfate.

Table 3: Acute Aquatic Toxicity Studies on Ammonium Sulfate[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Onchorhyncus mykiss, Salmo gairdneri	96-hour LC_{50} mortality	53	1	ECHA
Prosopium williamsoni	96-hour LC_{50}	57.2	1	ECHA
Ceriodaphnia acanthina	48-hour EC_{50} mobility	121.7	1	ECHA
Daphnia magna	48-hour EC_{50} mobility	169	1	ECHA

1 - Acute toxicity results were normalized to pH 8 and ammonium sulfate.

Chronic Studies

Chronic values were normalized to 25°C. As indicated, plants (algae) are more tolerant than fish or invertebrates to ammonia.

Fish: A 30-day study was conducted to determine the toxicity of ammonium sulfate to *Lepomis macrochirus.* The EC_{10} for ammonium sulfate was determined to be 5.29 mg/L (ECHA) [KI score 1].

Invertebrates: A 10-week study was conducted to determine the toxicity ammonium sulfate to *Hyallella azteca*. The EC_{10} for ammonium sulfate was determined to be 3.12 mg/L based on reproduction (ECHA) [KI score = 1].

Algae: An 18-day study was conducted to determine the toxicity of ammonium sulfate to *Chlorella vulgaris*. The EC_{50} value for ammonium sulfate was determined to be 2,700 mg/L (ECHA) [KI score = 2].

A 5-day study was conducted to determine the toxicity of ammonium sulfate to *Chlorella vulgaris*. The EC_{50} value for ammonium sulfate was determined to be 1,605 mg/L based on the growth rate (ECHA) [KI. Score = 2].

C. Terrestrial Toxicity

No reliable studies available.

D. Calculation of PNEC

The PNEC calculations for ammonium sulfate follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (53 mg/L) and invertebrates (121.7 mg/L). NOEC values from long-term studies are available for fish (5.29 mg/L), invertebrates (3.12 mg/L) and algae (1,605 mg/L). On the basis that the data consists of short-term results from two trophic levels and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported EC_{10} value of 3.12 mg/L for invertebrates. Therefore, the $PNEC_{water}$ is 0.312 mg/L.

PNEC sediment

No reliable experimental toxicity data on sediment organisms are available. Ammonium sulfate dissociates completely in water with its environmental distribution is dominated by its high water solubility. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as ammonium sulfate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sediment}$. Based on its properties, no adsorption of ammonium sulfate to sediment is to be expected, and the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No reliable experimental toxicity data on terrestrial organisms are available. The environmental distribution of ammonium sulfate is dominated by its water solubility. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as ammonium sulfate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, ammonium sulfate is not expected to significantly adsorb to soil, and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Ammonium sulfate is an inorganic salt that dissociates completely to ammonium and sulfate ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to ammonium sulfate or its dissociated ions.

The estimated log K_{ow} is for ammonium sulfate is equal to -5.1. This value suggests that ammonium sulfate is not expected to bioaccumulate (ECETOC, 2000). Therefore, ammonium sulfate does not meet the screening criterion for bioaccumulation.

The NOEC or EC10 values from chronic aquatic toxicity studies are > 0.1 mg/L. The acute $E(L)C_{50}$ values for fish and invertebrates are > 1 mg/L. Thus, ammonium sulfate does not meet the criteria for toxicity.

The overall conclusion is that ammonium sulfate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity: H302: Harmful if swallowed

Irritation: H315: Causes skin irritation

Eye: H318: Cause serious eye damage

STOT: H335: May cause respiratory irritation

B. Signal word

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for ammonium sulfate.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN number: 20506 (Solid). This UN number is for ammonium hydrogen sulfate.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECETOC. (2000). European Centre for Ecotoxicology and Toxicology of Chemicals The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and the Related Food Web. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Technical Report No. 68, Brussels.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

PubChem. National Institutes of Health. National Library of Medicine National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/

BUT-2-ENEDIOIC ACID (FUMARIC ACID)

This dossier on but-2-enedioic acid (fumaric acid) presents the most critical studies pertinent to the risk assessment of this substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): (2E)-but-2-enedioic acid

CAS RN: [redacted]

Molecular formula: $C_4H_4O_4$

Molecular weight: 116.07 g/mol

Synonyms: fumaric acid, 2-Butenedioic acid, trans-Butenedioic acid, Allomaleic acid, Boletic acid, (2E)-but-2-enedioic acid, Lichenic acid

SMILES: C(=CC(=O)O)C(=O)O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of But-2-enedioc Acid

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colourless crystalline solid	2	ECHA
Melting Point	287°C @ 101.3 kPa	2	ECHA
Boiling Point	Sublimes at 200°C; @ 0.23 kPa, fumaric acid sublimes at 165°C	2	ECHA
Density	1640 kg/m^3 at 20°C	2	ECHA
Vapour Pressure	0.02 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-4.02 @ 20°C (Experimental)	2	ECHA
Water Solubility	7 g/L @ 25°C	2	ECHA
Flash Point	Flash point is only relevant to liquids and low melting point solids	2	ECHA
Auto flammability	399°C	2	ECHA
Viscosity	Not applicable as substance is a solid	2	ECHA
Dissociation constant	K1 = 9.3 x 10^{-4} at 25°C K2 = 2.9 x 10^{-5} at 25°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Fumaric acid is readily biodegradable, is not expected to bioaccumulate, and has a low potential to adsorb to soil.

B. Partitioning

The pKa of fumaric acid is 3.03 and 4.54, indicating that this substance will exist partially in anion form in the environment and anions generally do not adsorb more strongly to soils containing organic carbon and clay than their neutral counterparts (PubChem).

Volatilisation of fumaric acid from moist soil surfaces is not expected to be an important fate process because the acid exists as an anion and anions do not volatilise (PubChem).

Hydrolysis is not expected to be an important environmental fate process since this substance lacks functional groups that hydrolyse under environmental conditions (PubChem).

C. Biodegradation

The ready biodegradability of fumaric acid was determined using the OECD 301B guideline in a GLP study.

Using a non-adapted sludge from a domestic source, the percentage of biodegradation observed comprised 60.1% after 11 days (i.e., within the 10-day window) and 67.5% after 28 days. The reference substance (sodium benzoate) incubated under the same conditions showed a percentage biodegradation of 60.1% after 11 days. Incubation of the test substance and the reference substance demonstrated that the test substance did not significantly inhibit the microbial activity of the activated sludge.

Accordingly, fumaric acid is considered readily biodegradable [KI score = 1]. If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

D. Environmental Distribution

No experimental data are available for fumaric acid. Using KOCWIN in EPI Suite™ (USEPA, 2017), the estimated K_{oc} values from the molecular connectivity index (MCI) is 0.865 L/kg. Thus, fumaric acid has a low potential for adsorption to soil and is expected to have very high mobility. Likewise, based on these values along with fumaric acid's high water solubility, if released to water, it will likely not adsorb to suspended solids or sediments.

E. Bioaccumulation

There are no bioaccumulation studies on fumaric acid. The substance has a low potential for bioaccumulation based on log $K_{ow} \leq 3$.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Fumaric acid is an organic dicarboxylic acid and is naturally found in plants and animals. Fumaric acid is approved for use as a food additive in Australia and use as a therapeutic agent in the treatment of psoriasis and other skin disorders, as wells as a feed additive for all animals without a maximum level. Dietary exposure results from the large volumes of fumaric acid used as a food acidulant in applications such as beverages, baking powders and fruit drinks. The Joint FAO/WHO Committee on Food Additives and Contaminants (JECFA, 1999) concluded that there is no safety concern at current levels of intake when used as a flavouring agent (ECHA).

Fumaric acid has low acute toxicity via oral, inhalation or dermal exposure and was practically nontoxic when tested in guideline-comparable studies of acute oral and acute dermal toxicity.

B. Acute Toxicity

Oral

An OECD Guideline 401 (Acute Oral Toxicity) was conducted using male and female Sprague Dawley rats. The substance was administered orally via gavage. The LD_{50} values for the oral administration of fumaric acid in rats range from 9,300 (female rats) to 10,700 mg/kg bw (male rats) (ECHA) [KI Score = 1].

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) was conducted using female New Zealand white rabbits. Single dose dermal toxicity of fumaric acid using female New Zealand albino rabbits was reported as 20,000 mg/kg (ECHA) [KI Score = 1].

Inhalation

An OECD Guideline 403 (Acute Inhalation Toxicity) was undertaken. An inhalation LD_{50} for rats is reported to be 1,306 mg/L (ECHA) [KI Score = 1].

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was conducted using small white Russian male and female rabbits. Dermal application of 0.5 g fumaric acid was mildly irritating to the skin of male and female rabbits. Fumaric acid did not elicit dermal reactions that would exceed the threshold for classification in accordance with EU criteria (ECHA) [KI Score = 1].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) was undertaken where test material was applied to the lower conjunctival sac of the right eye by pulling away the lower

eyelid. The left eye was treated in one animal. The contralateral eye served as a concurrent, inherent control.

Application of 0.1 g fumaric acid to the eyes of male and female rabbits was considered irritating to the eye and ocular mucous membrane. Fumaric acid is classified as an eye irritant (ECHA) [KI Score = 1].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) guinea pig maximisation test was conducted. Fumaric acid shows no sensitisation effect on the skin of female guinea pigs according to the Magnusson-Kligman maximisation test. Fumaric acid is not considered a skin sensitiser.

E. Repeat Dose Toxicity

A Peer-reviewed study comparable to OECD guideline 452 was conducted using male Osborne-Mendel rats over a two-year period.

In a two-year dietary study using male rats, a very slight increase in mortality rate and some testicular atrophy was observed after administration of 1.5% fumaric acid (approximately 750 mg/kg bw/day). Gross and microscopic examination of major organs revealed no abnormalities. The authors of this study concluded that inanition was partly responsible for testicular atrophy. A previous study conducted in a similar manner with female rats showed no adverse effects on reproductive organs after administration of up to 1.2% fumaric acid in the diet for 2 years. Based on the low incidence of mortality of male rats, 1.2% is very near a NOAEL for chronic exposure to fumaric acid (600 mg/kg bw/day). The 1.2% NOAEL (600 mg/kg bw/day) derived from the available long-term rat toxicity data was confirmed as the appropriate point of departure. No non-neoplastic or neoplastic effects were noted supporting the conclusion that the substance is not a carcinogen (ECHA) [KI Score = 2].

F. Genotoxicity

An OECD Guideline 476 (*In Vitro* Mammalian Cell Gene Mutation Test) was performed using mouse lymphoma L5178Y cells. Under the experimental conditions reported, fumaric acid did not induce mutations in the mouse lymphoma thymidine kinase locus assay using the cell line L5178Y in the absence and presence of metabolic activation. Thus, fumaric acid is not considered to be a mutagen.

G. Carcinogenicity

Fumaric acid is not considered to be a carcinogen and is not classified as such by the International Agency for Research on Cancer (IARC) or the United States Environment Protection Agency (USEPA). In agreement with the regulatory agency, the two-year repeated dose toxicity testing discussed above showed no carcinogenic effects.

H. Reproductive Toxicity

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed using male and female Charles River CD rats. Substance was administered orally via gavage in a corn oil vehicle at dosage levels of 20, 55 and 150 mg/kg/day.

In a multigeneration reproduction study (similar to OECD guideline 416) maleic anhydride (purity 99%) was administered to 10 male and 20 female rats/dose by gavage at dose levels of 0, 20, 55 and 150 mg/kg bw/day. The rats were mated to produce two generations, each with two litters. Groups of the same size from the second litter were used for subsequent generations and were given the same dose of maleic anhydride as were their parents. Since 100% mortality was observed among parental F1 female rats at 150 mg/kg bw/day, the high dose group was terminated in the F1 generation, and a parental systemic NOAEL of 55 mg/kg bw/day was the highest dose tested in the F1 generation. The study was reduced from a three-generation to a two-generation study.

Renal cortical necrosis occurred in high-dose P/F0 males and females. Increased kidney weights were observed in low- and mid-dose adult F1 females. Therefore, no NOAEL could be determined, and the LOAEL (systemic) was regarded as 20 mg/kg bw/day. With respect to fertility, neither a dose-related reduction nor a pattern (during the two consecutive matings) within the parental (P0) generation suggested a treatment-related effect. No adverse effects on fertility were observed. Based on these observations the NOAEL (fertility) was derived at 55 mg/kg bw/day (highest dose tested under the conditions of this study) (ECHA) [Kl Score = 1].

I. Developmental Toxicity

A peer reviewed dietary study was conducted on an unspecified strain of rat.

Rats were fed 1,000 or 10,000 ppm malic acid, a metabolite of fumaric acid, for 9 weeks prior to mating. One week after weaning of the last F1A litter, the P1 parents were remated to produce the F1B litter. Ten male and 20 female weanlings from each dose group were selected for the P2 generation and administered the appropriate diets. The animals were mated at 100 days of age to produce the F2A generation. One week after weaning of the F2A litter, the P2 parents were remated to produce the F2B litter.

Maternal Effects: Body weight gain of female animals was comparable to controls prior to mating. Body weight gains of male animals in test groups were slightly decreased compared to controls. Feed consumption, survival, appearance and behaviour were similar for P1 test and control rats. The P2 test and control animals were similar throughout the study and wheezing was observed in all groups during the F2B phase. A NOAEL for maternal systemic toxicity was determined to be > 10, 000 mg/kg/day.

Foetal Effects: The F2B generation showed no meaningful differences between test and control animals in the number and placement of implantation and resorption sites or in the number, weight or length of live neonates; none of the neonates died. The skeletal development of F2B neonates was similar between test and control animals. Slight differences in developmental indices were considered to be within the range of normal variations in foetal development and no trend toward lesser or greater skeletal development was observed (ECHA) [Kl Score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for fumaric acid follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021)

A. Non-Cancer

Oral

The repeated dose NOAEL for fumaric acid is 600 mg/kg/day and will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 50/(10 x 10 x 1 x 1 x 1) = 600/100 = 6 mg/kg/day.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (6 x 70 x 0.1)/2 = 21 mg/L

B. Cancer

The substance is not considered a carcinogen. Thus, a cancer reference value will not be calculated.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Fumaric acid does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Fumaric acid is of low acute toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 2 presents the results of acute aquatic toxicity studies on fumaric acid.

Table 2: Acute Aquatic Toxicity Studies on Fumaric Acid

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Danio rerio	96-hour LC_{50}	> 100	1	ECHA
Daphnia magna	48-hour EC_{50}	> 100	1	ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50}	> 100	1	ECHA

Chronic Studies

No data are available.

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

The PNEC calculations for the substance follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (> 100 mg/L), *Daphnia* (> 100 mg/L) and algae (> 100 mg/L). On the basis that the data consists of short-term results from three trophic levels, an assessment factor of 100 has been applied to the lowest reported NOEC of 100 mg/L for algae. The $PNEC_{water}$ is 1 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.637 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.8166/1280) \times 1000 \times 1$
$= 0.637$ mg/kg

Where:

$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 0.0346/1000 \times 2400]$
$= 0.8166\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= -0.865 \times 0.04$
$= 0.03460$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg) presented above as 0.865 L/kg.
f_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.0115 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.0173/1500) \times 1000 \times 1$
$= 0.0115$ mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 0.865 \times 0.02$
$= 0.0173\ m^3/m^3$

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg) presented above as 0.865 L/kg.
f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Fumaric acid is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Bioaccumulation of fumaric acid is not expected to occur based on it log K_{ow} value of -4.02 (Table 1). Thus, fumaric acid does not meet the screening criteria for bioaccumulation.

No chronic aquatic toxicity data exist on fumaric acid; however, the acute E(L)C_{50} values are > 1 mg/L in fish, invertebrates and algae. Therefore, fumaric acid does not meet the screening criteria for toxicity.

Therefore, fumaric acid is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H319: Causes serious eye irritation.

B. Labelling

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention if symptoms persist.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Get medical attention if symptoms persist.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray, powder or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours, or spray Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Pick up mechanically. If formation of dust cannot be avoided use respiratory filter device. Dispose of the material collected according to regulations.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for but-2-enedioic acid.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

But-2-enedioic acid is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DoEE. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1999. Fumaric acid. Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

PubChem. https://pubchem.ncbi.nlm.nih.gov/compound/Fumaric-acid#section=Computed-Descriptors. Accessed January 2022.

U.S. Environmental Protection Agency [EPA]. (2017). EPI Suite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

CALCIUM CHLORIDE

This dossier on calcium chloride presents the most critical studies pertinent to the risk assessment of calcium chloride in its use as use in coal seam gas extraction activities. It does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA) and the OECD-SIDS documents on calcium chloride (OECD, 2002). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Calcium dichloride

CAS RN: [redacted]

Molecular formula: $CaCl_2$

Molecular weight: 110.98 g/mol

Synonyms: Calcium chloride; calcium dichloride; calcium chloride anhydrous

SMILES: Cl(Ca)Cl

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Calcium Chloride

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White odourless solid; crystals; powder; or granules	2	ECHA
Melting Point	782°C @ 101.3 kPa	2	ECHA
Boiling Point	> 1,600°C @ 101.3 kPa	2	ECHA
Density	2150 kg/m^3 @ 25°C	2	ECHA
Vapour Pressure	-	-	-
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	745 g/L @ 20°C (very soluble)	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

Calcium chloride dissociates completely in aqueous solutions to calcium (Ca^{2+}) and chloride (Cl^-) ions. Calcium chloride and its dissociated ions are ubiquitous in the environment.

Because of its dissociation properties and high water solubility, calcium chloride is not expected to be adsorbed to soil. The calcium ion may bind to soil particulate or may form stable inorganic salts with sulfate and carbonate ions. The chloride ion is mobile in soil and eventually drains into the surface water because it is readily dissolved in water (OECD, 2002).

Calcium (Ca^{2+}) and chloride (Cl^-) ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated (Ganong, 1995). Neither calcium chloride nor its dissociated ions are expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Calcium chloride exhibits low acute toxicity by the oral and dermal routes. It is irritating to the eyes, but not to the skin. There was no toxicity or carcinogenic effects in rats given calcium chloride in the diet for 12 months. Calcium chloride is not genotoxic. No developmental toxicity was reported in pregnant female rats, mice or rabbits given oral doses of calcium chloride.

B. Acute Toxicity

The oral LD_{50} values in rats are 2,301, 4,179 and 3,798 mg/kg (ECHA) [KI score = 2]. The dermal LD_{50} in rabbits is > 5,000 mg/kg (ECHA) [KI score = 1].

C. Irritation

Application of 0.5 mL to the skin of rabbits for 4 hours under occlusive conditions was non-irritating. Erythema and edema scores at all time points were zero (ECHA) [KI score = 1].

Instillation of 100 mg of calcium chloride into the eyes of rabbits was moderately irritating. The mean of the 24, 48 and 72-hour scores were: 0.67 for conjunctival redness; 0.78 for chemosis; 1.0 for corneal opacity; and 0.0 for iridial lesions. There were no signs of irritation by Day 21 (ECHA) [KI score = 1].

Instillation of 100 mg of calcium chloride into the eyes of rabbits was highly irritating. The mean of the 24, 48 and 72-hour scores were: 1.9 for conjunctival redness; 2.2 for chemosis; 2.0 for corneal opacity; and 1.0 for iridial lesions. The effects were not fully reversible by Day 21 (ECHA) [KI score = 1].

Instillation of 100 mg of calcium chloride into the eyes of rabbits was irritating. The mean of the 24, 48 and 72-hour scores were: 1.54 for conjunctival redness; 1.65 for chemosis; 1.0 for corneal opacity; and 0.33 for iridial lesions. The effects were not fully reversible by Day 21 (ECHA) [KI score = 2].

D. Sensitisation

No reliable studies are available.

E. Repeated Dose Toxicity

<u>Oral</u>

Rats were fed a 20 mg calcium chloride/g body weight diet for 12 months. There were no differences in mortality, weight gain or feed consumption between treated and control groups. No neoplastic lesions were observed in the gastrointestinal tract, urinary tract, liver, heart, brain or spleen. The estimated daily intake of calcium chloride is 1,000 to 2,000 mg/kg/day (OECD, 2002) [KI score = 3].

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on calcium chloride are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Calcium Chloride

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium*)	-	-	2	ECHA
Bacterial reverse mutation (*S. typhimurium*)	-	-	2	ECHA
Chromosomal aberration (Chinese hamster lung cells)	-	NC	2	ECHA

*+, positive; -, negative; NC, not conducted.

In Vivo Studies

No studies are available.

G. Carcinogenicity

Rats were fed 20 mg calcium chloride/g diet for 12 months. There were no differences in mortality, weight gain or feed consumption between treated and control groups. No neoplastic lesions were observed in the gastrointestinal tract, urinary tract, liver, heart, brain or spleen. The estimated daily intake of calcium chloride is 1,000 to 2,000 mg/kg/day (OECD, 2002) [KI score = 3].

H. Reproductive Toxicity

No studies are available.

I. Developmental Toxicity

Pregnant female Wistar rats were dosed by oral gavage with 0, 1.76, 8.18, 38 or 176 mg/kg calcium chloride on GD 6-15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 176 mg/kg/day (ECHA) [KI score = 1].

Pregnant female CD-1 mice were dosed by oral gavage with 0, 1.89, 8.78, 40.8 or 189 mg/kg calcium chloride on GD 6-15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 189 mg/kg/day (ECHA) [KI score = 1].

Pregnant female Dutch rabbits were dosed by oral gavage with 0, 1.69, 7.85, 35.6 or 169 mg/kg calcium chloride on GD 6-18. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 169 mg/kg/day (ECHA) [KI score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Toxicological reference values were not derived from calcium chloride.

Calcium chloride dissociates in water to calcium and chloride ions. An Australian drinking water guidance value is not available for calcium (ADWG, 2021). The Australian drinking water guidance value for chloride is 250 mg/L based on aesthetics (ADWG, 2021).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Calcium chloride does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Calcium chloride is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on calcium chloride.

Table 3: Acute Aquatic Toxicity Studies on Calcium Chloride

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	4,630	2	OECD, 2002; ECHA
Lepomis macrochirus	96-hour LC_{50}	9,500-11,300	2	OECD, 2002; ECHA
Gambusia affinis	96-hour LC_{50}	13,400	2	OECD, 2002; ECHA
Lepomis macrochirus	96-hour LC_{50}	10,650	2	OECD 2002; ECHA
Daphnia magna	48-hour EC_{50}	2,400	1	OECD, 2002; ECHA
Daphnia magna	48-hour EC_{50}	2,770	2	OECD, 2002; ECHA
Ceriodaphnia dubia	48-hour EC_{50}	1,830	2	OECD, 2002; ECHA
Daphnia magna	48-hour EC_{50}	1,062	2	OECD, 2002; ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50}	2,900 (biomass)	1	OECD, 2002; ECHA

Chronic Studies

The 21-day EC_{50} and EC_{16} values for calcium chloride in a chronic *Daphnia* reproduction study were 610 and 320 mg/L, respectively (OECD, 2002).

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for calcium chloride follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (4,630 mg/L), invertebrates (1,062 mg/L) and algae (2,900 mg/L). Although a chronic *Daphnia* study is available, an NOEC or EC_{10} was not determined. On the basis that the data consist of short-term and long-term results from three trophic levels, an assessment factor of 100 has been applied to the lowest reported acute EC_{50} value of 1,062 mg/L from invertebrates. The $PNEC_{water}$ is 11 mg/L.

PNEC sediment

No experimental toxicity data on sediment organisms are available. Calcium chloride is highly soluble and dissociates completely in water. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as calcium chloride. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. Based on its properties, no adsorption of calcium chloride to sediment is to be expected, and the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No experimental toxicity data on soil organisms are available. Calcium chloride dissociates completely in water with its environmental distribution is dominated by its high water solubility. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as calcium chloride. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, no adsorption of calcium chloride to the soil is to be expected, and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Calcium chloride is an inorganic salt that dissociates completely to calcium and chloride ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both calcium and chloride ions are also ubiquitous and are present in most water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Calcium and chloride ions are essential to all living organisms, and their intracellular, and extracellular concentrations are actively regulated. Thus, calcium chloride is not expected to bioaccumulate.

A chronic toxicity has been conducted on calcium chloride, but an NOEC or EC_{10} was not determined. The acute E(L)C_{50} values for calcium chloride are > 1 mg/L in fish, invertebrates and algae. Thus, calcium chloride does not meet the screening criteria for toxicity.

The overall conclusion is that calcium chloride is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Eye Irritant Category 2

[Note: anhydrous calcium chloride requires the GHS classification Eye Irritant Category 1]

B. Labelling

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In the case of contact, immediately flush eyes with plenty of water for at least 15 minutes. If symptoms persist, seek medical advice.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on the conditions, decomposition products may include the following: hydrogen chloride gas, calcium oxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessarily provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for calcium chloride.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Calcium chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Ganong, W.F. (1995). Review of Medical Physiology, 17th Edition, Appleton & Lange, Norwalk, Connecticut, USA.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

OECD (2002). OECD-SIDS: Calcium chloride (CAS No. [redacted] UNEP Publications. Available at: https://hpvchemicals.oecd.org/UI/handler.axd?id=cb4247c6-7f28-4ca5-bf69-1f526956b6f9

CHOLINE CHLORIDE

This dossier on choline chloride (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the OECD-SIDS documents on choline chloride (OECD, 2004), and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-hydroxy-N,N,N-trimethylethanaminium chloride

CAS RN: [redacted]

Molecular formula: $C_5H_{14}NO.Cl$

Molecular weight: 139.6 g/mol

Synonyms: Choline chloride; 2-hydroxy-N,N,N-trimethylethanaminium chloride; trimethyl(2-hydroxyethyl)ammonium chloride; cholinium chloride; 2-hydroxyethyl(trimethyl)azanium chloride

SMILES: C[N+](C)(C)CCO.[Cl-]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Choline Chloride

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa*	White crystalline solid*	2	OECD (2004)
Melting Point	~ 200°C @ 101.3 kPa	1	ECHA
Boiling Point	Decomposition at 305°C @ 101.3 kPa prior to boiling	2	ECHA
Density	70% aq. solution: 1110 kg/m³@ 20°C	4	OECD (2004)
Partition Coefficient (log K_{ow})	75% aq. solution: -3.77 @ 25°C	1	ECHA
Vapour Pressure	2287.2 Pa @ 25°C (QSAR)	2	ECHA
Water Solubility	Powder containing 50% choline chloride: 650 g/L (temperature unknown	4	OECD (2004)
Auto flammability	330°C	2	ECHA

Property	Value	Klimisch score	Reference
Viscosity	75% aq. solution: 26.2 mPa.s @ 20°C; 14.1 mPa.s @ 40°C	1	ECHA
Henry's Law Constant	2.06 x 10-11 Pa.m^3/mol @ 25 °C (estimated using HENRYWIN v3.10)	-	OECD (2004)

*Choline chloride is a white crystalline solid; it is marketed as an aqueous solution (70-75% w/w in water), which is colourless with an amine-like odour.

Choline chloride is a quaternary amine salt that will dissociate in water into choline ($C_5H_{14}NO^+$) ions and chloride (Cl^-) ions.

III. ENVIRONMENTAL FATE PROPERTIES

A. Partitioning

Choline chloride is highly water soluble and non-volatile. When released to water under typical environmental conditions, the quaternary ammonium salt dissociates to release a positively charged choline ion and a negatively charged chloride ion (OECD, 2004). It is unlikely to partition to the atmosphere based on its low volatility (OECD, 2004).

B. Biodegradation

Choline chloride is readily biodegradable (93% within 14 days) in a MITI-I test (MITI, 1992; OECD, 2004). In another MITI-I test, biodegradation was $\geq$60%, indicating ready biodegradation (Tunkel *et al.*, 2000; OECD, 2004). A $BOD_5/ThOD_5$ ratio of 75% was obtained in a BOD_5 test performed according to DIN 38409 part 43 (BASF AG, 1984; OECD, 2004).

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

No experimental data are available for choline. Choline is a quaternary ammonium compound (QAC); these compounds are not included in the training set for the K_{oc} estimation of the QSAR model KOCWIN v. 2.00 in EPISuite™ (USEPA, 2016), and therefore outside the program's prediction domain. A K_{oc} value of 2.3 had been estimated using the older QSAR model PCKOCWIN v. 1.66 (OECD, 2004), indicating a low potential for soil adsorption.

Results from Mackay Level I modelling indicate that choline chloride will be distributed completely into water (OECD, 2004).

D. Bioaccumulation

No measured data on bioaccumulation of choline chloride is available. An experimental log K_{ow} is -3.77, which indicates a low potential to accumulate in organisms (OECD, 2004). Bioaccumulation is not expected in aquatic organisms.

E. Summary

Choline chloride is readily biodegradable. Distribution modelling using Mackay Level 1 shows choline to be distributed completely into water. Choline chloride will not adsorb on soil and sediments. It is not expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Choline is a vitamin-like essential nutrient. It has low acute toxicity by the oral route and is slightly irritating to the skin and eyes. Repeated high intake of choline in humans has been reported to cause a slight hypotensive effect. No adverse effects (including tumours) were seen in rats given choline in the diet for 72 weeks. Choline is not genotoxic. High dietary doses of choline to pregnant mice resulted in developmental toxicity (but no teratogenic effects) at levels that were maternally toxic.

NICNAS has assessed fumaric acid in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to human health[1]

B. Metabolism

Choline is a vitamin-like essential nutrient. Although the body can synthesise choline in small amounts, it is insufficient to maintain health and must be consumed in the diet. Choline is required for the synthesis of phospholipids in cell membranes, methyl group metabolism and acetylcholine synthesis (neurotransmitter) (Zeisel and Blusztajn, 1994).

Dietary choline is taken up into the body by transporter proteins present in the cells lining the small intestine (IOM, 2000). In the small intestine, prior to uptake into the small intestinal cells, some choline is metabolised by bacteria to betaine and methylamines (Zeisel et al., 1980). Dietary choline can be present as free choline or in esterified forms (i.e., phosphocholine, glycerophosphocholine, sphingomyelin, and phosphatidylcholine) (Zeisel and Blusztain, 1994). Free choline is formed from these esterified choline compounds by pancreatic enzymes.

Choline is involved in a number of biochemical pathways in eukaryotic and prokaryotic cells. It is a precursor for acetylcholine (a neurotransmitter); phospholipids (structural integrity and signaling roles for cell membranes); and a major source for methyl groups (IOM, 2000).

C. Acute Toxicity

<u>Oral</u>

The oral LD_{50} values of choline in rats are approximately 3,500 and 5,500 mg/kg (ECHA) [Kl. scores = 2].

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber= [redacted] 2C+

Inhalation

No acute inhalation or dermal toxicity studies are available.

D. Irritation

Skin

Application of a 70% aqueous solution to the skin of rabbits for 20 hours under occlusive conditions resulted in ambiguous skin irritation (BASF AG, 1963a; OECD, 2004) [Kl. score = 2].

Eye

Slight eye irritation was seen in the eyes of rabbits after instillation of a 70% aqueous solution of choline chloride; no effects were seen 24 hours after exposure (BASF AG, 1963b; OECD, 2004) [Kl. score = 2].

E. Sensitisation

No data are available in animals. In a Human Repeated Insult Patch Test (HRIPT), there was no evidence of dermal sensitisation in 200 subjects given 0.5% (w/v) aqueous solution of choline chloride during the induction phase and 0.2% (w/v) aqueous solution during the challenge phase (Colgate-Palmolive, 2003; OECD, 2004).

F. Repeated Dose Toxicity

Oral

A 72-week feeding study was conducted to investigate the impact of choline chloride on the liver tumour promoting activity of phenobarbital and DDT in diethylnitroamine-initiated Fischer 344 rats. Animals received approximately 500 mg/kg/day choline chloride. Following the end of the exposure period, the animals were kept on the same untreated diet as the control group until study termination at week 103. Histopathology was limited to the liver and organs that developed gross abnormalities. There were no significant differences between treated and control animals on survival rates, body weights, and relative liver weights. There were no increased number of neoplastic liver nodules, hepatocellular carcinomas, lung tumours, leukemia or other tumours between treated and control animals. The NOAEL for choline chloride in this study is 500 mg/kg-day (Shivapurkar *et al.*, 1986) [Kl. score = 3].

In humans, oral administration of 10,000 mg/day choline chloride in a pilot study treating a small number of patients with Alzheimer's disease resulted in a slight hypotensive effect (Boyd *et al.*, 1977). This dose was regarded as a LOAEL by the U.S. Institute of Medicine (IOM) Standing Committee on the Scientific Evaluation of Dietary Reference Intake (2000).

Inhalation

No adequate or reliable studies are available.

Dermal

No adequate or reliable studies are available.

G. Genotoxicity

In Vitro Studies

Choline chloride was not mutagenic to bacteria in reverse mutation assays (Haworth *et al.*, 1983, Litton Bionetics, 1977).

A small, but statistically significant, and dose-related increase in chromosomal aberrations was reported in Chinese Hamster Ovary (CHO) cells at doses of 50 and 500 µg/mL choline chloride in the absence of S9 only (Bloom *et al.*, 1982). No higher concentrations were examined. These results could not be confirmed in two studies using CHO cells at concentrations of choline chloride up to 5,000 µg/mL (Galloway *et al.*,1985).

In sister chromatid exchange (SCE) assays, ambiguous results were obtained in two parallel studies (at two different laboratories) in CHO cells at concentrations up to 50 and 5,000 µg/mL choline chloride, respectively. Cytotoxicity was observed at 5,000 µg/mL. In laboratory 2, the increase in SCEs, which was sporadic and not dose-related, that was observed with metabolic activation was not reproduced in laboratory 1. Laboratory 1 showed a weak positive at the top dose without metabolic activation, but a comparison with laboratory 2 was not possible due to the insufficient number of cells analysed (Bloom *et al.*, 1982; Galloway *et al.*, 1985).

Choline chloride was negative in a gene conversion assay with *Saccharomyces cerevisiae* strain D4 in the presence or absence of metabolic activation (Litton Bionetics, 1977; OECD, 2004).

In Vivo Studies

No studies are available.

H. Carcinogenicity

Oral

No studies are available.

Inhalation

No studies are available.

I. Reproductive Toxicity

No reliable studies have been conducted that address female fertility or reproductive toxicity by a relevant route of exposure.

J. Developmental Toxicity

Oral

Pregnant female mice were given in their feed 0, 1, 2.5, 5, or 10% choline chloride (0 or approximately 1,250, 4,160, 10,800, or 20,000 mg/kg choline chloride) on gestational days 1 to 18. Maternal body weight gain was reduced in all treated groups except for the 1,250

mg/kg group. Maternal weight gain of dams with embryonic/foetal absorptions showed no net weight gain at >4,160 mg/kg, but there was net weight loss in the 20,000 mg/kg group. All foetuses were resorbed in the 20,000 mg/kg group. Embryonic/foetal lethality of 35% and 69% were seen in the 4,160 and 10,800 mg/kg groups, respectively. No resorptions occurred in the 1,250 mg/kg group. Developmental toxicity was seen at >4,160 mg/kg group. There were no statistically significant increases in malformations in any dose group. The NOAEL for maternal and developmental toxicity is 1,250 mg/kg/day (BASF AG, 1966; OECD, 2004) [Kl. score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for choline chloride follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes selected hypotension as the critical effect from the study by Boyd *et al.* (1977) when deriving a Tolerable Upper Intake Level. Boyd *et al.* (1977) reported a LOAEL of 10,000 mg/day choline chloride (7,500 mg/day choline). An uncertainty factor of 2 was chosen because of the limited data regarding hypotension and the inter-individual variation in response to cholinergic effects. Thus, the value for the Tolerable Upper Intake Level or repeated exposure of adults to choline is 3,500 mg/day choline.

Note that the Australian National Health and Medical Research Council (2014) concluded that there are no data to suggest that there is increased susceptibility to choline during pregnancy or lactation; thus, the upper level of intake choline is the same for women during pregnancy or lactation as it is for adults (3,500 mg/day choline).

Oral Reference Dose (oral RfD)

An oral RfD for choline is derived as follows: the LOAEL of 7,500 mg/day from the Boyd *et al.* (1977) study is divided by an uncertainty factor of 2 to obtain a value of 3,500 mg choline/day or 50 mg choline/kg/day for a 70 kg person.

Oral RfD = 50 mg/kg/day [choline]

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (50 x 70 x 0.1)/2 = 175 mg/L [choline]

The Australian drinking water guideline value for chloride ions is 250 mg/L based on aesthetics (ADWG, 2021).

B. Cancer

There are no carcinogenicity studies on choline chloride. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Choline chloride does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL EFFECTS SUMMARY

A. Summary

Choline chloride is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies conducted on choline chloride.

Table 2: Acute Aquatic Toxicity Studies on Choline Chloride

Test Species	Endpoint	Results (mg/L)[1]	Klimisch score	Reference
Oryzias latipes	96-hour LC_{50}	>100 (nominal and measured)	1	MOE Japan (1999a); OECD (2004)
Leuciscus idus	96-hour LC_{50}	>10,000*	2	OECD (2004); ECHA
Daphnia magna	48-hour EC_{50}	349 (nominal and measured)	2	MOE Japan (1999b); OECD (2004)
Daphnia magna	48-hour EC_{50}	>500*	2	OECD (2004)
Pseudokirchneriella subcapitata	72-hour EC_{50}	>1,000 (nominal and measured)	1	MOE Japan (1999a); OECD (2004)

*78% aqueous solution of choline chloride

Chronic Studies

In a 21-day *Daphnia magna* reproduction test, the nominal and measured NOEC was reported to be 30.2 mg/L (MOE Japan, 1999d) [Kl. score = 1].

The NOEC from a 72-hr algae *Pseudokirchneriella subcapitata* study is 30.2 mg/L (MOE Japan, 1999c; OECD, 2004) [Kl. score = 1].

C. Terrestrial Toxicity

No data is available.

Choline is present in all plant and animal cells, mostly in the form of phospholipids (phosphotidylcholine or lecithin, lysophosphatidylcholine, choline plasmalogens and sphingomyelin), which are essential components of membranes (IOM, 2000).

D. Calculation of PNEC

The PNEC calculations for choline chloride follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (>100 mg/L), invertebrates (349 mg/L) and algae (>1,000 mg/L). Results from chronic studies are available for invertebrates (21-day NOEC = 30.2 mg/L) and algae (72-hour NOEC = 32 mg/L). On the basis that the data consists of chronic studies on two trophic level (albeit not on the species with the lowest $E(L)C_{50}$), an assessment factor of 100 has been applied to the lowest reported NOEC of 30 mg/L for *Daphnia*. The $PNEC_{aquatic}$ is 0.3 mg/L (0.22 mg/L for choline).

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.15 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1{,}000 \times PNEC_{water}$
$= (0.844/1280) \times 1{,}000 \times 0.22$
$= 0.15$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1{,}000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 0.092/1{,}000 \times 2400]$
$= 0.844\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg).

BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$

= 2.3 x 0.04

= 0.092 L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for choline is estimated to be 2.3 L/kg (OECD, 2004).

F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ for choline is 0.007 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1{,}000 \times PNEC_{water}$

= (0.05/1500) x 1,000 x 0.22

= 0.007 mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)

BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$

= 2.3 x 0.02

= 0.05 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for choline is estimated to be 2.3 L/kg (OECD, 2004).

F_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Choline chloride is readily biodegradable and thus it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of -3.77, choline chloride does not meet the criteria for bioaccumulation.

The NOEC values from chronic toxicity studies on choline chloride are >0.1 mg/L. Thus, choline chloride does not meet the criteria for toxicity.

The overall conclusion is that choline chloride is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not Classified

B. Labelling

No signal word.

C. Pictogram

None

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Keep product and empty container away from heat and sources of ignition. May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide, nitrogen oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Prevent from entering sewers, waterways, or low areas.

Steps to be Taken if Material is Released or Spilled

Soak up with inert absorbent material.

D. Storage And Handling

General Handling

Keep product and empty container away from heat and sources of ignition. Ensure adequate ventilation, especially in confined areas.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for choline chloride.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Choline chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Australian National Health and Medical Research Council (2014). Nutrient Reference Values for Australia and New Zealand: Choline. Accessed at: https://www.nrv.gov.au/nutrients/choline

BASF AG (1963a). Toxicity of choline chloride 70 % in water; skin irritation after exposure to choline chloride. Department of Toxicology. Unpublished results. Study No. XIII 9. 01 Mar. 1963.

BASF AG (1963b). Toxicity of choline chloride 70% in water; eye irritation. Department of Toxicology. Unpublished results. Study No. XIII 9. 01 Mar. 1963.

BASF AG (1966). Study on teratogenic effects of choline chloride in the mouse after oral application. Department of Toxicology. Unpublished results. Study No. XIV/156. 14 Oct. 1966.

BASF AG (1984). Department of Product Safety. Laboratory of Ecology. Pruefbericht ueber eine Untersuchung auf biologische Abbaubarkeit im BSB5-Test - Cholinchlorid (German). Test No. 01606. 16 Feb. 1984.BASF AG (2004b). Department of Product Safety. Unpublished calculation. Mackay Level I V2.11. 29 Jun. 2004.

Bloom A., Galloway, S., Nakamura, F.T., Teteviri, A., Armstrong, M., Lavappa, K.L., Duk, S., and Ahmed, M.A. (1982). Comparison of results for SCE and chromosome aberrations for eleven compounds tested in two laboratories by standardized methods. Environ. Mutagen. 4: 397.

Boyd, W.D., Graham-White, J., Blackwood, G., Glen, I., and McQueen, J. (1977). Clinical effects of choline in Alzheimer senile dementia. Lancet 2: 711.

Colgate-Palmolive (2003). Study No. DCR-200-137-TKL. TKL Research Inc. Paramus, NJ, USA. In: SCCNFP. Scientific Committee on Cosmetic Products and Non-Food Products. Choline Chloride. SCCNFP/0672/03. 9 Dec. 2003.

Department of the Environment, Water, Heritage and the Arts [DEWHA] (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA] (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Galloway, S.M., Bloom, A..D, Resnick, M., Margolin, B.H., Nakamura, F., Archer, P., and Zeiger, E, (1985). Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7: 1-51.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagenesis Suppl. 1: 3-142.

Institute of Medicine [IOM] (2000). Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. . Standing Committee on the Scientific Evaluation of Dietary Reference Intake, Institute of Medicine, National Academy Press, Washington D.C.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Litton Bionetics (1977). Mutagenic evaluation of compound FDA75-[redacted] choline chloride. FCC. Report No. PB-266 891. Mar. 1977.

MITI (1992). Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan. Edited by Chemicals Inspection & Testing Institute Japan, published by Japan Chemical Industry Ecology-Toxicology & Information Center. October 1992.

MOE Japan (1999a). Ministry of Environment. Acute toxicity study of choline chloride on the Orange killifish *Oryzias latipes*. Unpublished study. No. 1998-16.

MOE Japan (1999b). Ministry of Environment. Acute toxicity study of choline chloride on *Daphnia magna*. Unpublished study. No. 1998-14.

MOE Japan (1999c). Ministry of Environment. Acute toxicity study of choline chloride on the freshwater alga *Pseudokirchnerialla subcapitata*. Unpublished study. No. 1998-13.

MOE Japan (1999d). Ministry of Environment. Chronic toxicity study of choline chloride on the freshwater invertebrate *Daphnia magna*. Unpublished study. No. 1998-15.

OECD (2004). SIDS Initial Assessment Report for Choline chloride (CAS No. [redacted] UNEP Publications. Available at: http://www.inchem.org/documents/sids/sids/67481.pdf

Shivapurkar, N., Hoover, K.L., and Poirier, L.A. (1986). Effect of methionine and choline on liver tumor promotion by phenobarbital and DDT in diethylnitrosamine-initiated rats. Carcinogenesis 7: 547- 550.

Tunkel J., Howard, P.H., Boethling, R.S., Sitteler, W., and Loonen, H. (2000). Predicting ready biodegradability in the Japanese Ministry of international trade and industry test. Environ. Toxicol. Chem. 19: 2478-2485.

U.S. Environmental Protection Agency [EPA] (2016). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Zeisel, S.H., Story, D.C., Wurtman, R.J., and Brunengraber, H. (1980). Uptake of free choline by isolated perfused rat liver. Proc. Natl. Acad. Sci. USA 77(8): 4417-4419.

Zeisel, S.H., and Blusztajn, J.K. (1994). Choline and human nutrition. Ann. Rev. Nutr. 14: 269-296.

ACRYLAMIDE/SODIUM ACRYLATE COPOLYMER (CAS NO. [redacted]
ACRYLAMIDE/AMMONIUM ACRYLATE COPOLYMER (CAS NO. [redacted]
ACRYLAMIDE, SODIUM ACRYLATE POLYMER (CAS NO. [redacted]
2-PROPENOIC ACID, POTASSIUM SALT, POLYMER WITH 2-PROPENAMIDE (CAS NO. [redacted]
ACRYLATE TERPOLYMER (CAS NO. [redacted] [1]
SILICONE BASED EMULSION NEUTRALISED POLYACRYLIC BASED STABILISER (NO CAS NO.)

This group contains a sodium salt of a polymer consisting of acrylic acid, methacrylic acid or one of their simple esters and three similar polymers. They are expected to have similar environmental concerns and have consequently been assessed as a group. Information provided in this dossier is based on acrylamide/sodium acrylate copolymer (CAS No. [redacted]

This dossier on acrylamide/sodium acrylate copolymer and similar polymers presents the most critical studies pertinent to the risk assessment of these polymers in their use in coal seam gas activities. This dossier does not represent an exhaustive or critical review of all available data. Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-Propenoic acid, sodium salt, polymer with 2-propenamide

CAS RN: [redacted]

Molecular formula: $(C_3H_5NO.C_3H_4O_2.NA)_x$-

Molecular weight: No information is available. Based on the type and intended use of the copolymer, the molecular weight would likely range from 100,000 to > 3,000,000 daltons (Hamilton et al., 1997).

Synonyms: Acrylamide/sodium acrylate copolymer; 2-propenamide, polymer with 2-propenoic acid, sodium salt; 2-propenoic acid, sodium salt, polymer with 2-propenamide; 2-Propenamide-sodium 2 propenoate copolymer; sodium acrylate acrylamide polymer; sodium acrylate-acrylamide copolymer

SMILES: Not applicable.

II. PHYSICAL AND CHEMICAL PROPERTIES

No information is available.

III. ENVIRONMENTAL FATE PROPERTIES

No studies are available. The acrylamide/sodium acrylate copolymer is not expected to be readily biodegradable. The physico-chemical properties of the copolymer would preclude it from undergoing significant biodegradation (Guiney et al., 1997). Biodegradation is limited due to the very high molecular weight and the low water solubility of the copolymer. The copolymer will likely bind tightly to organic matter found within soils and sediments (Guiney et al., 1997). The copolymer is not expected to bioaccumulate because of its poor water solubility and high molecular weight.

[1] CAS name: 2-Propenoic acid, polymer with sodium 2-hydroxy-3-(2-propen-1-yloxy)-1-propanesulfonate (1:1) and alpha-sulfo-omega-(2-propen-1-yloxy)poly(oxy-1,2-ethanediyl) ammonium salt (1:1), sodium salt

IV. HUMAN HEALTH HAZARD ASSESSMENT

No studies are available.

NICNAS has assessed acrylamide/sodium acrylate copolymer in an IMAP Tier 1 assessment and considers it a "polymer identified as a low concern to human health by application of expert validated rules[2]."

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

No toxicological reference values or drinking water guidance values were developed.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Acrylamide/sodium acrylate copolymer does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

No studies are available. Acrylamide/sodium acrylate copolymer is expected to be a low concern for toxicity to aquatic organisms (Guiney et al., 1997). Due to its poor solubility and high molecular weight, it is not expected to be bioavailable. It does not contain any reactive functional groups (i.e., cationic groups).

A. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Acrylamide/sodium acrylate copolymer is not readily biodegradable; thus, it meets the screening criteria for persistence.

Acrylamide/sodium acrylate copolymer is expected to have a very high molecular weight and poor water solubility. It is not expected to be bioavailable. Thus, this copolymer does not meet the criteria for bioaccumulation.

There are no aquatic toxicity studies on acrylamide/sodium acrylate copolymer. It is expected to have low concern for aquatic toxicity because of its very high molecular weight and poor water solubility. Thus, the copolymer does not meet the criteria for toxicity.

The overall conclusion is that acrylamide/sodium acrylate copolymer is not a PBT substance.

[2] https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-i-human-health-assessments#cas-A [redacted]

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictograms

None.

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 5 minutes. If symptoms persist, seek medical advice.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

B. Fire Fighting Information

Extinguishing Media

Water fog, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Burning produces harmful and toxic fumes. Heat from fire may melt, decompose polymer and generate flammable vapours. Combustion products may include: Nitrogen oxides, carbon monoxide, carbon dioxide and unburned hydrocarbons (smoke). Dust can accumulate static charges which can cause an incendiary electrical discharge. Fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source, is a potential dust explosion hazard.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Potential combustible dust hazard. Avoid generating dust. Creates dangerous slipping hazard on any hard smooth surface.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove.

D. Storage and Handling

General Handling

Avoid dust accumulation in enclosed space. Avoid generating dust; fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard. Electrostatic charge may build up during handling. Equipment, container and metal containers should be grounded and bonded.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place. Use adequate ventilation to avoid excessive dust accumulation. Store away from excessive heat and away from strong oxidising agents. Take measures to prevent the build-up of electrostatic charge.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure limit for acrylamide/sodium acrylate copolymer.

Engineering Controls

Use in a well-ventilated area. Avoid creating dust. Take precautionary measures against static charge.

Personal Protection Equipment

Respiratory Protection: Not normally needed; however, if significant exposures are possible, then the following respirator is recommended: Dust/mist respirator.

Hand Protection: Normal work gloves.

Skin Protection: Normal work coveralls.

Eye Protection: Wear safety glasses or goggles to protect against exposure.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Acrylamide/sodium acrylate copolymer is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII.REFERENCES

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Guiney, P. D., McLaughlin, J. E., Hamilton, J. D., and Reinert, K. H. (1997). Dispersion Polymers. In: Ecological Assessment of Polymers Strategies for Product Stewardship and Regulatory Programs (Hamilton, J.D. and Sutcliffe, R. eds.), pp. 147-165, Van Nostrand Reinhold.

Hamilton, J. D., Vasconcellos, S. R., and Keener, R. L. (1997). Introduction. In: Ecological Assessment of Polymers Strategies for Product Stewardship and Regulatory Programs (Hamilton, J.D. and Sutcliffe, R. eds.), pp. 3-15, Van Nostrand Reinhold.

Klimisch, H. J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol Pharmacol. 25:1-5.

COPPER (II) SULFATE

This dossier on copper (II) sulfate (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): copper (II) sulfate

CAS RN: [redacted]

Molecular formula: $CuSO_4$

Molecular weight: 159.61 g/mol

Synonyms: copper sulfate;cupric sulfate; copper sulphate

Smiles: [O-]S(=O)(=O)[O-].[Cu+2]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Copper (II) Sulfate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White-green, odourless, amorphous powder or crystalline solid	2	ECHA
Melting Point	110°C @ 101.3 kPa	2	ECHA
Boiling Point	560°C @ 101.3 kPa	2	ECHA
Density	3600 kg/m^3 (temperature not available)	2	ECHA
Vapour Pressure	Not applicable as substance is solid	-	ECHA
Partition Coefficient (log K_{ow})	Not applicable	-	ECHA
Water Solubility	22 g/L at 25°C	2	ECHA
Flash Point	Not applicable as substance is solid	-	ECHA
Auto flammability	Not applicable as substance is solid	-	ECHA
Viscosity	Not applicable as substance is solid	-	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Copper is a natural element and transition metal with more than one oxidation state. Copper in its metallic form (Cu°) is not available. Copper needs to be transformed to its ionic forms to become available for uptake by living organisms (ECHA).

B. Biodegradation

Biodegradation as used for organic substances does not apply to inorganic substances such as copper and its compounds..

C. Environmental Distribution

In soil, copper (II) sulfate has a reported soil partition coefficient (Kd) value of 2,120 L/kg (ECHA). Based on this value, if released to soil, the substance is expected to strongly adsorb. Soil pH is a key factor governing attenuation (ECHA).

If released to water, copper binds to the sediment organic carbon (particulate and dissolved) and to the anareobic sulphides, resulting in the formation of copper sulfide (CuS). CuS has a very low stability constants/solubility limit (LogK=-41, ECHA) and therefore the 'insoluble' CuS keeps copper in the anaerobic sediment layers, limiting the potential for remobilization of Cu-ions into the water column (ECHA).

D. Bioaccumulation

Because copper is an essential nutrient, all living organisms have well developed mechanisms for regulating copper intake, copper elimination and internal copper binding. There is a considerable amount of copper accumulation data available, that could potentially be used to calculate bioconcentration factors (BCF) and bioaccumulation factors (BAF) and assess the corresponding potential risks in aquatic food chains. The information in the accumulation section demonstrates that copper is well regulated in all living organisms and that highest BCF/BAF values are noted when copper concentrations in water, sediments and soils are low and for organisms/ life stages with high nutritional needs. The BCF/BAF values therefore have no ecotoxicological meaning. Importantly, the literature review demonstrates that copper is not biomagnified in aquatic or terrestrial ecosystems (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Copper is an essential metal present in human body tissues and fluids at concentrations of parts per million or parts per billion. It is also under tight homeostatic mechanisms that can control excess copper exposure by changing the rate of systemic uptake or excretion via the bile in humans. Therefore, in assessing the human health effects of copper the essentiality and homeostaic mechanisms have to be taken into account (ECHA).

Copper (II) sulfate has low acute toxicity by the oral and dermal routes. This substance was determined to be severely irritating to the eyes. It is not irritating to the skin and is not a skin sensitiser. No systemic effects were observed in sub-chronic oral or inhalation toxicity studies. It is not genotoxic, nor is it a reproductive or developmental toxicant.

B. Acute Toxicity

Oral

In an OECD 401 (Acute Oral Toxicity) study, an LD_{50} of 481-482 was established for copper (II) sulfate (ECHA). [KI score = 1].

Inhalation

No data available (ECHA).

Dermal

In an OECD Guideline 402 study a LD_{50} is >2000 was established for copper (II) sulfate (ECHA) [Kl Score = 1].

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was conducted to determine the skin irritation potential of copper (II) sulfate using New Zealand White rabbits. Copper (II) sulfate was found to be non-irritating to the skin of rabbits (ECHA) [KI score = 1].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) primary eye irritation study was performed using copper (II) sulfate. This substance is considered severely irritating to the eyes of rabbits (ECHA) [Kl score = 1].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) study (i.e., Buehler test) was performed on Pirbright-Hartley guinea pigs. Copper (II) sulfate did not induce skin sensitisation in this study (ECHA) [Kl score = 1].

E. Repeated Dose Toxicity

Oral

An EU Method B.26 (Sub-Chronic Oral Toxicity Test: Repeated Dose 90-Day Oral Toxicity Study in Rodents) was performed using male and female F344/N rats. Copper (II) sulfate was administered orally via feed for 92 days at a dose of 0, 500, 1000, 2000, 4000 or 8000 ppm (providing estimated intakes of 0, 8, 17, 34, 67 or 138 mg Cu/kg bw/day). A NOAEL of 1,000 ppm (equivalent to 16.7 mg Cu/kg bw/day was established based on the absence of hyperplasia and hyperkeratosis of the forestomach and absence of inflammation of the liver (ECHA) [KI score = 1].

Inhalation

An OECD Guideline 412 study (Subacute Inhalation Toxicity: 28-Day study) was performed using male and female Sprague-Dawley rats. Copper (II) sulfate was administered via whole

body inhalation for 28 days. Inhalation exposure with cuprous oxide markedly affected neutrophil numbers at all exposure levels in this study (0.2, 004, 0.8, and 2.0 mq/m^3). However, the effects were reversible and there were no observed test substance-related effects on hematology parameters, bronchoalveolar lavage fluid (BALF) parameters, or lung histopathology following the 13-week recovery period. The NOAEL for the neutrophil effects is therefore considered> 2.0 mg/m^3. (ECHA) [KI score = 1].

Dermal

No data were available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on copper (II) sulfate are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Copper (II) Sulfate

Test System[1]	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA102	-	-	1	ECHA

*+, positive; -, negative.

In Vivo Studies

An EU Method B. 12 (Mutagenicity-In Vivo Mammalian Erythrocyte Micronucleus Test) study was performed using CD-1 mice exposed to copper (II) sulfate via oral gavage. Copper (II) sulfate did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of CD-1 mice, which indicates that this substance is not genotoxic (ECHA) [KI score = 1].

An OECD Guideline 486 (Unscheduled DNA Synthesis [UDS] Test with Mammalian Liver Cells *in vivo*) was performed using Wister rats exposed to copper (II) sulfate via oral gavage. The results indicate that copper (II) sulfate is not genotoxic because it did not induce cell repair greater than 1.0% (ECHA) [KI score = 1].

G. Carcinogenicity

Available studies on the carcinogenicity of copper are of limited value to ascertain the carcinogenic potential copper compounds. This is due to the fact that these studies are limited due to shorter exposure periods (<2 years) small sample sizes and limited histopathologic examination. However, when the 3 available studies are assessed on an overall balanced approach, they give useful information as to the carcinogenic potential of copper compounds (ECHA).

These results indicate that copper sulphate and other copper salts do not appear to have carcinogenic potential even at very high dose levels of up to 120 mg Cu/kg/bw/day (ECHA) [Kl. Score =3]. In addition, one of the studies indicates that excess copper may have a

protective effect on known carcinogens. In summary, the findings of these studies do not raise concerns with respect to carcinogenic activity (ECHA).

H. Reproductive Toxicity

An OECD Guideline 416 study (Two-Generation Reproduction Toxicity Study) was performed on male and female Crl:CD rats. Copper (II) sulfate was administered orally at doses of 0, 100, 500, 1000 and 1500 ppm via their feed for 70 days. There were no effects up to 1,500 ppm so the NOAEL was determined to be 1,500 ppm or 23.6 mg/kg/bw/day for reproductive toxicity The NOAEL for P1 and F1 rats and F1 and F2 offspring during lactation was 1000 ppm, based on reduced spleen weight in P1 adult females, and F1 and F2 male and female weanlings at 1500 ppm however the transient reduced spleen weights are not considered a reproductive endpoint as it did not affect growth or fertility. (ECHA). [KI score = 1].

I. Developmental Toxicity

New Zealand White rabbits were exposed to copper (II) sulfate via oral gavage (0, 7.5, 15 or 30 mg Cu/kg bw/day as copper hydroxide) during Day 7 to Day 28 of gestation. Maternal toxic effects were observed at all dose levels, and they were considered treatment related. Therefore, the maternal NOAEL was determined to be 7.5 mg/kg/bw/day based on based on mortality, gastric ulcers, haemolytic anaemia, renal damage, increased malformation, reduced foetal weights and increased resorptions. There was evidence of compound-related developmental toxicity at 30 mg Cu/kg bw/day. Mean foetal weights were reduced by 12 % relative to the control group. Foetal resorptions appeared slightly increased at this level and 4 foetuses (2 each from 2 litters) were observed with omphalocele (protrusion of intestines at the umbilicus). No evidence of developmental toxicity was observed at the other dose levels. One foetus of the 7.5 mg Cu/kg bw/day group had anasarca, domed head and a short tail. This finding was considered to be incidental since only one foetus showed these changes and no dose-response was observed. Therefore, a NOAEL of 15 mg/kg/bw/day was established for developmental toxicity (ECHA). [Kl. Score = 2].

An OECD Guideline 414 study (Prenatal Developmental Toxicity Study) was performed on Crl:CD rats. These animals were exposed to copper (II) sulfate via their feed. There were no reproductive effects observed at any concentration, so the NOAEL was determined to be 1,000 ppm for developmental effects [KI score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for copper (II) sulfate follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

An oral toxicological reference value was not derived for copper (II) sulfate.

The Australian drinking water guideline values for copper is 2 mg/L (ADWG, 2021).

B. Cancer

Copper (II) sulfate is not considered a carcinogen. Thus, a cancer reference value will not be calculated for this substance.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Copper (II) sulfate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Copper is an essential micronutrient, needed for optimal growth and development of micro-organisms, plants and animals. Copper and copper compounds may present a hazard for the environment depending on the release/bioaccessibility of copper ions and on the conditions of the receiving environment (pH, hardness, presence and type of organic matter, anions and competing cations). Copper (II) sulfate in acute aquatic toxicity studies is very toxic and in chronic aquatic toxicity studies is very toxic with long lasting effects.

B. Aquatic Toxicity

Acute Studies

USEPA (1985) reported acute toxicity data for copper in freshwater species in 41 genera. At a hardness of 50 mg/L, the values ranged from 17 µg/L for *Ptychocheilus* to 10,000 µg/L for *Acroneuria*. Skidmore & Firth (1983) found the acute toxicity of copper for ten Australian species ranged from 200 µg/L to 7800 µg/L. Bacher & O'Brien (1990) reported a range for Australian species ranged from 40 µg/L to 21,000 µg/L (ANZG, 2021).

Chronic Studies

The ANZG water quality guideline (2021) derived a very high reliability default guideline value (DGVs) for copper in freshwater from 130 data points covering 4 taxonomic groups, and these were adjusted to a common hardness of 30 mg/L as $CaCO_3$, as follows (data are reported as geometric means of NOEC after adjustment from other chronic end-points (pH range was 6.96 to 8.61):

- Fish: 10 species, 2.6 µg/L (*Ptylocheilus oregonensis*, from 7-day LC_{50}) to 131 µg/L (*Pimephales promelas*, 7-day LC_{50}); seven species had geometric means <25 µg/L
- Crustaceans: five species, 1.7 µg/L (*D. pulex* and *G. pulex*, NOEC, reproduction & mortality) to 12.1 µg/L (*Hyalella azteca*, from 10 to 14-day LC_{50})
- Insects: three species, 2.2 µg/L (*Tanytarsus dissimilis*, from 10-day LC*50*) to 11 µg/L (*Chironomus tentans*, 10 to 20-day LC_{50})
- Molluscs: three species, 1.64 µg/L (*Flumicola virens*, from 14-day LC_{50}) to 56.2 µg/L (*Corbicula manilensis*, from 7 to 42-day LC_{50}). The latter figure was not included in calculations as it was outside the pH range.

Additional chronic aquatic toxicity data is found in the ANZG Technical Brief (ANZG, 2021).

C. Sediment Toxicity

The freshwater sediment effect records include 62 high quality single-species chronic NOEC/L(E)C_{10} values from 6 different sediment- dwelling species of relevance. The individual NOEC values range between 18.3 mg/kg dry weight and >3,158 mg/kg (min-max value). Large intra-species variability are observed due to variations in organic carbon (OC) content and acid volatile sulphide (AVS) content of the sediments. Normalization of the effects data for AVS was not possible and therefore only NOEC/(L(E)C_{10} values generated under conditions that represent "aerobic" conditions (Low AVS) were retained (ECHA).

D. Terrestrial Toxicity

The copper terrestrial effects database contains more than 250 high quality, chronic NOEC/EC_{10} values. The chronic NOECs/EC_{10}s vary between 8.4 mg/kg for *Eisenia andrei* (cocoon production) and 2,402 mg/kg (maize respiration). The lowest value is actually below the limit for essentiality for the species (OECD, 2018). As described in ECHA, considering the importance of bioavailabilty for reducing the intra-species variability, the database includes supportive information related to the development/validation of the terrestrial copper bioavailability regression models. The bioavailability regression models are used for normalizing the NOECS (ECHA).

E. Calculation of PNEC

The PNEC calculations for copper (II) sulfate follow the methodology discussed in DEWHA (2009).

PNEC water

The ANZG water quality guideline (2021) derived a very high reliability DGV for copper in freshwater. The DGVs for 99, 95, 90 and 80% species protection are 1 µg/L, 1.4 µg/L, 1.8 µg/L and 2.5 µg/L, respectively. The 95% species protection level for copper in freshwater (1.4 µg/L) is recommended for adoption in the assessment of slightly-to-moderately disturbed ecosystems. It applies to waters of hardness of 30 mg/L as $CaCO_3$ (ANZG, 2021).

PNEC sediment

In the ECHA REACH database (ECHA), a $PNEC_{sediment}$ was derived for copper (II) sulfate using a weight of evidence approach and an assessment factor of 1. The $PNEC_{sediment}$ was determined to be 87 mg/kg sediment dry weight.

PNEC soil

In the ECHA REACH database (ECHA), a $PNEC_{soil}$ was derived for copper (II) sulfate using a bioavailability regression model and an assessment factor of 1. The $PNEC_{soil}$ was determined to be 65 mg/kg soil dry weight.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008). Note that PBT assessments are not relevant for metals (ECHA). Despite this, efforts were made to consider PBT for copper sulfate.

Copper (II) sulfate is an inorganic substance. Biodegradation is not applicable. For the purposes of this PBT assessment, the persistent criteria are not considered applicable..

Because copper is an essential nutrient, all living organisms have well developed mechanisms for regulating copper intake, copper elimination and internal copper binding. Bioaccumulation is not relevant. Further, copper is not biomagnified in aquatic or terrestrial ecosystems. As a result, bioaccumulation criteria are not considered applicable.

The chronic toxicity data on copper has a NOEC < 0.1 mg/L. Acute E(L)C50 values are < 1 mg/L. Thus, copper (II) sulfate does meet the criteria for toxicity.

The overall conclusion is that copper (II) sulfate overall is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Oral-Acute Tox.: 4H302: Harmful if swallowed.

Irritation-Eye category 2:H319: Causes serious eye irritation.

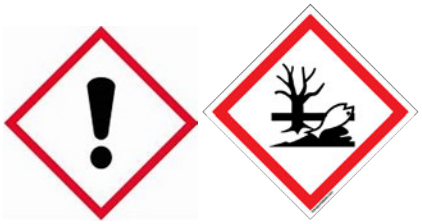
Irritation-Skin category 2: H315: Causes skin irritation.

Environmental: Aquatic: H410: Very toxic to aquatic life with long lasting effects.

B. Signal word

Warning

C. Pictogram



X. SAFETY AND HANDLING

A. First Aid

Please refer to the product SDS for additional information and confirmation of the information provided herein.

<u>Eye Contact</u>

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for copper (II) sulfate.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking, and using the lavatory; and at the end of the working

period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN number: 3288 (Solid)

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

ANZG (2021). Toxicant default guideline values for aquatic ecosystem protection: Boron in freshwater. Australian and New Zealand Guidelines for Fresh and Marine Water Quality. CC BY 4.0. Australian and New Zealand Governments and Australian state and territory governments, Canberra, ACT, Australia.

Bacher GJ & O'Brien TA. (1990). The sensitivity of Australian freshwater aquatic organisms to heavy metals. SRS 88/018. Victorian Environment Protection Authority, Melbourne.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

OECD. (2018). SIDS Initial Assessment Report: Copper and Copper Compounds. https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?id=e7b50eea-4f93-4918-9645-622c16b256ff

Skidmore JF & Firth IC. (1983). Acute sensitivity of selected Australian freshwater animals to copper and zinc. Australian Water Resources Council, technical paper 81, Australian Government Publishing Service, Canberra.

United States Environmental Protection Agency [USEPA]. (1985). Ambient water quality criteria for copper —1984. United States Environmental Protection Agency, Washington DC. EPA-440/5-84-031.

CRYSTALLINE SILICA, QUARTZ (CAS NO. [redacted]
CRYSTALLINE SILICA, CRISTOBALITE (CAS NO. [redacted]
CRYSTALLINE SILICA, TRIDYMITE (CAS NO. [redacted]
NON-CRYSTALLINE SILICA (IMPURITY) (CAS NO. [redacted]
DIATOMACEOUS EARTH (CAS NO. [redacted]
DIATOMACEOUS EARTH, CALCINED (CAS NO. [redacted]

This dossier on crystalline silica, quartz, cristobalite and tridymite; non-crystalline silica (impurity); diatomaceous earth; and diatomaceous earth, calcined presents the most critical studies pertinent to the risk assessment of these substances in their use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

For the purpose of this dossier, crystalline silica, quartz (CAS No. [redacted] has been reviewed as representative of crystalline silica cristobalite and tridymite, and non-crystalline silica (impurity). Crystalline silica, quartz is also considered representative of diatomaceous earth and diatomaceous earth, calcined, as they both consist mainly of silicon dioxide.

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): dioxosilane

CAS RN: [redacted]

Molecular formula: SiO_2

Molecular weight: 60.084 g/mol

Synonyms: Cristobalite, Dioxide, Silicon

SMILES: O=[Si]=O

II. PHYSICAL AND CHEMICAL PROPERTIES

Silica is an off-white granule that occurs naturally in various crystalline and amorphous or other non-crystalline forms. Crystalline silica is characterised by silicon dioxide (SiO_2) molecules oriented in fixed, periodic patterns to form stable crystals. The primary crystalline form of silica is quartz. Other crystalline forms of silica include cristobalite, tripoli and tridymite. Particle size is a key determinate of silica toxicity, since toxicity is restricted to particles that are small enough to be deposited into the target regions of the respiratory tract (OECD, 2011).

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Crystalline silica is characterised by silicon dioxide (SiO_2) molecules oriented in fixed, periodic patterns to form stable crystals. The primary crystalline form of silica is quartz. It is a stable solid under typical environmental conditions. It will not biodegrade, bioaccumulate, nor will it sorb to sediments or soils.

B. Biodegradation

No data are available. Based on the crystalline form of the substance, it is not expected to biodegrade.

C. Environmental Distribution

No experimental data are available for crystalline silica. As a stable inorganic solid, it is not soluble in water, and it will not sorb to soils or sediment.

D. Bioaccumulation

There are no bioaccumulation studies on crystalline silica.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Human exposure to crystalline silica via inhalation can lead to silicosis, lung cancer and pulmonary tuberculosis (WHO, 2000).

B. Acute Toxicity

No adequate acute oral, dermal or inhalation exposure studies are available for quartz, cristobalite or tridymite.

Most acute toxicity studies for quartz or cristobalite were conducted using intratracheal instillation. Intratracheal instillation is the introduction of the substance directly to the trachea and is used to test respiratory toxicity of a substance.

Single intratracheal instillation of quartz caused inflammatory effects and formation of discrete silicotic nodules in rats, mice and hamsters (IARC, 2012; WHO, 2000). Other effects like oxidative stress, cellular proliferation and increases in water, protein and phospholipid content of rat lungs, apoptosis (programmed cell death) and lung cancer were also noted.

In an acute dose study, rats were dosed once with 0, 0.75, 1.5, 3.0, 6.0 or 12 mg/kg bw/day quartz by intratracheal instillation (Seiler et al., 2001). The lowest observed adverse effect level (LOAEL) of 0.75 mg/kg bw/day was derived from these studies.

Two other similar studies of single intratracheal instillation of quartz reported higher LOAELs in rats (3 and 40 mg/kg bw/day) based on inflammation and fibrosis (Saffiotti et al., 1996).

C. Irritation

No data available.

D. Sensitisation

No data available.

E. Repeated Dose Toxicity

Oral

No data available.

Inhalation

Repeated inhalation exposure of crystalline is known to cause adverse effects (IARC, 2012). Silicosis has been identified as the main non-cancer effect of silica exposure, although available epidemiologic data as well as animal data provide evidence for several other effects associated with silica exposure, such as silicotuberculosis, enlargement of the heart (cor pulmonale), interference with the body's immune system and damage to the kidneys (Health Canada, 2013).

Dermal

No data available.

F. Genotoxicity

No data available.

G. Carcinogenicity

Oral

No data available.

Inhalation

The International Agency for Research on Cancer (IARC) has classified crystalline silica as a Group 1 carcinogen, as there was sufficient evidence for carcinogenicity in experimental animals and sufficient evidence for carcinogenicity of inhaled crystalline silica from occupational sources (IARC, 1997; IARC, 2012).

H. Reproductive Toxicity

No data available.

I. Developmental Toxicity

No data available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicity information on crystalline silica is inadequate and/or unreliable for deriving toxicological reference and drinking water guidance values for this substance.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Crystalline silica does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Although no data are available, crystalline silica is expected to exhibit low acute toxicity to aquatic organisms.

B. Aquatic Toxicity

No aquatic toxicity data were available.

C. Terrestrial Toxicity

No terrestrial toxicity data were available.

D. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Crystalline silica is an inorganic mineral. Thus, biodegradation is not applicable to this substance. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to crystalline silica.

As an inorganic complex it is not expected to bioaccumulate. Thus, crystalline silica does not meet the screening criteria for bioaccumulation.

Crystalline silica is not expected to cause adverse effects in environmental receptors. Thus, this substance does not meet the screening criteria for toxicity.

Therefore, crystalline silica is not a PBT substance.

IX. CLASSIFICATION AND LABELING

A. Classification

H373 – may cause damage to organs through prolonged or repeated exposure.

B. Labelling

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention if symptoms persist.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Get medical attention if respiratory irritation develops or breathing becomes difficult.

Ingestion

Rinse mouth. Do not induce vomiting. Get medical attention if symptoms occur.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use extinguishing media appropriate for surrounding material.

Specific Exposure Hazards

Reacts with hydrofluoric acid (HF) forming toxic gas (SiF_4).

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Pick up mechanically – vacuum up. Avoid generating dust. If formation of dust cannot be avoided, use respiratory filter device. Dispose of the material collected according to regulations.

D. Storage And Handling

General Handling

Handle in accordance with good industrial hygiene and safety practice. Avoid contact with eyes, skin and clothing. Avoid dust formation. Do not breathe dust. Wash thoroughly after handling. Use with adequate ventilation.

Storage

Provide adequate exhaust ventilation at places where dust is formed. Keep airborne concentrations below exposure limits. Keep containers tightly closed in a dry, cool, well-ventilated area.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has established an occupational exposure standard for exposure to crystalline silica of an 8-hour time weighed average (TWA) exposure limit of 0.05 mg/m^3.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls

to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; as well as before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Crystalline silica is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Health Canada. (2013). Environment Canada, Health Canada. Screening Assessment for the Challenge: Quartz (CAS [redacted] and Cristobalite (CAS [redacted] June 2013. https://www.ec.gc.ca/ese-ees/1EB4F4EF-88EE-4679-9A6C-008F0CBC191C/FSAR_B12%20-%[redacted]20%26%[redacted]20%28QC%29_EN.pdf

IARC. (1997). Silica, some silicates, coal dust and Para-aramid fibrils. International Agency for Research on Cancer (IARC) working group on the evaluation of carcinogenic risks to humans, Lyon, France, 15-22 October 1996. IARC Monogr Eval Carcinog Risks Hum. 1997;68:1–475.

IARC. (2012). Silica dust, crystalline, in the form of quartz or cristobalite. International Agency for Research on Cancer (IARC) working group on the evaluation of carcinogenic risks to humans, Lyon, France, 17-24 March, 2009. IARC Monogr Eval Carcinog Risks Hum. 2012;100C:355–405

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

OECD. (2011). OECD -SIDS Initial Targeted Assessment Profile on Quartz and Cristobalite, SIAM 32, 19-21 April 2011. https://hpvchemicals.oecd.org/ui/handler.axd?id=b68bb357-e6dd-4db9-b05c-8148223fc0ff.

Saffiotti, U., Williams, O., Lambert, N., Daniel, N., Kaighn, M.E., Mao, Y., Shi, X. (1996). Carcinogenesis by crystalline silica: animal, cellular, and molecular studies. In:Castranova V, Vallyathan V, Wallace WE, eds. Silica and silica-induced lung diseases. Boca Raton, FL, CRC Press, pp. 345–381.

Seiler, F., Rehn, B. and Bruch, J. (2001). Evidence of a no-effect level in silica–induced rat lung mutagenicity but not in fibrogenicity. Archives of Toxicology 74: 716-719.

WHO. (2000). Concise International Chemical Assessment Document 24 - Crystalline Silica, Quartz. Produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals. WHO Geneva.

OCTAMETHYLCYCLOTETRASILOXANE (CAS RN [redacted])
DECAMETHYLCYCLOPENTASILOXANE (CAS RN [redacted])
DODECAMETHYLCYCLOHEXASILOXANE (CAS RN [redacted])

This dossier on three cyclic polyorganosiloxanes (octamethylcyclotetrasiloxane, decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane) does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies pertinent to the risk assessment of these cyclic polyorganosiloxanes in their use in coal seam gas extraction activities. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2,2,4,4,6,6,8,8-octamethyl-1,3,5,7,2,4,6,8-tetroxatetrasilocane

CAS RN: [redacted]

Molecular formula: $C_8H_{24}O_4Si_4$

Molecular weight: 296.61 g/mol

Synonyms: Octamethylcyclotetrasiloxane; cyclic polyorganosiloxanes

SMILES: C[Si]1(O[Si](O[Si](O[Si](O1)(C)C)(C)C)(C)C)C

Chemical Name (IUPAC): 2,2,4,4,6,6,8,8,10,10-decamethyl-1,3,5,7,9,2,4,6,8,10-pentoxapentasilecane

CAS RN: [redacted]

Molecular formula: $C_{10}H_{30}O_5Si_5$

Molecular weight: 370.77 g/mol

Synonyms: Decamethylcyclopentasiloxane

SMILES: C[Si]1(O[Si](O[Si](O[Si](O[Si](O1)(C)C)(C)C)(C)C)(C)C)C

Chemical Name (IUPAC): Dodecamethylcyclohexasiloxane

CAS RN: [redacted]

Molecular formula: $C_{12}H_{36}O_6Si_6$

Synonyms: Cyclohexasiloxane, 2,2,4,4,6,6,8,8,10,10,12,12-dodecamethyl-; Cyclohexasiloxane, dodecamethyl-

Molecular weight: 444.92 g/mol

SMILES: C[Si]1(O[Si](O[Si](O[Si](O[Si](O[Si](O1)(C)C)(C)C)(C)C)(C)C)(C)C)C

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Cyclic Polyorganosiloxanes

Property	Octamethyl cyclotetrasiloxane CAS RN [redacted]	Decamethyl cyclopentasiloxane CAS RN [redacted]	Dodecamethyl cyclohexasiloxane CAS RN [redacted]	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colourless, volatile liquid	liquid	liquid	2	ECHA
Melting Point	17.7°C @ 101.3 kPa	-38°C @101.3 kPa	-3°C @101.3 kPa	2	ECHA
Boiling Point	175°C @ 101.3 kPa	210°C @101.3 kPa	245°C @101.3 kPa	2	ECHA
Density	950 kg/m^3 @ 20°C	960 kg/m^3 @ 20°C	980 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	132 Pa @ 25 °C	33.2 Pa @ 25 °C	4.7 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	6.98 @ 21.7 °C	8.07 @ 24.6 °C	8.87	2,1,2	ECHA
Water Solubility	0.000056 g/L @ 23°C	0.000017 g/L @ 23°C	0.0000051 g/L @ 23°C	2	ECHA
Viscosity	1.6 mm^2/s @ 20°C (kinematic)	3.7 mm^2/s @ 25°C (kinematic)	5.6 mm^2/s @ 20°C (kinematic)	2	ECHA
Dissociation Constant (pKa)	There are no ionizable groups	There are no ionizable groups	There are no ionizable groups	-	ECHA
Henry's Law Constant	1.2 x 10^6 Pa m^3/mol @ 21.7 °C	3.3 x 10^6 Pa m^3/mol @ 24.6 °C	2.5 x 10^6 Pa m^3/mol @ 23.6 °C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Cyclic polyorganosiloxanes are volatile and insoluble in water (hydrophobic). They are not readily biodegradable in water or sediment but are susceptible to biodegradation in soil. They have a moderate to high potential for bioaccumulation. However, they are not expected to biomagnify in the food chain.

B. Partitioning

All three cyclic polyorganosiloxanes are essentially insoluble in water. Volatilization from water surfaces is expected to be an important fate process based upon their Henry's Law constant. Estimated volatilization half-lives for a model river and model lake are 5 hours and 6.8 days, respectively (for octamethyltetrasiloxane). However, volatilization from water surfaces is expected to be attenuated by adsorption to suspended solids and sediment in the water column (Pubchem).

C. Biodegradation

Overall, none of the cyclic polyorganosiloxanes are readily biodegradable under test conditions.

In an OECD 310 (Ready Biodegradability test), octamethylcyclotetrasiloxane (CAS RN [redacted] degraded 3.7% in 29 days indicating that it is not readily biodegradable in water (ECHA). [KI Score =

1]. However, abiotic hydrolysis in the water compartment is a key degradation process in the environment. In the case of this substance, the longest observed half-life was for pH 7.0, with an average half-life of 3.9 days at 25°C. For 20°C, the lowest temperature allowed in a standard OECD 301 ready biodegradability study, the calculated hydrolysis half-life for D4 at pH 7.0 is 5.8 ± 1.7 days, which clearly meets the 16 day threshold criterion for rapid degradability (ECHA).

Decamethylcyclopentasiloxane (CAS RN [redacted] was evaluated in an OECD 310 Ready Biodegradability test. The results from the biodegradability test showed a rate of 0.14% in 28 days which indicates that this substance is not readily biodegradable in water (ECHA). [KI Score = 1].

In an OECD 310 Ready Biodegradability test, dodecamethylcyclohexasiloxane (CAS RN [redacted] degraded 4.47% after 28 days (ECHA). [KI Score = 1]. These results indicate that this substance is not readily biodegradable in water.

Degradation in sediment has been shown to be slow. An OECD 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems) was used to determine the half-life for octamethylcyclotetrasiloxane is 365 days at 24°C (ECHA). [KI Score = 1].

An OECD 308 (Aerobic and Anaerobic Transformation in Aquatic Sediment Systems) was used to determine that the half-life for decamethylcyclopentasiloxane is 1,200 days under aerobic conditions and 3,100 days under anaerobic conditions at 24°C (ECHA). [KI Score = 1].

There were no persistence studies conducted for dodecamethylcyclohexasiloxane. .

The fate of cyclic volatile methyl siloxanes in soil is strongly dependent both on the mineralogy of the soil and soil moisture levels. In a highly weathered soil with a high clay content, the degradation half-lives for these three substances were all less than 2 days at the same relative humidity (32%; in a closed system). The rate of degradation was slower in soils with a lower proportion of different clay minerals (NICNAS, 2020a).

D. Environmental Distribution

Based on an OECD 106 batch equilibrium method test, log K_{oc} values of 4.22 L/kg and 5.17 L/kg were derived for octamethylcyclotetrasiloxane (CAS RN [redacted] and decamethylcyclopentasiloxane (CAS RN [redacted] (ECHA). [Kl. Score = 1].

No experimental data are available for dodecamethylcyclohexasiloxane (CAS RN [redacted] A log K_{oc} value of 5.9 L/kg was experimentally derived (ECHA). [Kl. Score = 2].

Based upon these K_{oc} values, if released to soil, these cyclic polyorganosiloxanes have a high potential for adsorption and a low potential for mobility. If released to water, based on their K_{oc} and insolubility, these substances would also strongly adsorb to suspended solids and sediments.

E. Bioaccumulation

These three cyclic polyorganosiloxanes have moderate to high potential to bioaccumulate.

Octamethylcyclotetrasiloxane (CAS RN [redacted] has a very high potential to bioconcentrate in fish under optimised exposure conditions. The steady state BCF for the substance in fathead minnows (*Pimephales promelas*) was determined to be 12 400 L/kg after 28 days continuous exposure to radiolabelled test material in soft water at 21–22°C in an enclosed flow-through system. This study

did not identify any metabolites and the parent chemical was eliminated relatively slowly (NICNAS, 2020a).

A recent review of the available studies on the bioconcentration of decamethylcyclopentasiloxane (CAS RN [redacted] in fish recalculated BCF values for this chemical in the range 1040 to 4920 L/kg wet weight. The review of these studies highlighted the fact that depuration of the substance in fish is more rapid than would be expected for a very hydrophobic organic chemical. The faster than expected elimination of the substance in fish is attributed to biotransformation of the chemical into polar metabolites (NICNAS, 2020a).

The bioconcentration potential of dodecamethylcyclohexasiloxane (CAS RN [redacted] in aquatic life is moderate based on studies with fish and aquatic invertebrates. The steady state BCF for the chemical in the fathead minnow (*Pimephales promelas*) is in the range 240–1160 L/kg based on total radioactivity taken up during a 49 day exposure phase; depuration of the substance was reported to be slow. The majority of the tissue content (79%) was the parent chemical, although there was also an unidentified metabolite which accounted for 5% of the extracted radioactivity. The steady state BCF for the water flea, Daphnia magna, is approximately 2400 L/kg based solely on the uptake of the chemical (NICNAS, 2020a).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Cyclic polyorganosiloxanes exhibit low acute toxicity by the oral, dermal and inhalation routes. They are not a skin or eye irritant, nor are they considered to be skin sensitisers. Repeated oral, dermal or inhalation exposures did not identify significant or serious adverse health effects. The substances are not genotoxic, carcinogenic nor developmentally toxic. Octamethylcyclotetrasiloxane is considered to cause reproductive toxicity following inhalation exposure.

B. Acute Toxicity

Oral

In an OECD 401 (Acute Oral Toxicity) test for octamethylcyclotetrasiloxane (CAS RN [redacted] an oral LD_{50} of > 4,800 mg/kg bw was observed in male rats (ECHA). [KI Score = 2].

In an OECD 401 (Acute Oral Toxicity) test for decamethylcyclopentasiloxane (CAS RN [redacted] an oral LD_{50} of > 5,000 mg/kg bw was observed in male rats (ECHA). [KI Score = 1].

In an OECD 401 (Acute Oral Toxicity) test for dodecamethylcyclohexasiloxane (CAS RN [redacted] an oral LD_{50} of > 2,000 mg/kg bw was observed in male rats (ECHA) [KI Score = 1].

Inhalation

In an OECD 403 (Acute Inhalation Toxicity) test for octamethylcyclotetrasiloxane (CAS RN [redacted] the LC_{50} after 4 hours was determined to be 0.036 mg/m^3 (ECHA). [KI Score = 1].

In an OECD 403 (Acute Inhalation Toxicity) test and an EPA OTS 798.1150 (Acute Inhalation toxicity) test for decamethylcyclopentasiloxane (CAS RN [redacted] the LC_{50} after 4 hours was determined to be 0.00867 mg/m^3 (ECHA). [KI Score = 1].

There was no adequate data available for dodecamethylcyclohexasiloxane (CAS RN [redacted]

Dermal

An acute dermal LD_{50} value of > 2375 mg/kg bw was determined for octamethylcyclotetrasiloxane (CAS RN [redacted] using an OECD 402 (Acute Dermal Toxicity) test (ECHA) [KI Score = 2].

An acute dermal LD_{50} value of > 2,000 mg/kg bw was determined for decamethylcyclopentasiloxane (CAS RN [redacted] using an OECD 402 (Acute Dermal Toxicity) test (ECHA). [KI Score = 1].

An acute dermal LD_{50} value of > 2,000 mg/kg bw was determined for dodecamethylcyclohexasiloxane (CAS RN [redacted] using an OECD 402 (Acute Dermal Toxicity) test (ECHA). [KI Score = 1].

C. Irritation

Eye

In an OECD 405 (Acute Eye Irritation/Corrosion) test, octamethylcyclotetrasiloxane (CAS RN [redacted] did not induce eye irritation (ECHA). [KI Score = 1].

In an OECD 405 (Acute Eye Irritation/Corrosion) test, decamethylcyclopentasiloxane (CAS RN [redacted] did not induce eye irritation (ECHA). [KI Score = 1].

In an OECD 405 (Acute Eye Irritation/Corrosion) test, dodecamethylcyclohexasiloxane (CAS RN [redacted] did not induce eye irritation (ECHA) [KI Score = 1].

Skin

In an OECD 404 (Acute Dermal Irritation/Corrosion) test, octamethylcyclotetrasiloxane (CAS RN [redacted] did not induce skin irritation (ECHA) [KI Score = 2].

In an OECD 404 (Acute Dermal Irritation/Corrosion) test, decamethylcyclopentasiloxane (CAS RN [redacted] did not induce skin irritation (ECHA) [KI Score = 1].

In an OECD 404 (Acute Dermal Irritation/Corrosion) test, dodecamethylcyclohexasiloxane (CAS RN [redacted] did not induce skin irritation (ECHA) [KI Score = 1].

D. Sensitisation

Octamethylcyclotetrasiloxane (CAS RN [redacted] was not sensitising to the skin in an OECD 406 (Skin Sensitisation) test (ECHA) [KI Score = 1].

Decamethylcyclopentasiloxane (CAS RN [redacted] is not expected to be sensitising to the skin based on results from an OECD 429 (Skin Sensitisation Local Lymph Node Assay) study (ECHA) [KI Score = 1].

The OECD Test Guideline Study 406 found no indication of sensitisation potential for dodecamethylcyclohexasiloxane (CAS RN [redacted] (ECHA) [KI Score = 1].

E. Repeated Dose Toxicity

Oral

In two separate 14-day studies, octamethylcyclotetrasiloxane (CAS RN [redacted] (purity >98 %) in 0.5 % (w/v) methylcellulose vehicle was administered by gavage daily for two weeks to SD rats (8/sex/dose) at doses of 0, 25, 100, 400, or 1600 mg/kg bw/day or female NZW rabbits (n=6) at doses of 0, 500, or 1000 mg/kg bw/day. No overt signs of toxicity were observed in either species. Treatment-related effects in rats include decreased bodyweight at 1600 mg/kg bw/day (sex not specified) and increased liver weights in both sexes at 400 and 1600 mg/kg bw/day (SCCP, 2005; SCCS, 2010). Morphometric and electron microscopic examination of the liver showed that the increased liver weights were due to hepatocellular hyperplasia. All treated rabbits exhibited significant decreases in food consumption and bodyweight. Changes in the spleen and thymus were also observed in the rabbits but were reportedly not dose-dependent. A NOAEL was not established (NICNAS, 2020b). [Kl. Score = 4].

In a 28-day feeding study, octamethylcyclotetrasiloxane (as liquid drops encapsulated in a capsule composed of 80-90 % gelatine, 5 % modified cornstarch, and 15 % sucrose) was administered to SD rats (5/sex) in the diet. The dose level of the chemical was 2.1 % of the diet with an approximate daily intake estimated from 200 to 300 mg/kg bw/day. The chemical was fed to two groups, young and adult rats, with corresponding controls for each of the treatment groups. Reported clinical signs of toxicity include stress, rough fur and emaciation. Decreased food consumption and reduced bodyweight gain were observed. At necropsy, depleted body fat reserves and watery caecal contents were seen in the treated animals A NOAEL was not established (NICNAS, 2020b). [Kl. Score = 4].

Rats (unspecified strain) and rabbits (unspecified strain) administered the chemical at 500 mg/kg bw/day in the diet for 8 months (rats) and 12 months (rabbits) showed no effects of treatment. No other details were provided (NICNAS, 2020b).

In an OECD 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) study, Wistar rats were given decamethylcyclopentasiloxane (CAS RN [redacted] via oral gavage. The rats were treated for 13 weeks and observed for overt signs of toxicity. A NOAEL of 1,000 mg/kg bw/day was established due to histopathological changes (ECHA) [KI Score = 1].

In an OECD 422 (Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test) study, rats were administered dodecamethylcyclohexasiloxane CAS RN [redacted] via oral gavage for 28 days. A NOAEL of 1,000 mg/kg bw/day, the highest dose tested, was established due to systemic toxicity (ECHA) [KI Score = 1].

Inhalation

In a OCED Guideline 453 (Combined Chronic Toxicity/Carcinogenicity Studies) study, octamethylcyclotetrasiloxane (CAS RN [redacted] was administered to Fischer rats via whole body inhalation vapour for 24 months. A NOAEC of 150 ppm (1,820 mg/m^3) was established for general toxicity and local respiratory effects in the nasal cavity (ECHA). [KI Score = 1]

In an OECD 453 (Combined Chronic Toxicity/Carcinogenicity Studies) study, Fischer 344 rats were administered decamethylcyclopentasiloxane (CAS RN [redacted] via whole body inhalation vapour for up to 106 weeks. A NOEC for general toxicity was determined to be ≥160 ppm (2420 mg/m^3) based on local effects on the nasal cavity and adaptive increases in liver weights (ECHA) [KI Score = 1].

In an OECD Guideline 413 (Subchronic Inhalation Toxicity) study, Sprague Dawley rats were given dodecamethylcyclohexasiloxane (CAS RN [redacted] via whole body inhalation vapours for 90 days. Dodecamethylcyclohexasiloxane was found in the nasal tissues and in the livers and lungs of female rats. A NOAEL of 1 ppm (18.2 mg/m^3) was established based on permanent hyperplasia and inflammation of nasal tissues (ECHA). [KI Score = 1]

Dermal

In a three-week OECD 410 (Repeated Dermal Toxicity 21/28 Day) study, New Zealand White rabbits were exposed to octamethylcyclotetrasiloxane (CAS RN [redacted] and no adverse effects were observed. Therefore, the dermal NOAEL was determined to be ≥ 1 mL/kg-bw/day or 960 mg/kg bw/day (ECHA). [KI Score = 2]

In an OECD 410 (Repeated Dermal Toxicity 21/28 Day) study, Sprague Dawley rats were administered decamethylcyclopentasiloxane (CAS RN [redacted] for 28 days. No adverse effects were observed, a NOAEL of 1600 mg/kg bw/day was established (ECHA). [KI Score = 1]

There were no adequate Repeated Dermal Toxicity Studies available for dodecamethylcyclohexasiloxane (CAS RN [redacted] However, given the low dermal absorption of the chemical and the absence of serious systemic effects, repeated dermal exposure to the chemical is not expected to cause serious damage to health (NICNAS, 2020c).

F. Genotoxicity

The cyclic polyorganosiloxanes are not expected to be genotoxic.

In Vitro Studies

The majority of *in vitro* genotoxicity studies on cyclic polyorganosiloxanes indicated negative results including:

- bacterial reverse mutation assays (similar to OECD TG 471) in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, and *Escherichia coli* WP2 uvrA strain with and without metabolic activation;
- bacterial DNA repair assay (similar to EPA OPPTS 870.5500) in E. coli polA+ strain with and without metabolic activation;
- DNA damage and mitotic recombination assay in *Saccharomyces cerevisiae* with and without metabolic activation;
- mammalian cell gene mutation test (similar to OECD TG 476) in mouse lymphoma cells, with and without metabolic activation;
- mammalian chromosome aberration test (similar to OECD TG 473) in Chinese hamster ovary (CHO) cells with and without metabolic activation;
- mammalian chromosome aberration test (similar to OECD TG 473) in mouse lymphoma cells) with and without metabolic activation;
- DNA damage and/or repair assays (sister chromatid exchange [SCE], unscheduled DNA synthesis (UDS) and alkaline elution) in L5178Y cells with and without metabolic activation;
- SCE assay in CHO cells, with and without metabolic activation; and
- DNA repair assay in Escherichia coli strain W3110, with and without metabolic activation (NICNAS, 2020b, 2020c and 2020d).

Octamethylcyclotetrasiloxane (CAS RN [redacted] was positive in a chromosomal aberration test in mouse lymphoma cells. Chromosomal aberrations were induced following metabolic activation and at the high dose only. No dose-response relationship was reported in this test (NICNAS, 2020b).

In Vivo Studies

In an OECD 475 (Mammalian Bone Marrow Chromosome Aberration Test) study, Sprague Dawley rats were exposed to octamethylcyclotetrasiloxane (CAS RN [redacted] via whole body inhalation. The results from this study showed that the substance is negative for clastogenicity/chromosome aberrations. In an OECD 478 (Genetic Toxicity: Rodent Dominant Lethal Test) study, Sprague Dawley rats were exposed to the substance via oral gavage for 8 weeks. The results from this study indicate that octamethylcyclotetrasiloxane does not induce chromosome damage in germ cells (ECHA). [Kl. Score = 2].

In an OECD Guideline 486 (Unscheduled DNA Synthesis UDS test with Mammalian Liver cells in vivo)study, Fischer 344 rats were exposed to decamethylcyclopentasiloxane (CAS RN [redacted] via whole body inhalation. The results from this study shown that the substance does not induce unscheduled DNA syntheses. In an OECD Guideline 474 test (Mammalian Erythrocyte Micronucleus Test), Fischer rats were exposed to the substance via whole body inhalation for 7 days. The results indicate that decamethylcyclopentasiloxane does not induce micronuclei in cells (ECHA). [KI Score = 1]

In an OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) study, ICR mice were exposed to dodecamethylcyclohexasiloxane (CAS RN [redacted] via intraperitoneal injections for 24 to 78 hours. The results from this study indicate that the substance does not induce micronucleation *in vivo* (ECHA). [KI Score = 1]

G. Carcinogenicity

Based on the available information summarised below, cyclic polyorganosiloxanes are not considered to be carcinogenic.

Oral

No available studies.

Inhalation

In a OCED Guideline 453 (Combined Chronic Toxicity/Carcinogenicity Studies) study, octamethylcyclotetrasiloxane (CAS RN [redacted] was administered to Fischer rats via whole body inhalation vapour for 24 months. Inhalation exposure to the substance induced an increased incidence of endometrial adenomas and cystic endometrial epithelial hyperplasia in the uteri of female Fischer 344 rats exposed to 700 ppm for 24 months. There were no carcinogenic findings in male rats. The study authors indicated the NOAEL for carcinogenic effects was 150 and ≥700 ppm in females and males, respectively. However, based on fundamental differences between rats and humans with respect to the development of reproductive function, brain regulation of LH secretion, and the mechanism of reproductive aging and the hormonal environment of reproductive senescence the NOAEC for carcinogenic effects relevant to humans is ≥700 ppm (equivalent to ≥8492 mg/m^3 based on a molecular weight of 296.62) (ECHA). [Kl. Score = 1].

In an OECD 453 (Combined Chronic Toxicity/Carcinogenicity Studies) study, Fischer 344 rats were administered decamethylcyclopentasiloxane (CAS RN [redacted] via whole body inhalation vapour for up to 106 weeks. The NOAEC for carcinogenic effects was determined to be 160 ppm (2420 mg/m^3), the highest dose tested. There were no treatment-related effects on survival, body weight, ophthalmological parameters, haematology, clinical chemistry and urinalysis parameters in any of the groups. Non-neoplastic changes included increased incidence of hyaline inclusions in the nasal olfactory epithelium and increased liver weights at the highest concentration only. In females exposed to the highest concentration, there was a significantly increased incidence of endometrial adenocarcinoma. Endometrial adenomatous polyps and endometrial adenocarcinoma were also increased in females from the recovery group. Obligatory preceding lesions to these uterine neoplasms were not observed in these animals, e.g. uterine adenoma or endometrial hyperplasia. The mechanism by which the endometrial adenocarcinomas occur in F344 rats may be related to dopamine agonist activity of the chemical, leading to hormonal dysregulation that can stimulate the development and progression of these tumours (NICNAS, 2020d). These imbalances are common in rodents and are of no relevance to humans (ECHA). [Kl. Score = 1].

There are no adequate studies available for dodecamethylcyclohexasiloxane (CAS RN [redacted] No animal data are available for the chemical. Based on the information available from the genotoxicity studies and Quantitative Structure Activity Relationship (QSAR) modelling, the chemical is not expected to be carcinogenic (NICNAS, 2020c).

Dermal

No available studies.

H. Reproductive Toxicity

Octamethylcyclotetrasiloxane is considered to cause reproductive toxicity following inhalation exposure. Decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane are not considered to be reproductive toxicants.

A NOAEC of 300 ppm (3640 mg/m^3) was determined for reproductive toxicity in a two-generation reproductive study (OECD 416) using Sprague-Dawley rats exposed to octamethylcyclotetrasiloxane (CAS RN [redacted] via whole body inhalation. The animals were dosed as follows 70 ppm, 300 ppm, 500 ppm and 700 ppm. This NOAEC is based on reduced female fertility indices and reduced mean live litter sizes (ECHA). [KI Score = 1].

A NOAEL of at least 160 ppm was determined for reproductive toxicity in a two-generation reproductive toxicity study (EPA OPP 83-6 and EPA OPPTS 870.3800) in Sprague-Dawley rats exposed to decamethylcyclopentasiloxane (CAS RN [redacted] via whole body inhalation at exposure concentrations of 30, 70 and 160 ppm. Overall, there was no evidence of parental toxicity, reproductive toxicity, neonatal toxicity, or developmental neurotoxicity (ECHA). [KI Score = 1].

In an OECD 422 (Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test) study Sprague Dawley rats were administered dodecamethylcyclohexasiloxane (CAS RN [redacted] via oral gavage for 28 days. A NOAEL of ≥ 1,000 mg/kg/day, highest dose tested, was established due to no clear effect on reproductive toxicity in the screening study (ECHA) [KI Score = 1].

I. Developmental Toxicity

None of the substances are considered to be developmental toxicants.

An OECD 414 (Prenatal Developmental Toxicity Study) was performed on New Zealand White rabbits exposed to octamethylcyclotetrasiloxane (CAS RN [redacted] via whole body inhalation [KI Score = 1]. The animals were dosed as follows: 100 ppm, 300 ppm and 500 ppm. The substance did not affect foetal development and the NOAEL for this endpoint was therefore greater than the highest concentration tested (500 ppm or 6,066 mg/m^3). The NOAEC for maternal toxicity was 300 ppm (3,640 mg/m^3) based on reduced food consumption in the highest dose group (ECHA). [Kl. Score = 1].

An OECD 414 (Prenatal Developmental Toxicity Study) study was performed on Sprague Dawley rats administered decamethylcyclopentasiloxane (CAS RN [redacted] via whole body inhalation. A NOAEC of 161 ppm (2,427 mg/m^3), highest dose tested, was established for maternal toxicity and developmental toxicity as there were no adverse effects reported in this study (ECHA). [KI Score = 1]

An OECD 414 (Prenatal Developmental Toxicity Study) study was performed on Wistar Han rats exposed to administered dodecamethylcyclohexasiloxane (CAS RN [redacted] via oral gavage. The maternal and developmental NOAEL was determined to be 1,000 mg/kg bw/day, highest dose tested, based on no adverse effects (ECHA). [Kl. Score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for cyclic polyorganosiloxanes follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non Cancer

The lowest NOAEL reported in repeat dose toxicity studies is 1,000 mg/kg bw/day for decamethylcyclopentasiloxane (CAS RN [redacted] and dodecamethylcyclohexasiloxane (CAS RN [redacted] This value is lower than the NOAEC derived for reproductive toxicity via inhalation exposures from the inhalation combined chronic toxicity and carcinogenicity study conducted for octamethylcyclotetrasiloxane (CAS RN [redacted] and corrected for repeated dose systemic effects via the oral route (NOAEL of 2,990 mg/kg bw/day). The NOAEL of 1,000 mg/kg bw/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value for the cyclic polyorganosiloxanes.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

- UF_A (interspecies variability) = 10
- UF_H (intraspecies variability) = 10
- UF_L (LOAEL to NOAEL) = 1
- UF_{Sub} (subchronic to chronic) = 10
- UF_D (database uncertainty) = 1
- Oral RfD = 1000/(10 x 10 x 1 x 1 x 1) = 1000/1000 = 1 mg/kg/day.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (1 x 70 x 0.1)/2 = 3.5 mg/L

B. Cancer

The substances are not considered carcinogens. Thus, a cancer reference value will not be calculated.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane do not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

Octamethylcyclotetrasiloxane is flammable but is not oxidising or explosive.

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Substances in this category tend to have low water solubility, high adsorption and partition coefficients and slow degradation rates in the sediment compartment. For substances with a log K_{ow} of 8 and above (decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane), no long-term toxicity effects are seen with aquatic organisms due to the low water solubility limiting the bioavailability and uptake of the substance. While octamethylcyclotetrasiloxane has exhibited toxicity to water column organisms in the laboratory, it is not toxic up to its limits of functional water solubility under realistic environmental conditions. In the environment, the substances will adsorb to particulate matter and will partition to soil and sediment compartments.

B. Aquatic Toxicity

The high volatility from water and the very high hydrophobicity of chemicals in this group has presented challenges for the conduct of standard short- and long-duration aquatic toxicity tests. In an attempt to ensure consistent exposures of test organisms to these chemicals, some aquatic toxicity tests have been conducted in fully enclosed systems with no head-space. These tests, which are summarized below, indicate no toxic effects on aquatic life up to the limit of their respective

solubilities in water. Some toxic effects have been observed for octamethylcyclotetrasiloxane under optimised aquatic exposure conditions which indicate that these chemicals have a non-polar narcosis mode of toxic action (MOA) in aquatic organisms. These MOA effects are, therefore, expected to be both reversible and dependent on the kinetics of uptake and elimination by aquatic life (NICNAS, 2020a).

The rate of uptake from water is known to be a significant factor influencing both the toxicity and bioconcentration of very hydrophobic neutral chemicals. Recent modelling of the uptake of cyclic volatile methyl siloxanes from water by fish suggests that the time required for adult fish to achieve the assumed narcotic critical body residue associated with a 50% effect on the organism (CBR = 3 millimoles per kilogram) is 24.7 days for octamethylcyclotetrasiloxane, 101 days for decamethylcyclopentasiloxane and 397 days for dodecamethlcyclohexasiloxane; these calculations assume continuous exposure at the respective water solubility limits for each chemical and no metabolism of the chemicals. These findings are significant for ecological risk assessment as they suggest that significant acute toxic effects are unlikely to occur as a result of exposure to these chemicals in the water column because this would require unfeasibly long exposures at concentrations that are a significant fraction of the saturation concentration of each chemical. It also provides further evidence that exposure through aquatic food-chains will provide a more environmentally significant exposure pathway for these very hydrophobic chemicals (NICNAS, 2020a).

Acute Studies

Tables 2, 3 and 4 list the results of acute aquatic toxicity studies conducted on the three cyclic polyorganosiloxanes.

Table 2: Acute Aquatic Toxicity Studies on Fish for Cyclic Polyorganosiloxanes

	Octamethyl cyclotetrasiloxane CAS RN [redacted]	**Decamethyl cyclopentasiloxane CAS RN** [redacted]	**Dodecamethyl cyclohexasiloxane CAS RN** [redacted]
Test Species	*Oncorhynchus mykiss* (Rainbow trout)	*Oncorhynchus mykiss* (Rainbow trout)	No data*
Endpoint	96-hour LC_{50}	96-hour LC_{50}	-
Results (mg/L)	> 0.022 mg/L	> 0.016 mg/L	-
Klimisch score	2	1	-
Reference	ECHA	ECHA	-

Table 3: Acute Aquatic Toxicity Studies on Invertebrates for Cyclic Polyorganosiloxanes

	Octamethyl cyclotetrasiloxane CAS RN [redacted]	**Decamethyl cyclopentasiloxane CAS RN** [redacted]	**Dodecamethyl cyclohexasiloxane CAS RN** [redacted]
Test Species	*Daphnia magna*	*Daphnia magna*	No data*
Endpoint	48-hourEC_{50}	48-hour EC_{50}	-
Results (mg/L)	> 0.015 mg/L	> 0.0029 mg/L	-
Klimisch score	1	1	-
Reference	ECHA	ECHA	-

Table 4: Acute Aquatic Toxicity Studies on Algae for Cyclic Polyorganosiloxanes

	Octamethyl cyclotetrasiloxane CAS RN [redacted]	Decamethyl cyclopentasiloxane CAS RN [redacted]	Dodecamethyl cyclohexasiloxane CAS RN [redacted]
Test Species	*Pseudokirchneriella subcapitata*	*Pseudokirchneriella subcapitata*	*Pseudokirchneriella subcapitata*
Endpoint	96-hour LC_{50}	96-hour LC_{50}	72-hour EC_{50}
Results (mg/L)	> 0.022 mg/L	> 0.012 mg/L	> 0.002 mg/L
Klimisch score	1	1	1
Reference	ECHA	ECHA	ECHA

*Short-term toxicity tests are not needed because a long-term aquatic toxicity study is available. (ECHA).

Chronic Studies

Fish: A 93-day study was conducted to determine the toxicity of octamethylcyclotetrasiloxane (CAS RN [redacted] to Rainbow trout (*Oncorhynchus mykiss*). The NOAEC was determined to be ≥0.004 mg/L based on embryo viability, hatching success, larval survival and growth during early life stages However, to better define the potential NOEC, modelling (Mackay et al., 2015) to estimate fish critical body burden (CBB) levels and compare those CBB levels to those associated with a narcotic MOA, under which this substance and other volatile methyl siloxanes materials are proposed to operate was conducted. These results indicate that the substance dose levels up to 12 µg/l could have been successfully used in the 93-day trout study without adverse effect (ECHA). [KI Score = 2].

A 90-day (60 days post hatch) study was conducted to determine the toxicity of decamethylcyclopentasiloxane (CAS RN [redacted] Rainbow trout (*Oncorhynchus mykiss*). The NOAEC was determined to be ≥0.014 mg/L based on hatching, larval survival and growth (ECHA). [KI Score = 1].

Read across of decamethylcyclopentasiloxane (CAS RN [redacted] was used to determine the toxicity of dodecamethylcyclohexasiloxane (CAS RN [redacted] The NOAEC was determined to be ≥0.014 mg/L based on hatching, larval survival and growth in rainbow trout (ECHA). [KI Score = 2]Invertebrates: A 21-day study was conducted to determine the toxicity of octamethylcyclotetrasiloxane (CAS RN [redacted] to *Daphnia magna*. A NOEC of 0.0079 mg/L was determined for this substance based on survival (ECHA). [KI Score = 1]

A 21-day study was conducted to determine the toxicity of Decamethylcyclopentasiloxane (CAS RN [redacted] A NOEC of ≥0.015 mg/L was established based for *Daphnia magna* based on survival, reproduction and growth (ECHA). [KI Score = 1]

A 21-day study was conducted to determine the toxicity of dodecamethylcyclohexasiloxane (CAS RN [redacted] to *Daphnia magna* was conducted according to OECD Test Guideline 211 in sealed containers. A NOEC of ≥0.0046 mg/L was determined based on survival, growth and reproduction (ECHA). [KI Score = 1]

Algae: A static closed bottle test with P. subcapitata conducted according to OECD TG 201 showed no treatment related inhibition of growth and yield of green algae (relative to the solvent control) after 72 hours of exposure to dodecamethylcyclohexasiloxane at the highest measured exposure concentration (2.0 µg/L). A NOEC of 0.002 mg/L was determined. The highest exposure concentrations utilised in the short- and long-term tests were close to the functional solubility of the test substance in the exposure media. It is therefore concluded that the substance is not toxic to

fish, invertebrates and algae following short- and long-term exposure at its functional water solubility limit (ECHA). [KI Score = 1].

C. Sediment Toxicity

The chemicals in this group are expected to have low toxicity to benthic invertebrates (NICNAS, 2020a).

The 28-day no observed effect concentration (NOEC) for Oligochaete (*Lumbriculus variegatus*) exposed to octamethylcyclotetrasiloxane (CAS RN [redacted] is 13 mg/kg dry weight (ECHA) [KI score = 1].

The 28-day NOEC for *Chironomus riparius* exposed to decamethylcyclopentasiloxane (CAS RN [redacted] is 70 mg/kgdry weight (ECHA) [KI score = 1].

A read across study of results for decamethylcyclopentasiloxane was conducted to derive the 28-day NOEC of 130 mg/kgdry weight (135 mg/kg dry weight normalised to 5% OC) for dodecamethylcyclohexasiloxane (CAS RN [redacted] in *Hyalella azteca* (ECHA). [KI score = 2].

D. Terrestrial Toxicity

Terrestrial studies with siloxanes are considered to be difficult to conduct due to their high volatilisation potential (high HLC) and the potential for degradation in soil (ECHA). However, studies were available for decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane.

In an OECD Test Guideline 222 study, a 28-day LC_{50} value of >4074 mg/kg dry weight and a 56-day NOEC of ≥4074 mg/kg dry weight have been determined for the effects of decamethylcyclopentasiloxane (CAS RN [redacted] on mortality, and on reproduction and growth, respectively of the earthworm, *Eisenia andrei* (ECHA). [KI Score = 2]. T

A 56-day earthworm reproduction test for dodecamethylcyclohexasiloxane (CAS RN [redacted] at concentrations up to 1000 mg/kg soil dry weight, has been conducted in accordance with OECD TG 222 (earthworm reproduction test) and in compliance with GLP. No effects on survival or reproduction were observed. Based on the findings of the test, a 28-day NOEC value of ≥1000 mg/kg dry weight (highest concentration tested) was determined for the effects of the test substance on growth of adult earthworms, based on nominal concentrations. A 56-day NOEC value of ≥1000 mg/kg dry weight (highest concentration tested) was determined for the effects of on reproduction of the earthworm, based on nominal concentrations (ECHA). [KI Score = 2].

E. Calculation of PNEC

The PNEC calculations for cyclic polyorganosiloxanes follow the methodology discussed in DEWHA (2009).

<u>PNEC water</u>

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (> 0.015 mg/L), *Daphnia* (> 0.0029 mg/L) and algae (> 0.002 mg/L). There are long-term studies available for fish (≥ 0.012 mg/L), *Daphnia* (≥ 0.0046 mg/L) and invertebrates (> 0.002 mg/L). Before identifying an applicable effect concentration for the PNEC calculation, it is appropriate to consider that aquatic fate characteristics of the cyclic polyorganosiloxanes and how test conditions can

impact the findings of the toxicity studies. For example, the lowest NOEC value reported for algael inhibition (0.002 mg/L) was determined using a closed test system. As one of the cyclic polyorganosiloxanes (octamethylcyclotetrasiloxane) is highly volatile and rapidly hydrolyzes, this NOEC does not appear to be appropriate. Likewise, for the chronic invertebrate study. On the basis of the short-term and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC of 0.012 mg/L for fish. This NOEC values is lower (and more conservative) than the maximum achievable solubility of octamethylcyclotetrasiloxane (0.015 mg/L) used in the derivation of the PNEC for that substance by ECHA. The $PNEC_{water}$ is 0.0012 mg/L.

PNEC sediment

Siloxanes are expected to partition more readily to the sediment phase rather than the aquatic phase. No adverse effects were observed in any of the chronic studies on sediment-dwelling organisms. Experimental results are available for three sediment dwelling organisms. The lowest NOEC, which was observed in the study using Oligochaete (*Lumbriculus variegatus*), was 13 mg/kg dw. Using an assessment factor of 50, the $PNEC_{sediment}$ was determined to 0.26 mg/kg.

PNEC soil

Terrestrial studies with siloxanes are considered to be difficult to conduct due to their high volatilisation potential (high HLC) and the potential for degradation in soil (ECHA). However, studies were available for decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane. Experimental results are available for one tropic level. The lowest NOEC was observed in the study using earthworms (*Eisenia andrei*), and was 1,000 mg/kg dw. Using an assessment factor of 100, the $PNEC_{soil}$ was determined to 10 mg/kg.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Cyclic polyorganosiloxanes are not readily biodegradable in sediments. They have half-lives in excess of 1 year. Thus, they meet the screening criteria for persistence.

Based on measured BCF values in fish, which are greater than 2000 L/kg, both octamethylcyclotetrasiloxane and decamethylcyclopentasiloxane have a high potential to bioaccumulate. Thus, meeting the screening criteria for bioaccumulation. However, dodecamethylcyclohexasiloxane has a BCF value in fish of 1,160 mg/L. Thus, it does not meet the screening criteria for bioaccumulation..

The chronic toxicity data on the cyclic polyorgansiloxanes show NOECs < 0.1 mg/L. The acute LC_{50} values are also less than 1 mg/L. Thus, meeting the screening criteria for toxicity. However, for octamethylcyclotetrasiloxane, a classification of toxicity is uncertain as the observed toxic effects on aquatic life below the water solubility limit for this chemical were obtained under exposure conditions which may not be relevant to the ecological hazards of this chemical. Likewise, for decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane, no toxic effects on aquatic life were observed up to their respective water solubility limits.

The overall conclusion is that octamethylcyclotetrasiloxane is a PBT substance (with uncertainty) and that decamethylcyclopentasiloxane and dodecamethylcyclohexasiloxane are not PBT substances. Octamethylcyclotetrasiloxane has been identified as a PBT substance by the European Union (EU).

IX. CLASSIFICATION AND LABELLING

A. Classification

Octamethylcyclotetrasiloxane (CAS RN [redacted]

- H361: Suspected of damaging fertility or the unborn child.
- H361f: Suspected of damaging fertility.

Decamethylcyclopentasiloxane (CAS RN [redacted]

- H227: Combustible liquid.
- H413: May cause long lasting harmful effect to aquatic life.

Dodecamethylcyclohexasiloxane (CAS RN [redacted]

- H227: Combustible liquid.

B. Labelling

Warning Flammable liquids

C. Pictogram

Octamethylcyclotetrasiloxane

X. SAFETY AND HANDLING

Refer to the product SDS for additional information and confirmation of the information provided herein.

A. First Aid

Eye Contact

In the case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for any of the members of this group.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing closed work clothing is recommended.

F. Transport Information

Not regulated for transport.

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

National Industrial Chemicals Notification and Assessment Scheme [NICNAS]. (2020a). Cyclic volatile methyl siloxanes: Environment tier II assessment. June 16, 2020.

NICNAS. (2020b). Cyclotetrasiloxane, octamethyl-: Human health tier II assessment. July 1, 2016.

NICNAS. (2020c). Cyclohexasiloxane, dodecamethyl-: Human health tier II assessment. July 1, 2016.

NICNAS. (2020d). Cyclopentasiloxane, decamethyl-: Human health tier II assessment. June 30, 2017.

PubChem. National Institutes of Health. National Library of Medicine National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/

DIAMMONIUM PEROXODISULPHATE

This dossier on diammonium peroxodisulphate presents the most critical studies pertinent to the risk assessment of diammonium peroxodisulphate in its use in drilling muds. It does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained primarily from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Diammonium peroxodisulphate

CAS RN: [redacted]

Molecular formula: $H_8N_2O_8S_2$

Molecular weight: 228.21 g/mol

Synonyms: Diammonium peroxydisulfate; Diammonium peroxydisulphate; Diammonium persulfate; Peroxydisulfuric acid (((HO)S(O)2)2O2), ammonium salt (1:2); Peroxydisulfuric acid (((HO)S(O)2)2O2), diammonium salt; Peroxydisulfuric acid, diammonium salt; ammonium persulphate

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Diammonium Peroxodisulphate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, odourless, crystalline solid	1	ECHA
Melting Point	ND. Decomposes at ca. 393 K (= 120°C) at 100.66 kPa	1	ECHA
Boiling Point	ND. Decomposes at ca. 393 K (= 120°C) at 100.79 kPa	1	ECHA
Density	1260 kg/m³ at 20°C	1	ECHA
Vapour Pressure	0 Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})	Not applicable as substance is inorganic	-	ECHA
Water Solubility	850 g/L @ 25°C	2	ECHA
Viscosity	ND. Substance is a solid at room temperature	-	ECHA
Dissociation constant (pKa)	Diammonium persulfate dissociates completely to ammonium cation and persulfate anion when it is dissolved in water.	-	ECHA
Flammability	Non-flammable	1	ECHA

ND – not determined

Diammonium peroxidisulphate is widely used in cosmetics and personal care products, perfumes and fragrances, adhesives and sealants, anti-freeze products, coating products, fillers, putties, plasters, modelling clay, non-metal-surface treatment products, inks and toners, leather treatment products, lubricants and greases, polishes and waxes and textile treatment products and dyes.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Diammonium peroxodisulphate dissociates in aqueous media to the ammonium cation and persulfate anion. Biodegradation is not applicable to inorganic compounds. Diammonium peroxodisulphate is not expected to bioaccumulate; it will dissociate to ions that are ubiquitous in the environment. Diammonium peroxodisulphate is not expected to adsorb to soil or sediment because of its dissociation properties and high water solubility.

B. Partitioning

Persulfates dissociate in water to the corresponding cation and persulfate anion. Hydrolysis is temperature and pH dependent. The persulfate anion, independent from the cation, undergoes decomposition in normal water or acid conditions, readily oxidising water to oxygen, producing acid conditions. All degradation products are ubiquitous to the environment (ECHA).

Diammonium peroxodisulphate was shown to be hydrolytically stable at 10°C and pH 4, 7 and 9, a minor hydrolysis was observed at 25°C, whereas a very strong hydrolysis at 60°C was observed within four days. The DT50 at pH 4 and 60°C was determined to be 27.2 h, at pH 7 and 9 and 60°C the DT50 was determined to be 36.5 h. The DT50 at environmentally relevant temperature (12°C) and pH 7 was extrapolated to be 1698.18 h (70.76 d) (ECHA) [Kl. Score = 1].

C. Biodegradation

Biodegradation is not applicable to inorganic compounds.

D. Environmental Distribution

No experimental data are available for diammonium peroxodisulphate. Persulfates are soluble in water and their vapour pressures are negligible. Thus, persulfates released into the environment are distributed into the water compartment in ionic form of the cation and persulfate ion. Persulfates are not expected to sorb to soil due to their dissociation properties, instability (hydrolysis) and high water solubility. They behave as free ions and decompose into sulfate and bisulfate ions. All decomposition products are ubiquitous in the environment (ECHA).

E. Bioaccumulation

There are no bioaccumulation studies on diammonium peroxodisulphate. Substances of the persulfate category are inorganic salts sharing the same anionic persulfate moiety. Persulfates are very soluble in water and are not expected to bioaccumulate in soil or aqueous solutions. They will decompose into organic sulfate or bisulfate (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Diammonium peroxodisulphate is irritating to the eyes, skin and respiratory tract. Inhalation of dust may cause asthma-like reactions. Repeated or prolonged contact may cause skin sensitisation. In a 90-day oral toxicity study in rats, systemic effects (intestinal changes) were observed at the highest dose (200 mg/kg bw/day). It is not carcinogenic or genotoxic, nor does the substance show evidence of reproductive or developmental toxicity.

B. Toxicokinetics/Metabolism

Persulphates are inorganic salts that decompose on heating without a definite melting point at temperatures above 100°C. Due to their properties as inorganic salts and considering their low vapour pressures, an exposure via inhalation is not very likely. Absorption by the skin is also not very likely. Generally, salts largely do not penetrate the skin. Persulphate salts rapidly hydrolyse upon contact with water or water vapour. As a result, persulphates will rapidly degrade and will eventually form the corresponding cations (ammonium, potassium, sodium) and persulphate anions. The persulphate anion, independent of the cation, undergoes further decomposition upon contact with water to form sulphate species. Based on these fundamental properties of persulphates, they are not likely to become bioavailable by inhalation, ingestion or contact by skin.

C. Acute Toxicity

Diammonium persulfate was tested for acute toxicity via the oral, dermal and inhalation routes in rats. In an acute oral toxicity study LD_{50} and LD_0 values of 742 mg/kg bw and 300 mg/kg bw, respectively, in the male rat and LD_{50} value of 700 mg/kg bw in the female rat were determined. In an acute dermal toxicity study LD_{50} and LD_0 values of greater than 2000 mg/kg bw and 2,000 mg/kg bw were determined, respectively. In an acute inhalation toxicity study (whole body exposure) LC_{50} and LC_0 values of greater than 2.95 mg/L and 2.95 mg/L, respectively, were determined.

D. Irritation

Diammonium peroxodisulphate is slightly irritating to the eye and skin of rabbits. Studies in humans indicate that aqueous solutions of 5% persulphate or higher can cause skin irritation.

E. Sensitisation

Results of animal skin sensitisation tests were negative when persulphate was applied topically but were positive when persulphate was injected intradermally. Repeated or prolonged contact may cause skin sensitisation.

F. Repeat Dose Toxicity

In a repeated dose 90-day oral toxicity study in rats (OECD Guideline 408), rats were fed three levels of test material, sodium persulphate (0, 300, 1000 and 3,000 ppm). On day 48 of the study, the concentration of the group receiving 1,000 ppm was increased to 5,000 ppm for the remainder of the study. The body weight of the rats in the two highest dose groups decreased during the last six weeks of treatment. There were no significant differences seen among the groups in urine analytical parameters, haematological blood parameters or both organ weight and body weight ratios. All rats survived the study. Intestinal changes were noted in rats which received 3,000 ppm of sodium persulfate for 13 weeks. These changes were seen more frequently among females than males. The

former received 50 percent more test material than the latter on a dose per body weight basis. No significant changes were seen among the controls or the groups which received 300 ppm, or 1,000 ppm in the diet for eight weeks, followed by 5,000 ppm in the diet for the remainder of the study. No other microscopic changes were noted on comparison among these three groups. LOAEL and NOAEL values of 200 and 91 mg/kg bw/day (3,000 and 1,000 ppm), respectively were determined.

G. Genotoxicity

Diammonium persulphate did not show any mutagenic effects in a bacterial reverse mutation assay.

H. Carcinogenicity

Diammonium persulphate of the persulphate category was tested for its skin carcinogenic potential in a 51-week dermal study with mice following a guideline similar to OECD Guideline 451. Based on the data obtained, diammonium persulphate was not considered carcinogenic. Diammonium peroxidisulphate is not listed in the Chemical Carcinogenesis Research Information System (CCRIS) or International Agency for Research on Cancer (IARC) databases or documented by USEPA as carcinogenic.

I. Reproductive/Developmental Toxicity

Diammonium persulphate was tested for oral reproductive/developmental toxicity in a screening test with rats according to OECD Guideline 421. No test substance-related effects were observed in P and F1 generations. A NOAEL value of 250 mg/kg/day for parental toxicity, reproduction parameters and developmental toxicity was determined. Dose levels were chosen based on the acute lethality studies for the ammonium salt and on a 90-day repeat-dose study in rats with the sodium salt (high dose: 225 mg/kg/day). In the developmental/reproduction study, animals were dosed prior to and during mating through gestation until lactation day 4. There was a transient depression in pup body weight at the 250 mg/kg dose level on lactation day 0 which resolved by lactation day 4. This effect was not considered adverse. Based on the available data, the persulphates do not show evidence of reproductive or developmental toxicity. The NOAEL is 250 mg/kg/day.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for diammonium peroxidisulphate follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021). There are no existing drinking water guideline values for ammonium ions.

A. Non-cancer

The substance will readily disassociate to its respective cations and anions. As noted above, there are no drinking water guidelines for ammonium ions as there is insufficient data to set a guideline value based on health considerations. The Australian Drinking Water Guideline value for sulphate may apply to sulphate ions (500 mg/L for health and 250 mg/L for taste aesthetic threshold). An ammonia guideline based on aesthetics is however 0.5 mg/L and will be used as drinking water guideline for this dossier.

B. Cancer

A cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Diammonium peroxidisulphate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Diammonium peroxodisulphate is of low toxicity concern to aquatic and terrestrial organisms.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies conducted on diammonium peroxodisulphate.

Table 2: Acute Aquatic Toxicity Studies on Diammonium Peroxodisulphate

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-hour LC_{50}	76.3 mg/L	1	ECHA
Daphnia magna	48-hour EC_{50}	120 mg/L	1	ECHA
Phaeodactylum tricornutum	72-hour EC_{10}	320 mg/L	1	ECHA

Chronic Studies

Long-term toxicity testing to fish was considered scientifically unjustified, due to the results obtained in the short-term toxicity to fish studies, the substance's physical-chemical properties and hydrolysis behaviour (ECHA).

An OECD Guideline 211 (Daphnia magna reproduction test) was performed and yielded a 21-day NOEC of 20.8 mg/L based on reproduction (ECHA) [KI Score = 1].

C. Terrestrial Toxicity

No terrestrial toxicity studies are available.

Persulfates are not expected to be distributed into the terrestrial compartment and consequently not expected to cause toxicity to terrestrial organisms and plants (ECHA).

D. Calculation of PNEC

$PNEC_{water}$

Experimental results are available for three trophic levels. Acute EC_{50} values are available for fish (76 mg/L), Daphnia (120 mg/L) and algae (84 mg/L). On the basis that the data consists of short-term

results from three trophic levels, an assessment factor of 1,000 has been applied to the lowest reported effect concentration of 76 mg/L for fish. $PNEC_{water}$ is 0.076 mg/L.

$PNEC_{sediment}$

No experimental toxicity data on sediment organisms are available. Diammonium peroxydisulphate dissociates completely in water with its environmental distribution is dominated by its high water solubility. K_{ow} and K_{oc} do not readily apply to inorganics, such as diammonium peroxidisulphate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sediment}$. Based on these properties, no adsorption of diammonium peroxydisulphate to sediment is to be expected.

$PNEC_{soil}$

No experimental toxicity data on terrestrial organisms are available. The environmental distribution of diammonium peroxydisulphate is dominated by its water solubility. Sorption of diammonium peroxydisulphate should probably be regarded as a reversible situation, i.e., the substance is not tightly nor permanently bound. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as diammonium peroxidisulphate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, diammonium peroxydisulphate is not expected to significantly adsorb to soil, and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Diammonium peroxodisulphate is an inorganic salt that dissociates to respective cations and anions. Biodegradation is not applicable to these inorganic ions. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Diammonium peroxodisulphate is not expected to bioaccumulate; it will dissociate to ions that are ubiquitous in the environment. Thus, the substance does not meet the screening criteria for bioaccumulation.

Chronic aquatic toxicity data is > 0.1 mg/L and acute aquatic toxicity data is >1 mg/L. Thus, diammonium peroxodisulphate does not meet the screening criteria for toxicity.

The overall conclusion is that diammonium peroxodisulphate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H272: May intensify fire; oxidiser.

H302: Harmful if swallowed.

H315: Causes skin irritation.

H317: May cause an allergic skin reaction.

H319: Causes serious eye irritation.

H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled.

H335: May cause respiratory irritation.

B. Labelling

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Separate eyelids with fingers. Get medical attention.

Skin Contact

Remove contaminated clothing and shoes. Wash skin thoroughly with soap and water. Get medical attention.

Inhalation

If inhaled, remove from area to fresh air. Lay down quietly in recovery position. If breathing is difficult, give artificial respiration with breathing bag. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: sulphur oxides, nitrogen oxides, toxic pyrolysis products.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use personal protective clothing. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust. Wear respiratory protection if ventilation is inadequate. Avoid contact with skin, eyes and clothing.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove. Avoid dust formation. Store in closed containers and dispose of in accordance with federal, state and local regulations. Clean up spill area and treat as special waste.

D. Storage and Handling

General Handling

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust. Take off contaminated clothing and shoes. Wash thoroughly after handling. Do not eat, drink or smoke during work.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place. Do not store with alkalis, acids, or reducing agents.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for ammonium persulphate in Australia is 0.01 mg/m^3 as a peak exposure. A peak limitation is defined by Safe Work Australia as a maximum or peak airborne concentration of a substance determined over the shortest analytically practicable period of time which does not exceed 15 minutes.

Engineering Controls

Ensure adequate ventilation. Localised ventilation should be used to control dust levels below permissible exposure limits.

Personal Protection Equipment

Respiratory Protection: Use respiratory protection when airborne concentrations are expected to be high.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Wear suitable protective goggles (tightly fitting). Also wear face protection if there is a splash hazard. Ensure that eyewash stations and safety showers are close to the workstation location.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible. Remove and wash contaminated clothing before re-use. Contaminated work clothing should not be allowed out of the workplace.

F. Transport Information

UN1444 AMMONIUM PERISULPHATE

Class: 5.1

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol, Pharmacol. 25:1-5.

DICOCO DIMETHYL QUATERNARY AMMONIUM CHLORIDE

This dossier on dicoco dimethyl quaternary ammonium chloride (DQAC) (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. For the purposes of this dossier, a surrogate substance of like composition (Quaternary ammonium compounds, coco alkyltrimethyl, chlorides) (CAS RN [redacted] was evaluated. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Quaternary ammonium compounds, dicoco alkyldimethyl, chlorides

CAS RN: [redacted]

Molecular formula: $C_{26}H_{56}ClN$ (representative, UVCB substance)

Molecular weight: 418.18 g/mol (representative, UVCB substance)

Synonyms: dicoco dimethyl quaternary ammonium chloride; DQAC; dicocodimonium chloride; Quaternium-34; bis(coconut oil alkyl)dimethylammonium chloride

SMILES: CCCCCCCCCCCC[N+](CCCCCCCCCCCC)(C)(C).[Cl-] (representative, UVCB substance)

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of DQAC[1]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Amorphous wax-like oyster white solid	1	ECHA
Melting Point	No melting point could be determined, as the test substance undergoes decomposition before melting at a temperature >160°C	1	ECHA
Boiling Point	No boiling point could be determined as the test substance undergoes decomposition before boiling at >160°C.	1	ECHA
Density	935 kg/m^3 at 20°C	1	ECHA
Vapour Pressure	0.002 Pa at 25°C	1	ECHA
Partition Coefficient (log K_{ow})	2.39 at 20°C	1	ECHA
Water Solubility	1 g/L at 20°C	1	ECHA

Property	Value	Klimisch score	Reference
Flash Point	Flash point is only relevant to liquids and low melting point solids	1	ECHA
Auto flammability	No self-ignition temperature was observed up to the maximum temperature of 405°C	1	ECHA
Viscosity	30.2 mm^2/s at 20°C	1	ECHA

1 – Data taken from testing on the surrogate quaternary ammonium compounds, coco alkyltrimethyl, chlorides (Coco TMAC, CAS RN [redacted]

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

DQAC is readily biodegradable, is unlikely to bioaccumulate, and has the potential to bind to soils and sediments. Details of supporting studies are provided below.

B. Biodegradation

An OECD Guideline 301 D (Ready Biodegradability: Closed Bottle Test) was performed on DQAC. The test substance at 3 mg/L was incubated with sludge from activated sludge plant treating predominantly domestic waste and O_2 consumption was determined over a period of 28 days. The biodegradation was calculated as the ratio of the biochemical oxygen demand to the theoretical oxygen demand. The test substance reached a biodegradation of 75% at Day 28. Therefore, DQAC is considered readily degradable (ECHA) [KI Score = 2].

C. Environmental Distribution

An OECD Guideline 106 (Adsorption - Desorption Using a Batch Equilibrium Method) was performed on three soils and read across the quaternary ammonium salts (QAS) category. The experimentally-determined mead K_{oc} value of 1,640,329 L/kg is read across from QAS category substance. DQAC is expected to show a similar behaviour in soil (ECHA) [KI Score = 2].

D. Bioaccumulation

No data were available for bioaccumulation of DQAC. However, based on the low log K_{ow} of 2.39, substantial bioaccumulation is not expected (ECHA) [KI Score = 2].

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

DQAC has low acute toxicity by the oral and dermal routes. This substance was determined to be severely irritating to the skin and causes irreversible effects on the eyes. No systemic effects were observed in repeated dose oral or dermal toxicity studies. It is not genotoxic and is not expected to be a developmental toxicant.

B. Acute Toxicity

Oral

An OECD Guideline 401 (Acute Oral Toxicity) was performed. The study was conducted to determine the acute oral toxicity of the test substance in Sprague-Dawley rats according to OECD 401 and USEPA OPP 81-2 Guidelines, in compliance with GLP. Groups of 10 fasted animals (5 males and 5 females per dose except for 5 males only at the highest dose) were administered 0, 512, 620, 750 or 908 mg/kg bw of the test substance via the oral route. The animals were observed for 14 days after dosing and then sacrificed and subjected to gross pathological examination. There was no mortality in the 512 mg/kg bw group while 3 out of 10 and 7 out of 10 rats died in the 620 and 750 mg/kg bw groups, respectively. All 5 animals in the highest dose group (908 mg/kg bw) died. Under the study conditions, the acute oral LD_{50} of the test substance in Sprague-Dawley rats was determined to be 684 mg/kg bw (i.e., equivalent to 226 mg a.i./kg bw) (ECHA) [Kl. score =1].

Inhalation

No acute inhalation data were found for DQAC.

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) was performed using New Zealand White rabbits. Under the conditions of the test, the acute dermal LD_{50} for male and female albino rabbits were determined to be 1,300 mg/kg bw (i.e., equivalent to 429 mg a.i./kg bw) and 1,900 mg/kg bw (i.e., equivalent to 627 mg a.i./kg bw) respectively, and the combined dermal LD_{50} was determined to be 1,600 mg/kg bw (i.e., equivalent to 528 mg a.i./kg bw) (ECHA) [Kl Score=1].

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was conducted to determine the skin irritation potential of a surrogate quaternary ammonium substance, Coco TMAC (active ingredient 33%), using New Zealand White rabbits. Six animals were treated with 0.5 mL undiluted test substance (33%) in a semi-occlusive patch (1" X 1" gauze) that was overwrapped with a gauze binder and secured with dermiform tape. Plastic restraint collars were applied and remained on the animals for the duration of the 4-hour exposure period, after which the tape and test substance were removed. The Draize classification scoring criteria were used to evaluate the irritation potential. Application sites were observed for erythema and oedema at 4, 24, 48 and 72 hours after exposure and then daily up to 14 days. The test substance induced moderate erythema and moderate to severe oedema on all sites.

Remission of irritation signs occurred as the study progressed; however, moderate irritation was still present in one rabbit after study Day 12 (erythema: 2 'slight'; edema: 1 'barely perceptible'). In addition, desquamation was noted on all sites late in the study period and fissuring was present on two sites. The Primary Irritation Index was calculated to be 5.6 (indicative of moderate irritation). Under the study conditions, due to persistence of irritation reactions in one animal as well as desquamation on all sites and fissuring on two sites, the test substance is considered to be severely irritating to skin (ECHA) [Kl. score = 1].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) primary eye irritation study was performed using a surrogate substance, quaternary ammonium salt. Nine New Zealand White rabbits received 0.1 mL of undiluted solution in one eye. The other eye remained untreated. The eyelids were held closed for approximately 1 second after instillation. The eyes of three rabbits were washed for approximately 1 minute with 120 mL of lukewarm tap water commencing approximately 30 seconds after dosing. Both eyes were examined for ocular irritation in accordance with the method of Draize approximately 1, 24, 48 and 72 hours after dosing and at 96 hours and 7, 14 and 21 days. In addition, both eyes of all rabbits were further examined at 72 hours and 7, 14 and 21 days with sodium fluorescein and ultraviolet light. Body weights were obtained and recorded on study Day 0 (initiation) and at termination (Day 21). Based on the data obtained, the Maximum Average Scores (according to Kay and Calandra scoring system) for the test substance were calculated to be 96.8 (extremely irritating) at 14 days for the unwashed group and 69.7 (severely irritating) at both 72 and 96 hours for the washed group. Purulent discharge, clear discharge, petite haemorrhage, blanching, corneal epithelial damage and peeling, corneal neovascularisation, sodium fluorescein stain retention, and vascularised granulation scar tissue were observed in all 6 animals. Same effects were observed in the washed group, except for vascularised granulation scar tissue. There were no deaths or remarkable body weight changes during the study period. Under the study conditions, the test substance is considered to cause irreversible effects on the eye (ECHA) [Kl. score = 1].

D. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) study (i.e., Buehler test) was performed on Dunkin-Hartley guinea pigs.

The study was conducted to determine the sensitising potential of a read across substance, C12 -14 trimethyl ammonium chloride (TMAC). A pre-test was conducted to determine non-irritating concentrations to be used in the main study. For the main study the induction was carried out at: topical 0.1% w/v in aqueous ethanol for 6 hours, repeated after 7 and 14 days. Challenge was done two weeks after the last induction treatment (Day 28): control and test animals received 0.1% w/v in acetone for 6 hours on previously untreated site under closed patches. After 18 hours the sites were treated with depilatory cream, rinsed and dried. After 3 hours, challenge sites were evaluated for erythema on a scale of 0-3. Evaluation was repeated 24 hours later. Results of the first grading were: 0/20 (3/20 showed a grade of 0.5; in control 2/10 showed a grade 0.5). Second grading: 0/20 (no erythema was observed in any of the animals); test substance was considered to be non-sensitising (ECHA) [Kl. score = 1].

E. Repeated Dose Toxicity

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity Study in Rodents) was performed using Sprague Dawley rats. The 90-day study was conducted to determine the oral repeated dose toxicity of the test substance, Coco TMAC. Sprague-Dawley rats were administered the test substance at concentrations of 0, 100, 500 or 2,000 ppm (i.e., corresponding to 0, 22, 113 and 273 mg/kg bw/day in males and 0, 25, 121, 297 mg/kg bw/day in females) in the diet for 90 days. The active ingredient dose equivalent was calculated to be 0, 7.9, 40.3 and 96.9 mg a.i./kg bw/day in males and 8.8, 42.9, 105.3 mg

a.i./kg bw/day in females. The highest dose of 2,000 ppm was reduced to 1,000 ppm from Day 29 onwards due to deterioration in health of the test animals at 2,000 ppm. At the highest dose, the treatment-related findings were clinical signs of toxicity, reduced body weight gain and food efficiency, organ weight changes and microscopic changes in the spleen and kidneys. At the mid dose, reduced body weight gain (males) and reduced food consumption, reduced absolute heart weight and higher incidence of haemosiderin accumulation in the kidneys of males was observed. No treatment-related effects were observed at the lowest dose. Based on the results of the study, dietary administration of the test substance to rats for a period of 90 days at levels up to 273 mg/kg bw/day resulted in toxicologically significant effects at the high dose and marginal effects at the next lower dose of 113 mg/kg bw/day (500 ppm). No such effects were demonstrated at the lowest dose of 22 mg/kg bw/day (100 ppm). The changes observed at the mid dose (500 ppm) were considered to be minor, isolated effects associated with the reduced palatability of the test substance and were considered not to represent an adverse health effect. Therefore, based on effects on body weight, food efficiency and clinical signs the study authors established the NOAEL at the mid dose level of 500 ppm (i.e., equivalent to 40.3 mg ai./kg bw/day) (ECHA) [Kl. Score = 1].

Inhalation

No data were available.

Dermal

An OECD Guideline 410 (Repeated Dose Dermal Toxicity: 21/28-Day Study) was performed on New Zealand White rabbits. The 28-day study was conducted to determine the repeated dose dermal toxicity of the read across substance, C16 TMAC, in New Zealand albino rabbits (both sexes).

The purity was not specified, and the study included a lower than recommended number of animals (i.e., 10/group rather than 20/group as per the guideline) and histopathology was performed only on limited organs. The test substance (0 and 10 mg test substance/kg bw/day) was applied to the shaved, intact skin of groups of five New Zealand albino rabbits/sex/group for 6.5 to 7 hours, 5 days/week for 4 weeks.

Dermal irritation readings were recorded daily. The animals were weighed weekly during the exposure period. Blood was collected for haematology measurements before initiation of dosing and prior to termination. Liver and kidneys weights were recorded at necropsy and limited histopathology was conducted. There were no systemic treatment-related effects on body weights, haematology, organ weights, gross necropsy findings or histopathology. Treated areas of the skin showed mild to marked acanthosis with active mitosis, hyperkeratosis, and partial to extensive necrosis of the epidermis and hair follicles, partly with encrustation and exudate. Based on the results of the read across study, the NOAEL for systemic effects of DQAC (by read across to Coco TMAC) can therefore be considered to be at 10 mg/kg bw/day (ECHA) [Kl Score = 2].

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on DQAC based on read-across from aluminium compounds are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on DQAC[1]

Test System[1]	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) (Bacterial Reverse Mutation Assay)	-	[1]	2	ECHA

*+, positive; -, negative
1 – based on read across to Coco TMAC.

In Vivo Studies

An OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) was performed. The study was conducted to determine the clastogenic potential of a surrogate test substance, Coco TMAC (active ingredient 33%). Based on the results of a dose range finding assay, a dosage of 468 mg/kg bw (in1% methyl cellulose) was administered by oral gavage to male and female mice. Following dosing, the animals were examined regularly for any clinical signs of reaction.

Bone morrow smears were obtained at three sampling times: 24, 48 or 72 hours after dosing. One smear from each animal was examined for the presence of micronuclei in 1,000 polychromatic erythrocytes. The ratio of polychromatic to normochromatic erythrocytes was assessed by examination of at least 1,000 erythrocytes from each animal. A vehicle control (1% methylcellulose) and a positive control with mitomycin C by intraperitoneal injection were included. At all sampling times, mice treated with the test substance showed no significant increase in the frequency of micronucleated polychromatic erythrocytes. There was no significant decrease in the ratio of polychromatic to normochromatic erythrocytes at any of the three kill times after treatment. The positive control compound, mitomycin C, produced large, highly significant increases in the frequency of micronucleated polychromatic erythrocytes together with large decreases in the ratio of polychromatic to normochromatic erythrocytes and increases in the frequency of micronucleated normochromatic erythrocytes. Under the conditions of the study, the test substance, and by association DQAC, was found to show no evidence of clastogenic potential in the bone marrow cells of mice (ECHA) [Kl. score = 1].

G. Carcinogenicity

Oral

No substance specific data exist.

Inhalation

No studies are available.

Dermal

No studies are available.

H. Reproductive Toxicity

Oral

See discussion on developmental toxicity below.

I. Developmental Toxicity

Dermal

There are no oral developmental toxicity studies of DQAC. However, there is a dermal developmental toxicity study (OECD Guideline 414 - Prenatal Developmental Toxicity Study) of QAS category using C16 TMAC as a surrogate.

The study was conducted in New Zealand White rabbits. Twenty mated female rabbits per group were exposed topically (daily for 2 hours) from Days 7 to 18 of gestation at concentrations of 0, 0.5, 1.0, or 2.0% (equivalent to 0, 10, 20 and 40 mg a.i./kg bw/day, respectively). The control group was treated with deionised water only. Clinical condition and reactions to treatment were recorded at least once daily. Body weights were recorded on Days 0, 3, 6, 9, 12, 15, 18, 21, 24, 27 and 29 of gestation. All surviving females were sacrificed on Day 29 of gestation and the foetuses were removed by caesarean section. At necropsy the females were examined macroscopically. Live foetuses were weighed, sexed and were examined for visceral and skeletal abnormalities. Two control animals, one intermediate and one high dose died during the study. Two of the rabbits that died were aborted prior to death (one control and one intermediate dose). Two additional abortions occurred, one each in the intermediate and high dose groups. Deaths or abortions were not considered to be related to the test substance.

No treatment-related maternal body weight or food intake effects were noted. The incidence of foetal malformations, as well as genetic and developmental variations in the treated groups, was comparable to that of the control group. No other treatment-related effects were noted. Under the study conditions, the NOAEL of DQAC for maternal as well as developmental toxicity is considered to be 40 mg/kg bw/d in rabbits [Kl. score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for DQAC follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The repeated dose NOAEL for DQAC has been determined to be 40.3 mg a.i./kg bw/day. Thus, the NOAEL of 40.3 mg/kgday will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 50/(10 x 10 x 1 x 1 x 1) = 40.3/100 = 0.4 mg/kgday.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (0.4 x 70 x 0.1)/2 = 1.4 mg/L

B. Cancer

No data on carcinogenicity was available. Therefore, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

DQAC does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

DQAC in acute aquatic toxicity studies is very toxic and in chronic aquatic toxicity studies is very toxic with long lasting effects.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on DQAC.

Table 3: Acute Aquatic Toxicity Studies on DQAC[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Salmo gairdneri	96-hour LC_{50}	3.2	2	ECHA
Daphnia magna	48-hour EC_{50}	0.09	2	ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50}	0.062	2	ECHA

1 – data abstracted from quaternary ammonium compounds, Coco TMAC

Chronic Studies

Fish:

A study was conducted to determine the long-term toxicity to Fathead minnow (Pimephales promelas) of the read-across substance, C12-16 ADBAC (purity: 30%). Mortality, hatchability and growth were evaluated. Fish eggs (80 per concentration) were exposed for 34 days to mean measured concentrations of 0, 32.3, 75.9, 134.2, 186.8, 273.2 and 488.7 mg a.i./L of the radiolabelled test substance. Analytical determination was performed and the sample concentrations were verified by liquid scintillation counting. After 7 days, surviving fry from two replicates were thinned to 10 animals per replicate for each exposure group (total of 20 animals per concentration) and exposed to the same concentrations for a 28-day post-hatch static renewal toxicity test. Observations of symptoms and mortality were conducted daily. Under the conditions of the study, the 34-day NOEC for hatchability was 0.274 mg/L, the 34-day NOEC and LC_{50} for survival were 0.032 and 0.094 mg a.i./L, respectively, and the 34-day NOEC for growth was > 0.032 mg/L. Based on the results of the read across study, the 34-day NOEC of 0.032 mg/L is considered relevant for DQAC (ECHA) [KI Score = 2).

Invertebrates:

A study was conducted to determine the long-term toxicity to aquatic invertebrates of the read across substance, C16-18 and C18-unsaturated TMAC as a suitable surrogate for DQAC according to OECD Guideline 211.

Daphnia magna were exposed to six concentrations of the test substance in a 21-day static-daily renewal test in three different water types (i.e., laboratory blended water, well water and river water).

Analytical determination of the test substance was performed. Measured concentrations (µg/L; values represent the geometric mean of the 0- and 24-hour concentration analyses) were southwest well water at 1.6, 3.1, 6.8, 14.6, 30.6 and 60.8 µg a.i./L and river water at 35.7, 53.4, 68.3, 99.1, 122.3 and 309.3 µg a.i./L. The test in blended water was discontinued after 14 days due to inadequate reproduction by control organisms.

Mortality was monitored daily and the number of young produced in each beaker was recorded. Test substance concentrations were verified by analysis and represent the geometric mean of the 0 and 24-hour concentration. Under the test conditions, the 21-day NOEC of the test substance to *Daphnia magna* was equivalent to 0.0068 mg/L and 0.099 mg/L in southwest well and river water, respectively. The NOEC for DQAC was considered equal to 0.0068 mg/L (ECHA) [KI Score = 2].

C. Terrestrial Toxicity

No data were available.

D. Calculation of PNEC

The PNEC calculations for DQAC follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. The lowest acute EC_{50} value was 0.062 mg/L for algae. Results from chronic toxicity studies are available for invertebrates (0.0068 mg/L) and fish (0.032 mg/L). On the basis that the data consists of short-term studies for three trophic levels and long-term results for two trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC value of 0.0068 mg/L. Therefore, the $PNEC_{water}$ is 0.00068 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Moreover, the substance is expected to substantially disassociate to partition to sediments. Nonetheless, a $PNEC_{sed}$ was calculated using the equilibrium partitioning methodology. The $PNEC_{sed}$ is 31.6 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed}\text{-water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (5.95 \times 10^4/1280) \times 1000 \times 0.00068$
$= 31.6$ mg/kg

Where:

$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$PNEC_{water}$ = 0.00068 mg/L
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 1.2 \times 10^5/1000 \times 1,280]$
$= 5.95 \times 10^4$ m^3/m^3

And:

Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 3.1 \times 10^6 \times 0.04$
$= 1.2 \times 10^5$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} was calculated as the midpoint of modelled K_{oc} range and determined to be 3.1×10^6 L/kg.
f_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 28.1 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (6x10^4/1500) \times 1000 \times 0.00068$
$= 28.1$ mg/kg

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$PNEC_{water}$ = 0.00068 mg/L

And:
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 3.1x10^6 \times 0.02$
$= 6.2x10^4$ m^3/m^3

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} was calculated as the midpoint of modelled K_{oc} range and determined to be $3.1x10^6$ L/kg.
f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

DQAC is an organic substance that has been determined to be readily biodegradable. Thus, it does not meet the screening criteria for persistence.

The estimated log K_{ow} is equal to 2.39. Based on the log K_{ow}, DQAC will not have a tendency to bioaccumulate (ECETOC, 2000). Therefore, DQAC does not meet the screening criterion for bioaccumulation.

The chronic toxicity data on DQAC shows a NOEC of <0.1 mg/L. Thus, DQAC meets the screening criteria for toxicity.

However, based on PBT assessment guidance cited above, the overall conclusions for DQAC is that it is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute toxicity - oral

Acute Tox. 3 H301: Toxic if swallowed.

Acute toxicity - dermal

Acute Tox. H311: Toxic in contact with skin.

Skin corrosion / irritation Skin Corr. 1C H314: Causes severe skin burns and eye damage.

Serious eye damage / eye irritation

B. Eye Damage 1 H318: Causes serious eye damage.

C. Labelling

Danger

D. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for DQAC.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be an effective type of air-purifying respirator: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking, and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

DQAC is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECETOC. (2000). Persistent organic pollutants. Response to UNEC/INC/ CEG-1. Annex 1, Document No. 41. Brussels, Belgium.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

DIETHYLENE GLYCOL

This dossier on diethylene glycol presents the most critical studies pertinent to the risk assessment of diethylene glycol in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

NICNAS has assessed diethylene glycol in an Inventory Multi-tiered Assessment and Prioritisation (IMAP) Tier 1 assessment and concluded that it poses no unreasonable risk to the environment[1] .

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-(2-hydroxyethoxy)ethan-1-ol

CAS RN: [redacted]

Molecular formula: $C_4H_{10}O_3$ or $(CH_2CH_2OH)_2O$

Molecular weight: 106.12 g/mol

Synonyms: Diethylene glycol; 2,2'-oxydiethanol; diglycol; bis(2-hydroxyethyl) ether; 2-hydroxyethyl ether; 2,2'-oxybisethanol; 2-(2-hydroxyethoxy)ethanol; ethanol, 2,2'-oxybis-; 2-(2-hydroxyethoxy)ethan-1-ol; glycol ethyl ether; ethylene diglycol

SMILES: C(COCCO)O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of diethylene glycol

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	A colourless viscous liquid	2	ECHA
Melting point	-6.5°C @ 101.3 kPa	2	ECHA
Boiling point	244.9°C @ 101.3 kPa	2	ECHA
Density	1,118 kg/m^3 @ 20°C	2	ECHA
Vapour pressure	0.008 hPa @ 25°	2	ECHA
Partition coefficient (log K_{ow})	-1.98 (calculated)	2	ECHA
Water solubility	1,000 g/L @ 20°C	2	ECHA
Flash point	138°C	2	ECHA
Auto flammability	372°C	2	ECHA

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]%2C+

Property	Value	Klimisch Score	Reference
Viscosity	30 mPa s (dynamic) @ 25°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

The substance is readily biodegradable, is unlikely to bioaccumulate, nor is it likely to adsorb or desorb to soil or sediment to a great extent.

B. Biodegradation

Diethylene glycol is readily biodegradable. In an OECD 301B test, there was 70-80% and 90-100% degradation after 28 days, as determined by CO_2 evolution and DOC removal respectively (ECHA) [Kl.score=2].

In an OECD 301A test, there was 90-100% degradation after 28 days, although the 10-day window was missed (ECHA) [Kl.score=1]. In a modified MITI I test (OECD 301C), there was up to 92% degradation after 28 days (ECHA) [Kl.score=2].

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

No experimental data are available for diethylene glycol. Using KOCWIN in EPI Suite™ (USEPA, 2017), the estimated K_{oc} value from the molecular connectivity index (MCI) and log K_{oc} are 1 and -0.08 L/kg, respectively (ECHA) [Kl Score = 2]. Based on these K_{oc} values, if released to soil, diethylene glycol is expected to not adsorb to soil and have a very high mobility. If released to water, based on the K_{oc} value and its water solubility, it is also not expected to adsorb to suspended solids and sediment.

D. Bioaccumulation

The calculated log K_{ow} for diethylene glycol is -1.98 (Verschueren, 1983). Diethylene glycol has low potential to bioaccumulate. In a 3-day bioaccumulation fish study with *Leuciscus idus melanotus*, the BCF was determined to be 100 (Freitag et al., 1985) [Kl score = 2].

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The substance exhibits low oral acute toxicity. It is not a significant skin or eye irritant, nor is it considered to be a skin sensitiser. No dermal or inhalation repeat dose studies were available but oral repeat does studies suggest moderate urinary dysfunction with oxalate formation in rats. The substance is not genotoxic, carcinogenic nor developmentally toxic.

B. Acute Toxicity

The oral LD_{50}'s in rats is 19,600 mg/kg (Lenk et al., 1989; ECHA) [Kl.score=2] and 16,500 mg/kg (Laug et al., 1939; ECHA) [Kl.score=2].

No deaths were reported in rats exposed to a saturated vapour for 6 hours (OECD, 2007) [Kl score = 2]. No deaths were also reported in male and female Aplk:APfSD (Wistar-derived) rats exposed to 5,080 mg/m^3 diethylene glycol aerosol (MMAD = 2.83 µm, GSD = 2.05) for 4 hours (OECD, 2007) [Kl.score=2].

The dermal LD_{50} in rabbits was reported to be 12,500 mg/kg (OECD, 2007) [Kl score = 2]. The dermal LD_{50} in rabbits was reported to be 13,300 mg/kg (ECHA) [Kl.score=4].

C. Irritation

When applied to the skin of rabbits for 24 hours under occlusive conditions, diethylene glycol was essentially non-irritating with a PII score of 0.04 (Guillot et al., 1982, ECHA) [Kl.score=2]. In a human repeated irritation patch test, diethylene glycol was minimally irritating to the skin (OECD, 2007) [Kl.score=2].

Diethylene glycol was not considered a skin irritant in an *in vitro* reconstructed human epidermis test (ECHA) [Kl.score=1].

Instillation of 0.1 mL diethylene glycol into the eyes of rabbits produced minor, transient irritation; no corneal lesions were observed (OECD, 2007) [Kl score = 2]. When instilled into the eyes of rabbits, the ocular irritancy was 11.67 based on a modified Kay Calandra scale of 0 to 110 (Guillot et al., 1982, ECHA) [Kl.score=2].

D. Sensitisation

Diethylene glycol was not a skin sensitiser to guinea pigs in a maximisation test (OECD, 2007; ECHA) [Kl.score=1]. Diethylene glycol was not a skin sensitiser in a human repeat irritation patch test (OECD, 2007; ECHA) [Kl.score=4].

E. Repeated Dose Toxicity

Oral

Male and female Wistar rats were given 0, 0.085, 0.17, 0.4 and 2.0% diethylene glycol in their diet for 225 days. The corresponding average daily intakes were 0, 51, 105, 234 and 1,194 mg/kg/day for males, and 0, 64, 126, 292 and 1462 mg/kg/day for females. In the 0.4% and 2% groups, there were oxalate crystalluria and mild defects of renal function (increased urine volume), as measured by concentration tests. The only finding in the 0.17% group was a 13.2% increase in urinary oxalate excretion in males; no effects were observed in the 0.085% group. The NOAEL and NOEL for this study was 0.17% (approximately 105 mg/kg/day) and 0.085% (approximately 51 mg/kg/day), respectively (ECHA) [Kl score = 2].

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on diethylene glycol are shown in Table 2.

Table 2: *In vitro* genotoxicity studies on diethylene glycol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	OECD (2007), ECHA
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	ECHA
Chromosomal aberration (CHO cells)	-	-	2	OECD (2007), ECHA
Sister chromatid exchange (CHO cells)	-	-	2	OECD (2007), ECHA

*+, positive; -, negative

In Vivo Studies

Micronuclei were not increased in the bone marrow of NMRI mice given a single intraperitoneal injection of 0, 500, 1,000 or 2,000 mg/kg diethylene glycol (ECHA) [KI score = 1].

G. Carcinogenicity

Oral

Male and female F344 rats were given 0, 1.25 or 2.5% diethylene glycol (97% purity) in their drinking water for two years. The daily intake was estimated to be 0, 1,210 and 2,630 mg/kg/day for males and 0, 1,160 and 2,550 mg/kg/day for females. Mortality was increased in the 2.5% males; drinking water consumption was increased in the 2.5% males and females. There were no significant differences in the incidence of tumours between treated and control animals (Hiasa et al., 1990; ECHA) [KI score = 2].

Male Osborne-Mendel rats were given 0, 1, 2 or 4% diethylene glycol in their feed for two years. During the first 26 weeks of the study, weight gain was significantly reduced at all dose levels. After the first year, the growth of rats fed the 4% diets was significantly reduced relative to the controls. There were no significant differences in food consumption at any treatment level. Mortality in rats fed the 4% diet was significantly higher than the control group; all animals were found dead before the end of the study (most dying during the last 12 months), compared with 7/12 control deaths. The incidence of bladder stones and bladder tumours increased with diethylene glycol exposure, with 0, 0, 6 and 5 bladder tumours observed in the control, 1, 2 and 4% DEG groups, respectively. Bladder stones were observed in 0, 2, 7 and 11 rats in the control, 1, 2 and 4% groups, respectively. In all but one case, bladder stones were present when bladder tumours were observed, suggesting that chronic irritation was a factor in the production of bladder tumours. The severity and incidence of signs of kidney damage (hydronephrosis, hydroureter, focal tubular atrophy, hyalin cast formation, glomerular atrophy) increased in a treatment-related manner, with gross kidney lesions observed in 1/12, 3/12 and 8/12 of the rats in the low-, mid- and high-dose groups, respectively. Liver damage observed histologically also increased with the level of diethylene glycol exposure. It

cannot be ruled out that this older study, which showed a significant increase in bladder stones and bladder tumours, may have been influenced by the presence of ethylene glycol as an impurity (Fitzhugh and Nelson, 1946) [KI score = 3].

Male and female rats were given 0, 2 or 4% diethylene glycol (containing 0.031% ethylene glycol) in their feed for two years. Rats were either just weaned, 2 months old or 12 months old at the initiation of the exposure. The dietary concentration of diethylene glycol was adjusted for the food consumption and body weight of each group. For 4% diet, the dosage in weanlings was 5,400 mg/kg/day for the first 28 days, approximately 3,700 mg/kg/day during the next two-week period, gradually declined to about 2,000 mg/kg/day over the next three months and remained at that level for the rest of the study. A study average of 2,300 mg/kg/day for weanlings fed 4% in the diet was calculated from data provided by the authors. None of the 12-month old male rats included in the study survived, whereas all the females in that group survived to termination of the study. Although weanling rats developed more bladder stones than the other groups, the difference was insignificant. The yearling rats developed their bladder stones somewhat earlier. The yearling rats in the 4% groups had the highest stone formation (8 out of 20 rats) and had the only bladder tumour in this dose group; the rat with the bladder tumour also had bladder stones. No bladder stones or tumours were observed in rats of any age in the control or in the 2% groups. The bladder tumours associated with the stones were considered to be the result of mechanical irritation, and diethylene glycol was not considered to be a primary rat carcinogen. The LOAEL and NOAEL for this study were dietary concentrations of 4% and 2% (approximately 2,300 and 1,200 mg/kg), respectively. It cannot be ruled out that this older study, which showed a significant increase in bladder stones and bladder tumours, may have been influenced by the presence of ethylene glycol as an impurity (Weil et al., 1965) [KI score = 3].

H. Reproductive Toxicity

In a two-generation study, male and female rats were dosed by oral gavage with 1 mL/100 g body weight of a 20% aqueous solution of diethylene glycol (approximately 2 mL/kg/day) for 8 weeks. A control group was given daily oral gavage doses of 1 mL/100 g body weight distilled water. Five of the treated females were dosed with diethylene glycol until parturition, the other five until the pups were weaned. Treatment of the P-generation with diethylene glycol for 12 weeks did not impair reproduction. The test animals and the controls became pregnant at almost the same time, litter size averaged 8-10 young, and the young exhibited similar, uniform development. Growth and onset of oestrus were not affected by treatment. The endocrine glands investigated showed no differences from the controls with regard to weight and fine structure. The receptiveness and litter size of the untreated F_1 generation were the same as those of the P-generation, and the F_2 generation was normal with regard to weight gain, onset of sexual maturity and weight as well as histology of the organs examined. The NOAEL for this study was calculated to be 2,200 mg/kg/day (Wegener, 1953; ECHA) [KI score = 2].

A continuous breeding protocol (RACB) was used to study the reproductive toxicity of diethylene glycol in mice. Male and female CD-1 mice were administered in their drinking water 0, 0.35, 1.75 or 3.5% diethylene glycol. Mice were exposed for 7 days prior to mating, 98 days during cohabitation of breeding pairs and a further 23 days after segregation of each pair.

Breeding study: The mice given 1.75% or 3.5% diethylene glycol consumed significantly more drinking water than did the controls. Based on water consumption and body weight data, the 0, 0.35, 1.75 and 3.5% dose groups were equivalent to average daily intakes of 0, 612, 3,062 or 6,125 mg/kg/day, respectively. There was no treatment-related mortality. In the 3.5% dose group, there was significant decreases in the number of litters produced per pair, number of live pups per litter,

proportion of pups born alive, and the absolute and adjusted pup weights. A significant dose-related trend for reduced absolute pup weights was also observed. Exposure to the 3.55 dose group also resulted in a significant increase in the cumulative days to litter and fewer breeding pairs were able to produce litters: 82%, 76%, and 59% of the pairs exposed to 3.5% in the diet produced the third, fourth or fifth litters, respectively, whereas 97-100% of the control group produced litters.

Crossover mating: The mating index and the fertility of the 3.5% dosed males or females were unaffected compared with the control mice. However, live pup weight was decreased in the highest-dose group, in which a 9% difference was observed for the offspring of the control males and the treated females. At the end of this test the parental animals (F0 of breeding study) were necropsied. For the male mice there were no significant differences in the body or organ weights, either absolute or adjusted for body weight. Analysis of the cauda epididymal contents of F0 males at necropsy indicated that there were no effects of diethylene glycol in the highest-doses group on the sperm concentration or the percentage of motile or abnormal sperm. The mean body weight of the 3.5% dosed F0 females was significantly decreased relative to the control females. The magnitude of this decrease was approximately 7%. These animals also exhibited significantly decreased absolute liver and pituitary weights, but their organ-to body weight ratios were not different from controls. There were no significant treatment-related gross or histopathological lesions in the organs examined from the male and female F0 mice (Williams et al., 1990) [Kl score = 2].

I. Developmental Toxicity

Time-pregnant CD rats were dosed by oral gavage with 0, 1,118, 4,472 or 8,944 mg/kg on gestational days 6-15. In the high-dose females, there were reduced body weight gain, reduced food consumption, increased water consumption, increased liver and kidney weights and histopathological changes in the kidney. The mid-dose females exhibited only increased water consumption. There were no treatment-related effects on corpora lutea or implantations. Foetal body weights were reduced in the high-dose animals. Total or individual external or visceral variations were similar between treated and control groups; however, individual skeletal variations were significantly increased in the mid- and high- dose groups. The pattern of delayed ossification was considered consistent with reduced foetal body weight. Malformations were similar between treated and control groups. The maternal and developmental NOELs for this study were 1,118 mg/kg/day (Ballantyne and Snellings, 2005) [Kl score = 2].

Time-pregnant CD-1 mice were dosed by oral gavage with 0, 559, 2,795 or 11,180 mg/kg/day during gestational days 6-15. In the high-dose females, there was mortality, clinical signs, and increased water consumption; only increased water consumption was observed in the mid-dose females. Foetal body weights were significantly reduced in the high-dose animals. There were no increases in variations or malformations between treated and control animals. The maternal and developmental NOELs were 559 and 2,795 mg/kg/day, respectively (Ballantyne and Snellings, 2005) [Kl score = 2].

Groups of 15 pregnant Himalayan rabbits were administered oral (gavage) doses of 0, 100, 400 or 1,000 mg/kg DEG on gestational days 7-19. No maternal toxicity was observed at any of the DEG doses administered. The foetal and litter incidence of skeletal, soft tissue and external anomalies or variations were comparable to those of the control and/or historical control groups. The authors set the maternal and developmental toxicity NOEL at greater than 1,000 mg/kg (Hellwig et al., 1995) [Kl score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for diethylene glycol follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The lowest NOAEL reported in the repeat dose toxicity study is 105 mg/kg/day based on the 225-day rat dietary study. Although, there was a 13.2% increase in oxalate excretion at this dose level, this was considered a biomarker and not an indicator of toxicity. At 0.4% (the LOAEL), there were oxalate crystalluria and mild defects of renal function (increased urine volume), as measured by concentration tests. The NOAEL of 105 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / ($UF_A \times UF_H \times UF_L \times UF_{Sub} \times U_{FD}$)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 105/(10 × 10 × 1 × 1 × 1) = 105/100 = 1.0 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) × (human weight) × (proportion of intake from water) / (volume of water consumed) × (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) × (human weight) × (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (1.05 × 70 × 0.1)/2 = 3.7 mg/L

B. Cancer

A two-year study of in rats showed no carcinogenic effects when diethylene glycol was administered in drinking water (Hiasa et al., 1990). In older studies, bladder tumours were observed in rats given diethylene glycol in feed; the tumours are considered to be the result of physical irritation from the bladder stones that also were noted in the same animals (Fitzhugh & Nelson, 1946; Weil et al.,

1965). It cannot be ruled out that these older studies, which showed a significant increase in bladder stones and bladder tumours, may have been influenced by the presence of ethylene glycol as an impurity. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Diethylene glycol does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The substance is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on diethylene glycol.

Table 3: Acute aquatic toxicity studies on diethylene glycol

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Pimephales promelas	96-hour LC_{50}	75,200	2	ECHA
Oncorhynchus mykiss	96-hour LC_5	66,000	2	ECHA
Daphnia magna	24-hour EC_{50}	>10,000	2	ECHA
Daphnia magna	48-hour EC_{50}	65,980	2	ECHA
Daphnia magna	48-hour EC_{50}	62,630	2	ECHA

Chronic Studies

In ECHA, the aquatic toxicity of the 'ethylene glycol and higher glycols' (mono-, di-, tri-, tetra- and pentaethylene glycol) is evaluated in a read-across approach. Data on all three trophic levels (fish, *daphnia*, algae) are available to describe the aquatic toxicity of the glycol read-across members. Due to the fact, that not for each single substance data for all required endpoints are available, a weight of evidence approach is used, which includes additional information based on QSAR calculation with the EpiWin-Program ECOSAR v1.11. Measured data, as well as estimated data, demonstrate that all glycols within the read-across are not harmful to aquatic organisms. No adverse effects on aquatic organisms occurred up to concentrations above 100 mg/L (ECHA).

No data for fish was available for diethylene glycol. However, chronic studies for fish are available for ethylene glycol (CAS No.: [redacted] The 7-day NOEC for the fathead minnow (*Pimephales promelas*) was determined to be 15,380 mg/L based on the weight of the test organisms (ECHA) [Kl.score=2].

No data for invertebrates was available for diethylene glycol. However, three studies were conducted with Dapnids (*Ceriodaphnia dubia* or *Daphnia magna*) for ethylene glycol (CAS-No.: [redacted] or triethylene glycol (CAS No.: [redacted] The study with ethylene glycol was conducted according to USEPA guideline 600/4-89/001 with *Ceriodaphnia dubia* as test species. The 7-day NOEC for reproduction was determined to be 8,590 mg/L ethylene glycol (nominal). Two studies measured the effect of triethylene glycol on the reproduction of *Daphnia magna*. One study was conducted according to the national standard ASTM (E 47.01, Draft No. 1, "Draft proposed standard practice for conducting renewal life cycle toxicity tests with Daphnia magna"). In this test the Daphnids were exposed to triethylene glycol for 21 days. Based on reproduction the reported NOEC is > 15,000 mg/L triethylene glycol (nominal) (ECHA) [Kl Score = 2].

Data for algae was available for diethylene glycol. The 8-day TGK to algae *Scenedesmus quadricauda* was determined to be 2,700 mg/L for diethylene glycol (ECHA) [Kl score = 2].

From the QSAR calculations it can be expected for diethylene glycol that algae are slightly more sensitive (ChV = 1,200 mg/L) than invertebrates (ChV = 1,891 mg/L) or fishes (ChV = 7,694 mg/L) (ECHA) [Kl Score = 2].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for diethylene glycol follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C50 values are available for fish (66,000 mg/L), and Daphnia (> 10,000 mg/L). Results from a chronic algae study is available on diethylene glycol (2,700 mg/L). On the basis that the data consists of short-term results from two trophic levels and a long-term result from one trophic level, an assessment factor of 100 has been applied to the lowest reported value, which is the chronic value for algae. The $PNEC_{water}$ is 27 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 17.3 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.89/1280) \times 1000 \times 27$
$= 17.3$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.04/1000 \times 2400]$
$= 0.89\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg)

BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$

$= 1 \times 0.04$

$= 0.04$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for diethylene glycol based on the molecular connectivity index (MCI) is 1 L/kg (USEPA, 2017).

F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.36 mg/kg soil dry weight.

The calculations are as follows:

$PNECsoil = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$

$= (0.02/1500) \times 1000 \times 27$

$= 0.36$ mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)

BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$

$= 1 \times 0.02$

$= 0.02$ m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for diethylene glycol based on the molecular connectivity index (MCI) is 1 L/kg (USEPA, 2017).

f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (IChEMS, 2022; ECHA, 2023).

Diethylene glycol has been shown to be readily biodegradable; thus, it does not meet the screening criteria for persistence.

The calculated log K_{ow} is -1.98, and the experimental BCF is 100. Thus, diethylene glycol does not meet the screening criteria for bioaccumulation.

The lowest chronic toxicity value for diethylene glycol is > 0.1 mg/L. Thus, diethylene glycol does not meet the criteria for toxicity.

Therefore, diethylene glycol is not a PBT substance.

IX. CLASSIFICATION AND LABELING (ABSTRACTED FROM PUBCHEM)

A. Classification

Irritant

B. Labelling

Danger

C. Pictogram

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS) (ABSTRACTED FROM PUBCHEM)

A. First Aid

Eye Contact

First check the victim for contact lenses and remove if present. Flush victim's eyes with water or normal saline solution for 20 to 30 minutes while simultaneously calling a hospital or poison control centre. Do not put any ointments, oils or medication in the victim's eyes without specific instructions from a physician. IMMEDIATELY transport the victim after flushing eyes to a hospital even if no symptoms (such as redness or irritation) develop.\

Skin Contact

IMMEDIATELY flood affected skin with water while removing and isolating all contaminated clothing. Gently wash all affected skin areas thoroughly with soap and water. If symptoms such as redness or irritation develop, IMMEDIATELY call a physician and be prepared to transport the victim to a hospital for treatment.

Inhalation

IMMEDIATELY leave the contaminated area; take deep breaths of fresh air. If symptoms (such as wheezing, coughing, shortness of breath, or burning in the mouth, throat, or chest) develop, call a physician and be prepared to transport the victim to a hospital. Provide proper respiratory protection to rescuers entering an unknown atmosphere. Whenever possible, Self-Contained Breathing Apparatus (SCBA) should be used; if not available, use a level of protection greater than or equal to that advised under Protective Clothing.

Ingestion

DO NOT INDUCE VOMITING. If the victim is conscious and not convulsing, give 1 or 2 glasses of water to dilute the chemical and IMMEDIATELY call a hospital or poison control centre. Be prepared to transport the victim to a hospital if advised by a physician. If the victim is convulsing or unconscious,

do not give anything by mouth, ensure that the victim's airway is open and lay the victim on his/her side with the head lower than the body. DO NOT INDUCE VOMITING. IMMEDIATELY transport the victim to a hospital.

Notes to Physician (abstracted from PubChem)

The patient should be resuscitated with isotonic crystalloidal fluids, and acidosis should be corrected. Early treatment with a competitive ADH inhibitor (e.g., 4-methylpyrazole or ethanol), hemodialysis and supportive care offer the best hope for patient recovery.

Ensure that adequate decontamination has been carried out. If patient is not breathing, start artificial respiration, preferably with a demand-valve resuscitator, bag-valve-mask device or pocket mask, as trained. Perform CPR as necessary. Immediately flush contaminated eyes with gently flowing water. Do not induce vomiting. If vomiting occurs, lean patient forward or place on left side (head-down position, if possible) to maintain an open airway and prevent aspiration. Keep patient quiet and maintain normal body temperature.

Basic treatment: Establish a patent airway (oropharyngeal or nasopharyngeal airway, if needed). Suction if necessary. Watch for signs of respiratory insufficiency and assist ventilations if necessary. Administer oxygen by nonrebreather mask at 10 to 15 L/min. Monitor for pulmonary oedema and treat if necessary. Monitor for shock and treat if necessary. Anticipate seizures and treat if necessary. For eye contamination, flush eyes immediately with water. Irrigate each eye continuously with 0.9% saline (NS) during transport. Do not use emetics. For ingestion, rinse mouth and administer 5 mL/kg up to 200 mL of water for dilution if the patient can swallow, has a strong gag reflex and does not drool. Administer activated charcoal.

Advanced treatment: Consider orotracheal or nasotracheal intubation for airway control in the patient who is unconscious, has severe pulmonary oedema or is in severe respiratory distress. Positive-pressure ventilation techniques with a bag-valve-mask device may be beneficial. Consider drug therapy for pulmonary oedema. Monitor cardiac rhythm and treat arrhythmias if necessary. Start IV administration of D5W /SRP: "To keep open", minimal flow rate. Use 0.9% saline (NS) lactated Ringer's (LR) if signs of hypovolemia are present. For hypotension with signs of hypovolemia, administer fluid cautiously. Consider vasopressors if patient is hypotensive with a normal fluid volume. Watch for signs of fluid overload. Treat seizures with diazepam or lorazepam. Use proparacaine hydrochloride to assist eye irrigation.

Medical Conditions Aggravated by Exposure

Respiratory conditions (asthma, etc.)

Emergency Personnel Protection

Wear a self-contained breathing apparatus in pressure-demand, MSHA/NIOSH (approved or equivalent), and full protective gear. During a fire, irritating and highly toxic gases may be generated by thermal decomposition or combustion. Use water spray to keep fire-exposed containers cool.

B. Fire Fighting Information (abstracted from Comet Chemical SDS 2013)

Extinguishing Media

Use powder, alcohol-resistant foam, water spray, carbon dioxide.

Specific Exposure Hazards

Combustible when exposed to heat or flame; can react with oxidising materials.

Special Protective Equipment for Firefighters

Firefighters must use standard protective equipment including flame retardant coat, helmet with face shield, gloves, rubber boots, and in enclosed spaces, SCBA. Firefighters should wear proper protective equipment and self-contained breathing apparatus with full face piece operated in positive pressure mode. Move containers from fire area if safe to do so. Water spray may be useful in cooling equipment exposed to heat and flame.

C. Accidental Release Measures

Personal Precautions

Restrict access to area until completion of clean-up. Ensure clean-up is conducted by trained personnel only. All persons dealing with clean-up should wear the appropriate protective equipment including self-contained breathing apparatus.

Environmental Precautions

Ventilate the area. Stop spill or leak at source if safely possible. Dike for water control. Contain and absorb spilled liquid with non-combustible, inert absorbent material (e.g., sand), then place absorbent material into a container for later disposal.

Steps to be Taken if Material is Released or Spilled

Absorb spill with inert material (e.g., vermiculite, sand or earth), then place in suitable container. Clean up spills immediately, observing precautions in the Protective Equipment section. Provide ventilation.

D. Storage and Handling

General Handling

Wear protective gloves/clothing and eye/face protection. Use with adequate ventilation. Do not ingest. Do not breathe mist or vapour. Avoid contact with eyes, skin and clothing. Wash with soap and water after handling. Keep away from extreme heat and flame. Keep away from acids and other incompatibles. Keep containers tightly closed when not in use.

Other Handling Precautions

Wash thoroughly after handling. Use with adequate ventilation. Avoid breathing vapours from heated material. Avoid contact with eyes, skin and clothing. Keep container tightly closed. Wash clothing before reuse. Avoid breathing spray or mist.

Storage

Store in a cool, dry, well-ventilated area. Store away from areas of excessive heat, open flames, sparks and other possible sources of ignition. Keep away from incompatibles. Storage area should be

clearly identified, clear of obstruction and accessible only to trained and authorised personnel. Inspect periodically for damage or leaks.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for diethylene glycol.

Engineering Controls

Good general ventilation should be used. Localised ventilation should be used where vapours, mist or aerosols may be generated.

Personal Protection Equipment

Respiratory Protection: Wear an approved respirator with dust/mist pre-filters if any exposure to dust or mist is possible.

Hand Protection: Wear appropriate chemical-resistant gloves.

Skin Protection: Wear protective clothing to minimise skin contact.

Eye Protection: Wear chemical splash goggles and face shield.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Diethylene glycol is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

Australian Drinking Water Guidelines [ADWG]. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council. Updated September 2022. https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines

Ballantyne, B., & Snellings, W.M. (2005). Developmental toxicity study with diethylene glycol by gavage to CD rats and CD-1 mice. *Food Chem. Toxicol., 43*, 1637–1646.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra. https://www.dcceew.gov.au/water/coal-and-coal-seam-gas/national-assessment-chemicals/consultation-risk-assessment-guidance-manual

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. ECHA REACH database: http://echa.euroa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2023). Chapter R.11: vPvB assessment. In *Guidance on information requirements and chemical safety assessment*. Version 4.0. https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Fitzhugh, O.G., & Nelson, A. (1946). Comparison of the chronic toxicity of triethylene glycol with that of diethylene glycol. *J. Ind. Hyg. Tox., 25*, 40–43.

Freitag, D., Ballhorn, L., Geyer, H., & Korte, F. (1985). Environmental hazard profile of organic chemicals. An experimental method for the assessment of the behavior of organic chemicals in the ecosphere by means of simple laboratory tests with 14C labeled chemicals. *Chemosphere, 14*, 1589–1616.

Guillot, J. P., Martini, M. C., Giauffret, J. Y., Gonnet, J. F., & Guyot, J. Y. (1982). Safety evaluation of some humectants and moisturizers used in cosmetic formulations. *Int. J. Cosmetic Sci., 4*, 67–80.

Hellwig, J., Klimisch, H. J., & Jäckh, R. (1995). Investigation of the prenatal toxicity of orally administered diethylene glycol in rabbits. *Fundam. Appl. Toxicol., 28*, 27–33.

Hiasa, Y., Kitahori, Y., Morimoto, J., Konishi, W., & Ohshima, M. (1990). Absence of carcinogenic or promoting effects of diethylene glycol on renal tumourigenesis in rats. *J. Toxicol. Pathol., 3*, 97–104.

Industrial Chemicals Environmental Management Standard [IChEMS]. (2022). Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals. https://www.dcceew.gov.au/sites/default/files/documents/australian-pbt-criteria.pdf

Klimisch, H. J., Andreae, M., & Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol., 25*, 1–5.

Laug, E., Calvery, H. O., Morris, H. J., & Woodward, G. (1939). The toxicology of some glycols and derivatives. *J. Ind. Hyg. Toxicol., 21*, 173–201.

Lenk, W., Löhr, D., & Sonnenbichler, J. (1989). Pharmacokinetics and biotransformation of diethylene glycol and ethylene glycol in the rat. *Xenobiotica, 19*, 961–979.

Organisation for Economic Co-operation and Development [OECD]. (2007). SIDS Dossier on the HPV Chemical Diethylene Glycol (CAS No. [redacted]).

Pubchem. https://pubchem.ncbi.nlm.nih.gov/compound/DI_Hydroxyethyl_ether#section=InChI Accessed January 2022.

U.S. Environmental Protection Agency [EPA]. (2017). EPISuite™ v. 4.11. Office of Pollution Prevention and Toxics and Syracuse Research Corporation. https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

Verschueren, K. (1983). *Handbook of environmental data on organic chemicals*. 2nd Edition. Van Nostrand: 1,310

Wegener, H. (1953). The reproductive capacity of rats after the action of diethylene glycol. *Arch. Exper. Path. u. Pharmakol., 220*, 414–417.

Weil, C. S., Carpenter, C. and Smyth, H. F. (1965). Urinary bladder response to diethylene glycol. *Arch. Environ. Health, 77*, 569–581.

Williams, J., Reel, J., George, J., and Lamb, IV, J. (1990). Reproductive effects of diethylene glycol and diethylene glycol monoethyl ether in Swiss CD-1 mice assessed by a continuous breeding protocol. *Fundam. App. Toxicol., 74*, 622–635.

DIUTAN (CAS NO. [redacted]
DIUTAN GUM (CAS NO. [redacted]

This dossier on diutan and diutan gum presents the most critical studies pertinent to the risk assessment of these substances in its use in coal seam gas extraction activities. Diutan (CAS No. [redacted] can also be referred to as diutan gum (CAS No. [redacted] This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained for diutan gum from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): (2R,3R,4S,5S)-2,3,4,5-tetrahydroxyhexanal (2R,3S,4R,5R)-2,3,4,5,6-pentahydroxyhexanal (2S,3S,4S,5R)-2,3,4,5-tetrahydroxy-6-oxohexanoic acid acetic acid calcium dihydride hydrate magnesium dihydride potassium hydride sodium hydride

CAS RN: [redacted]

Molecular formula: $C_{20}H_{46}CaKMgNaO_{21}$

Molecular weight: Not applicable as substance is a UVCB.

Synonyms: Diutan gum; S 657; S-657 Gum; GEOVIS XT; GEOVIS XTL; KELCO-CRETE DG

Chemical Name (IUPAC): D-glucuronic acid, polymer with 6-deoxy L-mannose and D-glucose, acetate, Ca Mg K Na salt

SMILES: Not applicable

CAS RN: [redacted]

Molecular formula: $(C_6H_{12}O_6.\ C_6H_{12}O_5.\ C_6H_{10}O_7)x.C_2H_4O_2.\ xCa.xK.xMg.xNa$

Molecular weight: Not applicable as substance is a UVCB.

Synonyms: Diutan; D-Glucurono-D-gluco-6-deoxy-L-mannan, acetate, calcium magnesium potassium sodium salt.

SMILES: Not applicable

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1:Overview of the Physico-chemical Properties of Diutan Gum (CAS No. [redacted]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Off-white solid powder	1	ECHA
Melting Point	No melting point was determined. Test substance decomposed at >175°C.	2	ECHA

Property	Value	Klimisch score	Reference
Boiling Point	No data	-	-
Density	1430 Kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	~0.1 kPa @ 25°C	-	NICNAS, 2010
Partition Coefficient (log K_{ow})	-3.56 @ 20°C	2	ECHA
Water Solubility	40 g/L @ 20°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Diutan/diutan gum is readily biodegradable, is not expected to bioaccumulate, and has a low potential to adsorb to soil.

B. Biodegradation

A GLP-compliant study conducted in accordance with the OECD guideline was available. The test material (diutan gum) attained 95% degradation after 28 days and satisfied the 10-day window validation criterion, whereby 60% degradation must be attained within 10 days of the degradation rate exceeding 10%. The test material can therefore be considered to be readily biodegradable under strict terms and conditions of the OECD guideline 301B [KI Score = 1] (ECHA).

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

No experimental data are available for diutan/diutan gum. Based on the low experimentally determined log K_{ow} (-3.56) value, the substance has a low potential to adsorb to soil and will be highly mobile in soil.

D. Bioaccumulation

No experimental data are available for diutan/diutan gum. Based on the low log K_{ow} (-3.56), the potential for bioaccumulation is low.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Diutan has low acute toxicity by the oral and inhalation routes. It is not irritating to the skin and eyes and is not a skin sensitiser. No systemic effects were seen in repeated dose oral toxicity studies in rodents. The substance is not carcinogenic or genotoxic. No reproductive or developmental toxic effects were identified.

B. Toxicokinetics

A screening level toxicokinetic study was performed using male and female Sprague-Dawley rats. Radio labeled Gellan Gum mixed with corn oil was administered via gavage. Specific activity of formulated dose was checked by sample combustion and scintillation counting.

The study was performed in three stages. Stage 1 involved CO_2 collection from 1 male, 1 female. Stage 2 consisted of faeces collection and tissue distribution analysis from 4 males, 4 females. One female was excluded from the study due to abnormal findings at necropsy suggestive of maldosing. Stage 3 involved collection of blood levels from 4 males, 4 females.

Stage 1 results showed less than 0.55% of dosed radioactivity was expired in the form of $^{14}CO_2$. Stage 2 results indicated that females excreted 1.85 +/- 0.55% of dosed ^{14}C in urine, 86.79 +/- 3.08% in faeces. The Stage 3 results recorded low levels of radioactivity in the blood: mean peak blood radioactivity in both sexes was close to 3,000 DPM/mL blood, occurring around 5.5 hours post-dosing in males, 5.25 hours post-dosing in females.

The low levels of radioactivity recorded in tissues and blood samples and the high levels of radioactivity excretion in faeces suggest very little absorption from the gastrointestinal tract occurred following oral dosing. No potential for bioaccumulation was indicated by the study findings. Based on the close chemical similarity between gellan gum and diutan, it is reasonable to predict that a comparable pattern of non-absorption would be seen if diutan were to be similarly tested (ECHA) [Kl. score = 2].

C. Acute Toxicity

Oral

An acute Limit Test, in accord with USEPA test guideline USEPA 40 CFR 163.81-1 was performed. Six male and six female Sprague Dawley rats were administered 5,000 mg/kg in corn oil via gavage. Rats were weighed prior to dosing, then 7 and 14 days later and were observed 1, 2 and 4 hours post-dose, then daily up to 14 days after dosing. Gross pathology observations were made at necropsy. No evidence of toxicity was seen. A no observed effect level (NOEL) of 5,000 mg/kg was determined (ECHA) [Kl Score = 2].

Inhalation

A standard acute inhalation study was performed according to method USEPA 40 CFR 163.81-3. Five male and five female Sprague-Dawley rats were exposed whole body to substance dust for 4 hours in air at a measured test atmosphere of 0.316 mg/L (mean across sampling times). Particle size distribution (measured using Andersen plate sampler during the final 15 minutes of exposure): 100% < 10 microns, 28.9% ≤ 1.1 microns.

After 14 days post-exposure observation, all rats were terminated. Following gross pathology observations at necropsy, lungs and tracheal structures were collected into buffered formalin. Lungs and tracheal samples were also collected from a sample of rats taken at the time of animal delivery (pre-study) and from a supplementary non-exposed control group (additional to the air-exposed controls) at study termination.

No evidence of toxicity was seen after 4-hour exposure of rats to the test substance in a dust atmosphere (nominally 4.9 mg/L and measured at 0.316 mg/L). The difference between nominal and

measured concentrations may indicate that close to a maximum practicable concentration was achieved (ECHA) [KI Score = 2].

Dermal

No studies were available.

D. Irritation

Skin

A non-guideline dermal irritation study was performed on Dunkin-Hartley guinea pigs. The substance was applied in arachis oil at four different concentrations at separate sites on the clipped flanks: 5, 10, 25, 50%. Application sites were occluded for 24 hours and observed 1, 24 and 48 hours after dressing removal. Erythema and oedema scores at 50% concentration did not indicate test substance was irritating (ECHA) [KI Score = 2].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) was performed on albino rabbits. 100 mg substance was applied to one eye while the contralateral eye served as a control. Ocular reactions were observed at 24, 48 and 72 hours post-treatment. Cornea opacity, iris and conjunctivae scores were not indicative of irritation. Therefore, diutan is considered not irritating (ECHA) [KI Score = 2].

E. Sensitisation

An OECD Guideline 406 (Skin Sensitisation) was performed on male Dunkin-Hartley guinea pigs. Intradermal induction was performed with 5% w/w in dried arachis oil. Topical (epicutaneous) induction was performed with 50% w/w in dried arachis oil. Topical challenge was performed with 25% and 10%, w/w in dried arachis oil. The test material produced a 0% (0/10) sensitisation rate and was determined as a non-sensitiser to guinea pig skin under the conditions of the test (ECHA) [KI score = 1].

F. Repeated Dose Toxicity

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) was performed using the structural analogue K9A50: gellan gum (EC 275-117-5). Male and female Sprague-Dawley rats (20 each) were dosed at 3%, 4.5% and 6% nominally in the diet.

Mortality was checked twice daily; clinical signs were recorded once daily. Bodyweights and food consumption recorded pre-treatment and weekly during treatment. Opthalmoscopy checks (control and high-dose groups) were performed pre-treatment and prior to termination.

Haematology, blood chemistry and urinalysis were checked pre-treatment (health screen satellite group) and (together with faecal moisture content) in weeks 6 and 12 of treatment period (10 or 12 rats/sex/group).

Rats fed 6% gellan gum in diet for 13 weeks (corresponding to daily intakes ranging from 2.95 to 7.26 g/kg/day) showed no evidence of treatment related toxicity. It is reasonable to predict that a similar

pattern of low subchronic toxicity would be seen if diutan were to be tested in the same way (ECHA) [KI score = 2].

Inhalation

No adequate studies for human health risk assessment are available.

Dermal

No adequate studies for human health risk assessment are available.

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on diutan are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Diutan[1]

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-*	-*	2	ECHA

1 – Surrogate substance (Biozon - EC 476-190-8) evaluated
*+, positive; -, negative.

Diutan is not expected to induce mutations in the mouse lymphoma thymidine kinase locus assay using the cell line L5178Y in the absence and presence of metabolic activation.

In Vivo Studies

An OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) was performed using the surrogate, Gellan gum (EC 275-117-5). Oral administration of gellan gum at up to 2 x 450 mg/kg produced no detectable increase in the frequency of micronucleated bone marrow cells in treated mice. It is predictable that diutan would give a similarly negative result if tested in the same manner.

H. Carcinogenicity

A mouse carcinogenicity study of the close chemical analogue gellan gum found that inclusion in diet at up to 3% had no significant toxic effect and did not increase the incidence of neoplastic (malignant or benign) or non-neoplastic lesions. The overall mean achieved intake of gellan gum at the highest tested level was calculated to be 4.9 g/kg/day (males) or 6.2 g/kg/day (females).

The open literature also includes a short summary of a rat carcinogenicity study which supports the conclusion that gellan gum is non-carcinogenic. The Joint FAO/WHO Expert Committee on Food Additives(1990) cites a carcinogenicity study in which rats first exposed to gellan gum in utero were then fed gellan gum at up to 5% in the diet for approximately 104 weeks.

No neoplastic or non-neoplastic changes were associated with gellan gum exposure.

The close chemical analogue gellan gum showed no evidence of carcinogenicity in rodent carcinogenicity studies. It is predictable that diutan would give a similarly negative result if tested in the same manner (ECHA) [KI Score = 2].

I. Reproductive Toxicity

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed. Male and female Sprague Dawley rats were dosed with the diutan surrogate Gellan gum (EC 275-117-5) at 2.5, 3.8 and 5% in the diet per study guidelines.

Details on results (P0): No toxicologically significant effects were noted for general toxicity or reproductive function. No evidence of parental toxicity and no effect on reproductive performance seen at highest treatment level (5%).

Details on results (F1 and F2): No evidence of toxicity, no effect on reproductive performance and no effect on development of F1 rats seen at the highest treatment level (5%). No effects on F2 development seen at the highest treatment level (5%).

Administration of gellan gum to P and F1 rats at levels up to 5% in diet resulted in achieved adult intakes within the range 2.8-6.5 g/kg (males), 3.0-4.2 g/kg (females). No evidence of toxicity or adverse effects on reproductive performance or development was seen. Given the close similarity between gellan gum and diutan, it is reasonable to predict that diutan would show a similar lack of toxicity to reproduction (ECHA) [KI Score = 2].

J. Developmental Toxicity

An OECD Guideline 414 (Prenatal Developmental Toxicity Study) was performed with the diutan surrogate gellan gum (EC 275-117-5). The substance was administered via diet and restricted to the period of organogenesis (gestation dates 6-15). Females mated with one male of proven fertility; mating confirmed by presence of spermatozoa in vaginal lavage (designated gestation day 0).

Maternal Toxicity

No evidence of maternal toxicity was seen. Minor gross pathology findings at termination were considered unrelated to treatment. Pregnancy rate was at least 88% in all groups.

Embryotoxic / Teratogenic effects

The incidence of major malformations in test groups was no different from that among controls. Subcutaneous oedema and accompanying skin changes in 7 foetuses from one litter made the occurrence of minor external/visceral anomalies significantly raised at 3.8%. Cases of reduced ossification at 2.5% (mainly ribs) and 3.8% (mainly parietal bones) made group values significantly different from controls. Common skeletal (sternebrae 1-4) variants were significantly increased at 3.8%. None of the above minor anomalies/variants were seen in rats of the highest treatment group (5% in diet); it was concluded that they were not related to gellan gum exposure. It is reasonable to predict that diutan would show a similar lack of toxicity to development (ECHA) [KI score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for diutan follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

An OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) was performed using the structural analogue K9A50: gellan gum (EC 275-117-5). The lowest NOAEL of 2.95 g/kg/day (i.e., 2,950 mg/kg bw/day) from this study was used to determine the oral RfD and drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 2950/(10 x 10 x 1 x 1 x 1) = 2950/100 = 29.5 mg/kg bw/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (29.5 x 70 x 0.1)/2 = 103.25 mg/L

B. Cancer

The single carcinogenicity study by the oral route indicates diutan is not a carcinogen. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Diutan does not exhibit the following physico-chemical properties:

- Flammability
- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Diutan is of low acute toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 presents the results of acute aquatic toxicity studies on diutan/diutan gum.

Table 3: Acute Aquatic Toxicity Studies on Diutan Gum

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss (Rainbow Trout)	96-hour LC_{50}	100	1	ECHA
Daphnia magna	48-hour LC_{50}	> 100	1	ECHA
*Desmodesmus subspicatus (*previous name*: Scenedesmus subspicatus)*	72-hour EC_{50}	> 100 (growth rate and biomass)	1	ECHA

Chronic Studies

No data is available.

C. Terrestrial Toxicity

No data is available.

D. Calculation of PNEC

PNEC calculations for diutan acid follow the methodology discussed in DEWHA (2009).

PNEC water

Acute experimental results are available for three trophic levels (Table 3). Acute E(L)C50 values are available for fish (100 mg/L), invertebrates (> 100 mg/L) and algae (>100 mg/L). On the basis that the data consists of short-term results from three trophic levels, an assessment factor of 100 has been applied to the lowest reported value. The $PNEC_{water}$ for diutan is 1.0 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Moreover, the low K_{ow} indicates that diutan is not expected to partition to sediments. Therefore, a the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.63 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
= (0.809/1280) x 1000 x 1.0
= 0.63 mg/kg sediment wet wt.

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
= 0.8 + [(0.2 x 0.035/1000 x 2400]
= 0.82 m^3/m^3

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
= 0.865 x 0.04
= 0.035 L/Kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for calculated from EPI Suite™ using the MCI is 0.865 L/kg .
F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Moreover, diutan is biodegradable and due to its low K_{ow}, is not expected to partition to soil. Therefore, a $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.01 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
= (0.02/1500) x 1000 x 1.0
= 0.01 mg/kg soil dry weight

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
= 0.865 x 0.02
= 0.017 m^3/m^3

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for calculated from EPI Suite™ using the MCI is 0.865 L/kg.
F_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Diutan/diutan gum is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Bioaccumulation of diutan/diutan gam is not expected to occur based on it log K_{ow} value of -3.56. Thus, diutan/diutan gum does not meet the screening criteria for bioaccumulation.

No chronic toxicity data is available. The E(L)C_{50} values from the acute aquatic toxicity studies on diutan/diutan gum are > 1 mg/L. Thus, diutan/diutan gum does not meet the criteria for toxicity.

Therefore, diutan/diutan gum is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not Classified

B. Labelling

Not Classified

C. Pictogram

Not Classified

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. If eye irritation persists, seek medical attention, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

No significant adverse health effects are expected to develop if only small amounts (less than a mouthful) are swallowed. Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas. Not expected to cause an environmental hazard as a result of its intended use, disposal or incineration.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage and Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid dust formation. Avoid conditions that generate airborne dust in handling, transfer and cleanup. Keep away from heat, flame sparks and other ignition sources. Static charge may cause flash fire. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Store in a roofed and well-ventilated area. Keep container tightly closed. Store away from heat and light.

E. Exposure Controls/Personal Protection

Occupational Exposure Standards

If handling generates dust levels which cause irritation, or results in personal exposure exceeding the Occupational Exposure Standard (OES) of 10 mg/m^3 (8 hr time-weighted average [TWA] reference period) for total inhalable dust, then suitable approved dust respirator should be used.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Although this product does not present a significant skin concern, minimise skin contamination by following good industrial practice. Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: This product does not cause significant eye irritation or eye toxicity requiring special protection. Where there is significant potential for eye contact, wear chemical goggles and have eye flushing equipment available.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, as well as before eating, smoking and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Diutan is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DoEE. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Joint FAO/WHO Expert Committee on Food Additives (1990). Toxicology Monograph 724 (Food Additive Series 28.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

NICNAS. (2010). National Industrial Chemicals Notification and Assessment Scheme. Full Public Report. Diutan Gum https://www.industrialchemicals.gov.au/sites/default/files/SN20%20Public%20Report%20PDF.pdf

ETHYLENE GLYCOL

This dossier on ethylene glycol presents the most critical studies pertinent to the risk assessment of ethylene glycol in its use in hydraulic fracturing fluids. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Ethane-1,2-diol

CAS RN: [redacted]

Molecular formula: $C_2H_6O_2$ ($HOCH_2CH_2OH$)

Molecular weight: 62.07 g/mol

Synonyms: Ethylene glycol; ethane-1,2-diol; 1,2-ethanediol, 2-hydroxyethanol; monoethylene glycol; MEG; glycol alcohol; EG

SMILES: C(CO)O

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Ethylene Glycol

Property	Value	Klimisch score	Reference
Physical state at 20oC and 101.3 kPa	Colourless and odourless syrupy liquid	2	ECHA
Melting Point	-13°C @ 101.3 kPa	2	ECHA
Boiling Point	197.4°C @ 101.3 kPa	2	ECHA
Density	1110 kg/m3@ 20°C	2	ECHA
Vapour Pressure	12.3 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-1.36 (calculated) @ 25°C	2	ECHA
Water Solubility	1000 g/L @ 20°C	2	ECHA
Flash Point	111°C	2	ECHA
Auto flammability	398°C	2	ECHA
Viscosity	16.1 mPa s @ 25°C	2	ECHA
Henry's Law Constant	0.133 @ 25°C (QSAR)	2	ECHA

III. ENVIRONMENTAL FATE SUMMARY

A. Summary

Ethylene glycol is readily biodegradable, and it is not expected to bioaccumulate. Ethylene glycol has low potential to adsorb to soil and sediment.

B. Biodegradation

Ethylene glycol was readily biodegradable in an OECD 301A test. After 10 days, degradation was 90-100% (ECHA) [Kl. score = 1]. There was 97% degradation after 20 days in a BOD test; and 96% degradation after 28 days in an OECD 301D test (Waggy et al., 1994; OECD, 2004a,b) [Kl. score = 2]. If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

The aerobic degradation of ethylene glycol was measured from grab river water samples at 4, 8 and 20°C. At 20°C, ethylene glycol was completely degraded in three days in all river waters tested; at 8°C, degradation was complete within 14 days. Degradation at 4°C was substantially slower, with degradation of < 20% after 14 days in river samples with limited suspended matter and a starting concentration of 10 mg/L (Evans and David, 1974).

C. Environmental Distribution

No experimental data are available for ethylene glycol. Using KOCWIN in EPISuite™ (USEPA, 2017), the estimated K_{oc} values from the molecular connectivity index (MCI) and from the log K_{ow} are 1 and 0.2239 L/kg, respectively.

Based upon these K_{oc} values, if released to soil, ethylene glycol is expected to have low potential for adsorption and a high potential for mobility. If released to water, based on its K_{oc} and high water solubility values, ethylene glycol is likely to remain in water and not adsorb to sediment. From the water surface, the substance will not evaporate into the atmosphere (ECHA).

D. Bioaccumulation

The calculated log K_{ow} for ethylene glycol is -1.36 (ECHA). The BCF for ethylene glycol in golden ide (*Leuciscus idus melanotus*) after three days of exposure was determined to be 10 (Freitag *et al.*, 1985). Bioaccumulation is not to be expected.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Following acute ingestion of ethylene glycol, the critical effects in humans in three subsequent stages are central nervous system toxicity, metabolic acidosis and kidney toxicity. The lethal effects of ethylene glycol in human adults occur at oral doses of $\geq$ 1,600 mg/kg. Ethylene glycol is not a skin irritant or a skin sensitiser in laboratory animals. In humans, ethylene glycol may cause skin irritation; there is also a low potential for skin sensitisation. It is not an eye irritant. The kidney is the primary target organ from repeated exposures. The proposed mode-of-action (MOA) for the kidney damage involves the formation of a precipitate or crystals from the ethylene glycol metabolite oxalic acid with calcium in the urine. Ethylene glycol is not genotoxic or carcinogenic to rodents. Ethylene glycol did not affect fertility in animal studies, but it did cause developmental effects. In rodents, the

developmental effects caused by oral doses of ethylene glycol include teratogenic effects (craniofacial and axial-skeletal malformations and variations). In contrast, no developmental toxicity was seen in rabbit studies. The relevant metabolite for the developmental toxicity seen in rodent, but not rabbit, studies appears to be glycolic acid. This metabolite can be reached at higher concentrations in rats than in rabbits. Based on a physiologically-based pharmacokinetic (PBPK) model for ethylene glycol, humans are unlikely to achieve blood levels of glycolic acid necessary for developmental toxicity.

B. Metabolism

Ethylene glycol is almost completely absorbed in laboratory animals by the oral route (OECD, 2004a; Frantz et al., 1996a). A range of 1-51% of ethylene glycol is absorbed by the dermal route based on *in vivo* studies in rodents (Frantz et al., 1996a,b).

The main metabolic pathway for metabolism of ethylene glycol is oxidation via alcohol dehydrogenases and aldehyde dehydrogenases. The main metabolites of ethylene glycol are carbon dioxide, oxalic acid and glycolic acid (OECD, 2004a).

The relevant metabolite for the repeated dose toxicity studies is oxalic acid, which is slowly transported from the liver to the kidneys, where is forms calcium-oxalate crystals (Corley et al., 2005a).

The relevant metabolite for the developmental toxicity seen in rodent, but not rabbit, studies appears to be glycolic acid. This metabolite can be reached at higher concentrations in rats than in rabbits (Carney et al., 1998).

A physiologically-based pharmacokinetic (PBPK) model has been developed for ethylene glycol. When internal dose surrogates were compared in rats and humans over a wide range of exposures, it has been concluded that humans are unlikely to achieve blood levels of glycolic acid necessary for developmental toxicity (Corley et al., 2005b).

C. Acute Toxicity

The oral LD_{50} in rats was reported to be 7,712 mg/kg (ECHA) [Kl. score = 2]. The 6-hour inhalation LC_{50} value for male and female rats was > 2.5 mg/L (Tyl et al., 1995a) [Kl. score = 2]. The dermal LD_{50} for male and female mice is > 3,500 mg/kg (Tyl et al., 1995b) [Kl. score = 2].

Following acute ingestion of ethylene glycol, the critical effects in humans in three subsequent stages are central nervous system toxicity, metabolic acidosis and kidney toxicity (ECHA). The lethal effects of ethylene glycol in human adults occur at oral doses of $\geq$ 1,600 mg/kg (Hess et al., 2004).

D. Irritation

Application of 0.5 mL of ethylene glycol to the skin of rabbits for 23 hours under occlusive conditions was not irritating (Guillot et al., 1982) [Kl. score = 2].

In a Human Repeated Insult Patch Test (HRIPT), ethylene glycol was applied to the skin for 24 hours under occlusive or semi-occlusive conditions for nine times during the induction phase. The induction phase was followed by a rest period of two weeks, followed by a 24-hour challenge on the sixth week of the study. Erythema was seen in a small proportion of the 401 subjects that completed the study. Under the conditions of the study, three subjects had reactions on challenge that were

indicative of possible irritation and/or low-level sensitisation. These three subjects were re-challenged under occlusive or semi-occlusive conditions one or two weeks later. Re-challenge testing was negative for one subject, but the other two subjects were judged to have irritant reactions to ethylene glycol since their reactions were similar or lesser compared to the skin responses observed during the induction period, and the skin reactions were not greater over time after the challenge or re-challenge (ECHA).

Instillation of 0.05 mL of ethylene glycol into the eyes of rabbits was not irritating (ECHA) [Kl. score = 2].

E. Sensitisation

Ethylene glycol was not a skin sensitiser to guinea pigs in a Magnusson and Kligman test (Kurihara et al., 1996) [Kl. score = 2]. In a HRIPT, ethylene glycol was considered to have a low potential for dermal sensitisation in humans (ECHA).

F. Repeated Dose Toxicity

Oral

Male and female Fischer 344 rats were given in their feed 0, 0.32, 0.63, 1.25, 2.5 or 5% ethylene glycol for 13 weeks. Mortality was seen in the 5% males, but not in females. Mean weight gain was significantly decreased in the 2.5 and 5% males; there was no significant differences in female rats. Feed consumption was similar across all groups. A significant increase was seen in the left kidney weight in the 2.5 and 5% dose groups (both sexes); this was not seen in the right kidneys. Mean thymus ratio to terminal body weight was significantly decreased in the 5% males. Serum urea nitrogen levels were significantly increased in the 2.5 and 5% males, and significantly increased in the ≥ 0.32% females. Creatinine levels were decreased in the 0.32% groups and significantly increased in the 2.5 and 5% groups. The 2.5% and 5% male rats had kidneys that were rough, granular and/or pitted appearances. The 5% females showed nephrosis, and the 5% males had clusters of crystals in the brain. The NOAEL for this study is 1.25%, which was estimated to be 600 to 1,000 mg/kg/day (Melnick, 1984) [Kl. score = 2]

Male and female Sprague Dawley rats were given in their drinking water ethylene glycol for 90 days. The concentrations for females were 0, 0.5, 1.0, 2.0 or 4.0% (0, 597, 1,145, 3,087 or 5,744 mg/kg/day). The concentrations for males were 0, 0.25, 0.5, 1.0 or 2.0% (0, 205, 407, 947 or 3,134 mg/kg/day). In the 4% groups, there was mortality and decreased body weights (males only). Significant organ weights were noted only in males. Kidney weights were significantly increased in the 1% and 2% males; heart, liver and lung were significantly decreased in the 2% males. The 4% males also had a significant increase in the brain and gonads relative to body weights. Leukocyte levels were significantly decreased in the 0.5, 2 and 4% females, but not in males. Significant differences were noted in LDH, creatinine, ALT, calcium and glucose in the 1% males; and phosphorus, BUN and creatinine in the 2% males. There were significant increases in phosphorus in the 1% females and glucose in the 0.5 and 4% females. Kidney lesions were seen in the ≥ 2% females and in the ≥ 1% males, with the lesions more prominent in males than in females. The kidney changes consisted of tubular dilation, tubular degeneration, acute inflammation, birefringent crystals in tubules and pelvic epithelium. The NOAEL for this study is 407 mg/kg/day for males. The LOAEL for females is 597 mg/kg/day; a NOAEL was not established (Robinson et al., 1990) [Kl. score = 2]

Male and female B6C3F$_1$ mice were given in their feed 0, 0.32, 0.63, 1.25, 2.5 or 5.0% ethylene glycol for 13 weeks. There was no mortality and no treatment-related effect on mean weight gain and feed consumption. Organ/body weight ratios were similar across all groups. Serum urea nitrogen and creatinine levels were unaffected. Kidney effects were seen in the male, but not female, mice. Kidney lesions were observed in half of the 5% male mice and one mouse in the 2.5% dose level. Lesions were tubular dilation, cytoplasmic vacuolisation and regenerative hyperplasia of tubular cells. There was no evidence of crystal formation in the tubules. These changes were focal, randomly distributed and of minimal to mild severity. Hyaline degenerative of the liver was present in the centrilobular hepatocytes in all of the 2.5% and 5% males. These cells showed cytoplasmic accumulations of non bifringent, eosinophilic (hyaline), globular or crystalline material which resembled erythrocytes in size, shape and tinctorial properties. The NOAEL for this study is 1.25%, which was estimated to be 600 to 1,000 mg/kg/day (Melnick, 1984) [Kl. score = 2].

Male Fischer 344 and Wistar rats were given in their feed 0, 150, 500 or 1,000 mg/kg ethylene glycol for 16 weeks. At 1000 mg/kg, the following effects were seen: mortality in Wistar strain (2/10) with prior clinical observations of emaciation and dermal atonia and macroscopic findings of changes in kidneys (pale, calculi) and small seminal vesicles in these animals; mean body weight losses, lower mean body weights and mean cumulative body weight changes in Wistar strain (weeks 2 – 16); lower mean food consumption in Wistar strain; higher mean water consumption in both F344 and Wistar strains; lower mean specific gravity and higher mean total urine volume in both F344 and Wistar strains; macroscopic findings of pale kidneys, presence of calculi, rough surface and dilated pelvis; higher mean absolute and relative kidney weights in both F344 and Wistar strains; renal macroscopic findings of crystal nephropathy in Wistar and F-344 rats, with more severe nephropathy in Wistar strain than in the F344 strain. At 500 mg/kg, the following effects were seen: lower mean body weights (study weeks 3, 6-8 and 10-12) and mean cumulative body weight changes in the Wistar strain throughout the study with slightly lower mean food consumption throughout the study; higher mean water consumption in the Wistar strain; lower mean urine specific gravity and higher mean total urine volume in the Wistar strain; macroscopic findings in the Wistar strain consisting of predominantly pale kidneys, presence of calculi, rough surface and dilated pelvis; higher mean absolute and relative kidney weight in the Wistar strain; renal macroscopic findings of crystal nephropathy in Wistar and F-344 strains, with more severe nephropathy in the Wistar strain than in the F344 strain. The NOAEL in both the F344 and Wistar rats is 150 mg/kg/day (Cruzan et al., 2004) [Kl. score = 2].

Male Wistar rats were given in their feed 0, 50, 150, 300 or 400 mg/kg ethylene glycol for 12 months. There was mortality in the 300 and 400 mg/kg dose groups (5/20 and 4/20, respectively); the remaining 400 mg/kg animals were euthanised early (Day 203) due to excessive weight loss. The 300 mg/kg animals had increased water consumption and urine volume with decreased specific gravity, most likely due to osmotic diuresis. Calculi (calcium oxalate crystals) were found in the bladder and kidney pelvis in the ≥ 300 mg/kg animals. The ≥ 300 mg/kg rats that died prematurely had transitional cell hyperplasia with inflammation and haemorrhage of the bladder wall. Crystal nephropathy (basophilic foci, tubule or pelvic dilatation, birefringent crystals in the pelvic fornix, or transitional cell hyperplasia) was seen in all of the 400 mg/kg and most of the 300 mg/kg rats. These effects were not seen in the 50 or 150 mg/kg rats. Kidney oxalate levels, the metabolite responsible for the kidney toxicity, was not increased in the 50 and 150 mg/kg animals compared to the controls. The NOAEL for this study is 150 mg/kg/day (Corley et al., 2005) [Kl. score = 1].

Male and female Sprague-Dawley rats were given in their feed 0, 0.1, 0.2, 0.5, 1.0 or 4.0% ethylene glycol for two years. There was significant reduction in growth in the 4% males after week 16, and in the 1% males after week 70. The 4% females did not gain any weight past the first year of the study. Water consumption was double that of the controls in the 4% males that initiated soon after the

start of the study. The 1% males had significant increases in water consumption after 6 months and some increase was observed in the 0.5% males. Females only showed increased water consumption in the 4% group. There was 100% mortality in the 1 and 4% males, while mortality of additional dose levels were below that of the controls. There was 100% mortality in the 4% females, while the 1% females were similar to the controls; the 0.1, 0.2 and 0.5% females were increased compared to the controls. Since the 1 and 4% males and the 4% females all died before the study termination date, there are no data for these groups on terminal organ weight. For males, the terminal organ weights were decreased in all dose levels compared to the controls. For females, the organ weights were similar to the controls. The 1 and 4% males and females had kidneys with stones and crystals. The NOAEL for this study is 0.2% (data was insufficient to calculate the dose) (Blood, 1965) [Kl. score = 2].

Male and female Fischer 344 rats were given in their feed 0, 40, 200 or 1,000 mg/kg ethylene glycol for 24 months. There were numerous adverse effects in the 1,000 mg/kg males and, to a lesser degree, in the 1,000 mg/kg females. The most remarkable effect was the production of urinary calculi in the kidneys, ureters and urinary bladders of the 1,000 mg/kg males, along with the presence of high levels of calcium oxalate in the urine. Increased incidences of tubular cell hyperplasia, tubular dilation, peritubular nephritis and focal granulomatous nephritis occurred in the 1,000 mg/kg males. Other significant findings in these males were markedly lower body weight gain, increased absolute and relative kidney weights, decreased absolute and relative liver weights, various hematopoietic changes and increased water consumption (likely a result of impaired kidney function). Histopathological changes in the 1,000 mg/kg males were mineralisation of the heart, lungs, stomach and vas deferens being the most noteworthy. The various adverse effects in these males resulted in reduced survival; there was increased mortality which became apparent by 8 months, with all males in this group died by month 16. Although calcium oxalate crystals were found in the urine of the 1,000 mg/kg females, no urinary calculi were seen. Absolute and relative kidney weights were increased in these rats. The most significant histopathologic finding in the 1,000 mg/kg females was fatty metamorphosis of the liver. There were transient changes in organ weights, erythroid parameters, water consumption rates and urine specific gravity in the 200 and 40 mg/kg rats; these effects were considered to be statistical artifacts attributable to chance. Focal soft mineralisation was observed in certain organs of the 200 and 40 mg/kg rats, which were considered to be the result of altered calcium metabolism associated with ingestion of ethylene glycol. The NOAEL for this study is considered to be 200 mg/kg/day (DePass et al., 1986a; ECHA) [Kl. score = 2].

Male and female B6C3F_1 mice were given in their feed 0, 6,250 ppm (males only), 12,500 and 25,000 ppm (males and females) or 50,000 ppm (females only) for 103 weeks. These concentrations are approximately equivalent to 0, 1,500, 3,000, 6,000 or 12,000 mg/kg/day. Survival, mean body weights and feed consumption was similar across all groups. There were no treatment-related clinical signs of toxicity. Liver lesions (males only) and arterial hyperplasia (females only) were observed at 12,500 ppm, but no adverse effects were observed at 6,250 ppm. The NOAEL for this study is 6,250 ppm in males, which corresponds to 1,500 mg/kg/day (NTP, 1993) [Kl. score = 2].

Inhalation

No studies are available.

Dermal

No studies in rodents or rabbits are available.

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on ethylene glycol are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Ethylene Glycol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	1	ECHA
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	+/-	-	2	McGregor et al. (1991)
Chromosomal aberration (CHO cells)	-	-	2	ECHA

*+, positive; -, negative

In Vivo Studies

A dominant lethal study was conducted in F344 rats given 0, 40, 200 or 1,000 mg/kg/day ethylene glycol in feed. There were slight increases in the dominant lethal mutation index in the high-dose and low-dose groups; these appear to be random occurrences and were not considered to be treatment-related. It was concluded that ethylene glycol was not genotoxic in this study (DePass et al., 1986b) [Kl. score = 2].

H. Carcinogenicity

Oral

Male and female Fischer 344 rats were given in their feed 0, 40, 200 or 1,000 mg/kg ethylene glycol for 24 months. There was increased mortality in the 1,000 mg/kg males, starting at 8 months and resulting in all males in this group dead by 16 months. Survival for the 1,000 mg/kg females and the 200 and 40 mg/kg males and females were similar to the controls. The incidence of mononuclear cell leukemia was statistically significantly higher in the 200 mg/kg males compared to the male controls, but not when compared to the pooled controls (males and females). Evaluation of the data by the method of Thomas et al. (2007), however, showed no treatment-related effect. It was concluded that ethylene glycol was not carcinogenic to rats in this study (DePass et al., 1986) [Kl. score = 2].

Male and female B6C3F_1 mice were given in their feed 0, 6,250 ppm (males only), 12,500 and 25,000 ppm (males and females) or 50,000 ppm (females only) ethylene glycol. These concentrations were approximately equivalent to 0, 1,500, 3,000, 6,000 or 12,000 mg/kg/day. Body weights, survival and incidence of tumours were similar between treated and control mice (NTP, 1993) [Kl. score = 2].

Inhalation

No studies are available.

Dermal

No studies are available.

I. Reproductive Toxicity

Ethylene glycol was assessed in a Reproductive Assessment by Continuous Breeding (RACB) protocol (Chapin and Sloane, 1997). The parental mice were administered ethylene glycol via drinking water during pre-mating exposure, cohabitation, pregnancy and lactation. The F_1 generation received prenatal exposure via maternal exposure during gestation, with the exposure continuing during lactation, weaning and mating of F_1 animals and production of an F_2 litter. The doses were 0, 0.25, 0.5 or 1% ethylene glycol, which corresponded to approximately 0, 410, 840 or 1,640 mg/kg/day. No adverse effects were noted in the parental animals at doses up to 1%. There was a small, but statistically significant, effects on the numbers of litters per fertile pair, the number of live pups per litter, and live pup weight in the 1% dose group. Neither the 0.25 nor 0.5% dose groups were significantly affected. The number of live pups per litter was lower in the treated groups, but differences were not statistically significant. Unusual facial features (i.e., shorter snout and wide-set eye) and skeletal defects (shortened frontal, nasal and parietal bones; fused ribs abnormally shaped or missing sternebrae, abnormally shaped vertebrae; and twisting of the spine) were noted on some of the offspring of the treated mice in the 1% group, but not in the controls. The parental NOAEL is 1% (approximately 1,640 mg/kg/day), and the NOAEL for reproductive toxicity is 0.5% (approximately 840 mg/kg/day (Lamb et al., 1985) [Kl. score = 2].

In a three-generation reproductive toxicity study, Fischer 344 rats were given in their diet 0, 40, 200 or 1,000 mg/kg/day ethylene glycol. There were no treatment-related effects on clinical signs of toxicity or survival in the parental animals. There were no significant effects on fertility index, gestation index, gestation survival for all three generations. Mean pup weights for each of the hree generations were similar between treated and control animals. The NOAEL for parental and reproductive toxicity is 1,000 mg/kg/day (DePass et al., 1986b) [Kl. score = 2].

J. Developmental Toxicity

Pregnant Sprague-Dawley rats were dosed by oral gavage with 0, 50, 150, 500, 1,000 or 2,500 mg/kg ethylene glycol during gestational days (GD) 6-15. Maternal toxicity was observed in the 2,500 mg/kg group and consisted of significantly decreased body weights, increased water consumption, decreased uterine weights, increased kidney weights and increased relative liver weights. At 500 mg/kg, there were developmental effects, which included reduced foetal body weights, extra or missing ribs, missing arches and poor ossification in thoracic and lumbar centra. In the 2,500 mg/kg group, in addition to skeletal malformations, there was gastroschisis, hydrocephaly, lateral ventricle dilated (tissue depressed), umbilical hernia and atelectasis. The NOAELs for maternal and developmental toxicity are 1,000 and 500 mg/kg/day, respectively (Neeper-Bradley et al., 1995) [Kl. score = 2].

Pregnant CD rats were dosed by oral gavage with 0, 1,250 2,500 or 5,000 mg/kg ethylene glycol during GD 6-15. In the ≥ 2,500 mg/kg groups, the dams had increased relative kidney weights, decreased gravid uterine weight and increased water consumption. Maternal body weight gain was significantly decreased in the 1,250 mg/kg group. Live litter size was significantly decreased in the 5,000 mg/kg group and foetal body weights were decreased in the 1,250 and 5,000 mg/kg groups. Litters with malformed foetuses were observed in the ≥ 1,250 mg/kg groups. The LOAELs for maternal and developmental toxicity are 1,250 mg/kg/day; NOAELs were not established (Price et al., 1985) [Kl. score = 2].

Pregnant Fischer 344 rats were given by oral gavage 0, 40, 200 or 1,000 mg/kg ethylene glycol during GD 6-15. No maternal toxicity was observed at any dose level. There were no significant effects on preimplantation loss, foetal length, foetal weight, total implantations or litter size. There was an increased incidence of skeletal alterations in the 1,000 mg/kg group, which consisted of poorly ossified and unossified vertebral centra. No significant increases in the incidence of major malformations were observed. The NOAELs for maternal and developmental toxicity are 1,000 and 400 mg/kg/day (Maronpot et al., 1983) [Kl. score = 2].

Pregnant CD-1 mice were dosed by oral gavage with 0, 50, 150, 500 or 1,500 mg/kg ethylene glycol during gestational days (GD) 6 to 15. There was no maternal toxicity. At 1,500 mg/kg, there were reduced foetal body weights, fused ribs and arches, poor ossification in thoracic and lumbar centra and increased occurrence of an extra 14^{th} rib. At 500 mg/kg, there was slight reductions in foetal body weight and increased incidences of extra ribs. The NOAELs for maternal and developmental toxicity were 1,500 and 150 mg/kg/day, respectively (Neeper-Bradley et al., 1995) [Kl. score = 2].

Pregnant CD-1 mice were dosed by oral gavage with 0, 750, 1,500 or 3,000 mg/kg ethylene glycol during GD 6 to 15. There was a significant decrease in maternal gain, gravid uterine weights and liver weights in the 1,500 mg/kg group. A decreased number of implantation sites per litter was observed in the 1,500 mg/kg group. Significant decrease in liver litter size was observed in the 3,000 mg/kg group and decreased foetal body weights were seen at ≥ 750 mg/kg. Litters with a significant increase in malformed foetuses were observed in the ≥ 750 mg/kg groups. There was a significant dose-related increase in post-implantation loss per litter, though there were no significant pairwise comparisons. The NOAEL for maternal toxicity is 750 mg/kg/day. The LOAEL for developmental toxicity is 750 mg/kg/day; the NOAEL was not established (Price et al., 1985) [Kl. score = 2].

In a short-term reproductive and developmental toxicity screen test, male and female Swiss Crl:CD-1 mice were allowed to mate over a three-day period. The males were dosed by oral gavage from study Day 3 to study Day 20. The Group A females were exposed throughout the 21-day test period; the Group B females were exposed during GD 8-14. The doses were 0, 250, 700 or 2,500 mg/kg ethylene glycol. The Group A females were sacrificed after 19 days of treatment, and the Group B females were allowed to litter and rear to postnatal day (PND) 4. There was no maternal or paternal toxicity. The 2,500 mg/kg females in Group A had significantly fewer liver implants and more dead implants. The 2,500 mg/kg in Group B had significantly lower total litter weights on PND 1 and 4. The NOAELs for parental and developmental toxicity are 2,500 and 700 mg/kg/day (Harris et al., 1992) [Kl. score = 2].

In a Chernoff/Kavlock assay, pregnant CD-1 mice were dosed by oral gavage with 0 or 11,090 mg/kg ethylene glycol during GD 7-14. The females were allowed to litter and rear to PND 3. Ten percent of the maternal animals died. The number of surviving pups per litter (40% survived), birth weight and pup weight gain were reduced. The LOAELs for maternal and developmental toxicity are 11,090 mg/kg; NOAELs were not established (Schuler et al., 1984; Hardin et al., 1987) [Kl. score = 2].

Pregnant female New Zealand White rabbits were dosed by oral gavage with 0, 100, 500, 1,000 or 2,000 mg/kg ethylene glycol on GD 6 to 19. At 2,000 mg/kg, eight of the 17 does (42.1%) died. Maternal body weights and body weight gain were similar across all groups. There was no developmental toxicity. The NOAEL for maternal toxicity is 1,000 mg/kg/day. The NOAEL for developmental toxicity is 2,000 mg/kg/day, the highest dose tested (ECHA) [Kl. score = 2].

Pregnant female CD rats were dosed by oral gavage with 0, 250, 1,250 or 2,250 mg/kg ethylene glycol on GD 6 to 20. At 2,250 mg/kg, maternal body weight, body weight gain, kidney weight and postpartum uterine weight were significantly reduced. At 1,250 mg/kg, the gestational period was

lengthened and maternal kidney histopathological effects were noted. Developmental toxicity was noted in the 2,250 mg/kg group and included reduced pup weight, reduced viability and increased malformations (primarily hydrocephaly and abnormalities of the axial skeleton). No developmental toxicity was seen in the 1,250 mg/kg group. The NOAEL for maternal and developmental toxicity is 250 mg/kg/day (ECHA) [Kl. score = 2].

Inhalation

Pregnant female CD rats were exposed by inhalation (whole-body) to 0, 150, 1,000 or 2,500 mg/m^3 ethylene glycol aerosol 6 hours/day on gestational days 6 to 15. There was no treatment-related mortality; a dose-related increased in clinical signs (red fur discoloration on the head and neck) was noted, which was considered to be a non-specific indication of stress. Body weights and body weight gain were unaffected by treatment. There was some evidence of treatment-related reductions in ossification of the foetal skeleton at 1,000 and 2,500 mg/m^3 (considered as fetotoxicity). The NOAECs from inhalation exposure cannot be determined due to confounding oral exposure during whole-body exposure. However, there was no maternal or embryotoxicity at 150 mg/m^3 and no teratogenicity at any aerosol concentration tested (Tyl et al., 1995a) [Kl. score = 2].

Pregnant female CD-1 mice were exposed by inhalation (whole-body) to 0, 150, 1,000 or 2,500 mg/m^3 ethylene glycol aerosol 6 hours/day on gestational days 6 to 15. Reduced maternal body weight was observed in the 2,500 mg/m^3 group on GD 12,15 and 18 and in the 1,000 mg/m^3 group on GD 18. Reduced maternal weight gain was also seen during GD 6-12, 6-15 and GD 6-18 for the ≥ 1000 mg/m^3 groups and for GD 5-18 for the 2,500 mg/m^3 group. Terminal body weights were reduced in the ≥ 1,000 mg/m^3 groups. Gravid uterine weight was also reduced in the ≥ 1,000 mg/m^3 groups, so that body weight corrected for gravid uterine weight was unaffected. The number of viable implantations per litter was reduced at 2,500 mg/m^3. The number of non-viable implantations per litter was elevated at ≥ 1,000 mg/m^3 because of a significant increase in late resorptions at 1,000 mg/m^3, and a significant increase in late resorptions and in dead foetuses at 2,500 mg/m^3. The number of early resorptions at 2,500 mg/m^3 was also elevated but not statistically. foetal body weights per litter (male, female and total) were reduced at ≥ 1,000 mg/m^3. There was a significant increase in the incidence of a number of external, visceral and skeletal malformation, as well as skeletal variations, at ≥ 1,000 mg/m^3. There was no observable maternal or developmental toxicity at 150 mg/m^3. However, a NOAEC cannot be determined because of the amount of ethylene glycol that may have been ingested from the presence of ethylene glycol on the fur (Tyl et al., 1995a) [Kl. score = 2].

Pregnant female CD-1 mice were exposed by inhalation (nose-only) to 0, 500, 1,000 or 2,500 mg/m^3. The study also included a group exposed to 2,100 mg/m^3 (not discussed here). Reduced maternal body weight gain were seen in the 2,500 mg/m^3 for GD 9-12, 12-15, 6-15 and 0-18. Absolute kidney weights were increased in the ≥ 1,000 mg/m^3 groups. foetal body weights per litter were significantly reduced for the 2,500 mg/m^3. In the 2,500 mg/m^3, there was a significant increase in one skeletal malformation (fusion of the ribs) and an increased incidence of skeletal variations. No other teratogenic effects were observed. The NOECs for maternal and developmental toxicity are 500 and 1,000 mg/m^3, respectively (Tyl et al., 1995c) [Kl. score = 2].

Dermal

Pregnant CD-1 mice were administered by dermal applications of 0, 400, 1,677 or 3,549 mg/kg ethylene glycol 6 hours/day on GD 6-15. There was minimal, if any, treatment-related maternal toxicity. Copora lutea, total implants, percentage of live foetuses per litter, foetal body weights and incidence of external or visceral malformations were unaffected by treatment. There was, however,

a significant increase in two skeletal variations in the 3,549 mg/kg group. The NOAELs for maternal and developmental toxicity were considered to be 3,549 mg/kg/day (Tyl et al., 1995b) [Kl. score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for ethylene glycol follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The NOAEL from a 24-month rat dietary study was reported to be 200 mg/kg/day based on kidney lesions in male F344 rats at 1,000 mg/kg/day (DePass et al., 1986b). A subsequent 12-month rat dietary study using male Wistar rats reported a NOAEL of 150 mg/kg/day also based on kidney toxicity at 300 mg/kg/day and higher (Corley et al., 2008). The Wistar rat strain was shown to be more sensitive (approximately three-fold) to the kidney toxicity of ethylene glycol than F344 rats (Cruzan et al., 2004). The NOAEL of 150 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Snellings et al. (2013) derived an oral reference dose for ethylene glycol using benchmark dose modelling, with toxicokinetic (PBPK modelling) and toxicodynamic data. The human equivalent dose ($[BMDL_{05}]_{HED}$) was calculated to be 150 mg/kg/day.

Oral RfD = $[BMDL_{05}]_{HED}$ / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 1
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 150/(1 x 10 x 1 x 1 x 1) = 150/10 = 15 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (15 x 70 x 0.1)/2 = 53 mg/L

B. Cancer

Ethylene glycol was not carcinogenic to rats and mice in two-year dietary studies. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Ethylene glycol does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Ethylene glycol is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on ethylene glycol.

Table 3: Acute Aquatic Toxicity Studies on Ethylene Glycol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	>72,860	1	Pillard (1995)
Oncorhynchus mykiss	96-hour LC_{50}	22,810 24,591	2	OECD (2004a,b)
Daphnia magna	48-hour EC_{50}	>100	1	ECHA
Daphnia magna	48-hour EC_{50}	46,300	2	Gersich et al. (1986)
Ceriodaphnia dubia-affinis	48-hour EC_{50}	25,800 (20°C) 10,000 (24°C)	2	Cowgill et al. (1985)
Daphnia magna	48-hour EC_{50}	46,300 (20°C) 51,000 (24°C)	2	Cowgill et al. (1985)
Selenastrum capricornutum	96-hour IC_{50} NOEC	10,940 10,000	2	Pillard and DuFresne (1999)

Chronic Studies

Table 4 lists the results of chronic aquatic toxicity studies conducted on ethylene glycol.

Table 4: Chronic Aquatic Toxicity Studies on Ethylene Glycol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	7-day NOEC	15,380	2	Pillard (1995)
Ceriodaphnia dubia	7-day NOEC (reproduction)	8,590	2	Pillard (1995)
Pseudokirchneriella subcapitata	72-hr NOEC	>100 *	2	ECHA

*Read-across to pentaethylene glycol (CAS No. [redacted]

C. Terrestrial Toxicity

No guideline studies have been conducted on ethylene glycol.

D. Calculation of PNEC

The PNEC calculations for ethylene glycol follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (22,810 mg/L), *Daphnia* (>100 mg/L), and algae (10,940 mg/L). NOEC values from long-term studies are available for fish (15,380 mg/L), invertebrates (8,590 mg/L) and algae (10,000 mg/L). On the basis that the data consists of short-term and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported E(L)C_{50} value of 100 mg/L for fish. The E(L)C_{50} value is used because the value for fish is lower than the NOEC values for all three trophic levels. The $PNEC_{aquatic}$ is 10 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 6.4 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.82/1280) \times 1000 \times 10$
$= 6.4$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.04/1000 \times 2400]$
$= 0.82\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg)

BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$

= 1 x 0.04

= 0.04 L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for ethylene glycol calculated from EPISUITE™ using the MCI is 1 L/kg.

F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.13 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$

= (0.02/1500) x 1000 x 10

= 0.13 mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)

BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$

= 1 x 0.02

= 0.02 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for ethylene glycol calculated from EPISUITE™ using the MCI is 1 L/kg.

F_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Ethylene glycol is readily biodegradable and thus does not meet the screening criteria for persistence.

The measured BCF in fish is 10. Thus, ethylene glycol does not meet the criteria for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on ethylene glycol are > 0.1 mg/L. The acute $E(L)C_{50}$ values from the acute aquatic toxicity studies on ethylene glycol are > 1 mg/L. Thus, ethylene glycol does not meet the criteria for toxicity.

The overall conclusion is that ethylene glycol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

STORE Category 2 (target organ: kidney)

B. Labelling

Warning

A. Pictogram

IX. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention.

Ingestion

Rinse mouth with water and then drink a glass of water. Get medical attention. Never give anything by mouth to an unconscious person.

Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Keep product and empty container away from heat and sources of ignition. May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

B. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Handle in accordance with good industrial hygiene and safety practice.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

For large amounts: dike spillage and pump off product. For residues: pick up with suitable absorbent material. Dispose of contaminated material as prescribed.

C. Storage And Handling

General Handling

Keep product and empty container away from heat and sources of ignition. Ensure adequate ventilation, especially in confined areas.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

D. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standards for ethylene glycol in Australia is as follows: 10 mg/m^3 as an 8-hour TWA for ethylene glycol (particulate); 20 ppm (52 mg/m^3) as an 8-hour TWA for ethylene glycol (vapour). There is also a skin notation indicating that absorption through the skin may be significant source of exposure.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. Ensure that eyewash stations and safety showers are close to the workstation location.

X. TRANSPORT INFORMATION

Ethylene glycol is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Blood, F.R. (1965). Chronic toxicity of ethylene glycol in the rat. Food Cosmet. Toxicol. 3: 229-234.

Carney, E.W., Pottenger, L.H., Bartels, M.J., Jaeckh, R., and Quast, J.F. (1998). Comparative pharmacokinetics and metabolism of ethylene glycol in pregnant rats and rabbits. Toxicol. Lett. 95: 208.

Chapin, R.E. and R.A. Sloane. (1997). Reproductive assessment by continuous breeding: evolving study design and summaries of ninety studies. Environ Health Perspect. 1997 Feb; 105(Suppl 1): 199–205.

Corley, R.A., Meek, M.E., and Carney, E.W. (2005a). Mode of action: oxalate crystal-induced renal tubule degeneration and glycolic acid-induced dysmorphogenesis – renal and developmental effects of ethylene glycol. Crit. Rev. Toxicol. 35: 691-702.

Corley, R.A., Bartels, M.J., Carney, E.W., Weitz, K.K., Soelberg, J.J., and Gies, R.A. (2005b). Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. Toxicol. Sci. 85: 476-490.

Corley, R.A., Wilson, D.M., Hard, G.C., Stebbins, K.E., Bartels, M.J., Soelberg, J.J., Dryzga, M.D., Gingell, K.E and Snellings, W.M.(2008). Dosimetry considerations in the enhanced sensitivity of male Wistar rats to chronic ethtlene glocol-induced nephrotoxicity. Toxicology and Applied Pharmacology. Volume 228, Issue 2: 165-178.

Cowgill, U.M., Takahash, I.T., and Applegath, S.L. (1985). A comparison of the effect of four benchmark chemicals on Daphnia magna and Ceriodaphnia dubia-affinis tested at two different temperatures. Environ. Toxicol. Chem. 4: 415-422.

Cruzan, G., Corley, R.A., Hard, G.C., Mertens, J.J., McMartin, K.E., Snellings, W.M., Gingell, R., and Deyo, J.A. (2004). Subchronic toxicity of ethylene glycol in Wistar and F-344 rats related to metabolism and clearance of metabolites. Toxicol Sci. 81: 502-11.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DePass, L.R., Garman, R.F., Woodside, M.D., Giddens, W.E., Maronpot, R.R., and Weil, C.S. (1986a). Chronic toxicity and oncogenicity studies of ethylene glycol in rats and mice. Fundam. Appl. Toxicol. 7: 547-565.

DePass, L.R., Woodside, M.D., Maronpot, R.R., and Weil, C.S. (1986b). Three-generation reproduction and dominant lethal mutagenesis studies with ethylene glycol in the rat. Fundam. Appl. Toxicol. 7: 566-572.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Evans, W.H., and David, E.J. (1974). Biodegradation of mono-, di-, and triethylene glycols in river waters under controlled laboratory conditions. Water Res. 8: 97-100.

Frantz, S.W., Beskitt, J.L., Grosse, C.M., Tallant, M.J., Dietz, F.K., and Ballantyne, B. (1996a). Pharmacokinetics of ethylene glycol. I. Plasma disposition after single intravenous, peroral, or percutaneous doses in female Sprague-Dawely rats and CD-1 mice. Drug Metab. Dispos. 24: 911-921.

Frantz, S.W., Beskitt, J.L., Grosse, C.M., Tallant, M.J., Dietz, F.K., and Ballantyne, B. (1996b). Pharmacokinetics of ethylene glycol. II. Tissue distribution, dose dependent elimination, and identification of urinary metabolites following single intravenous, peroral, or percutaneous doses in female Sprague-Dawely rats and CD-1 mice. Xenobiotica 26: 1195-1220.

Freitag, D., Ballhorn, L., Geyer, H., and Korte, F. (1985). Environmental hazard profile of organic chemicals. Chemosphere 14: 1589-1616.

Gersich, F.M., Blanchard, F.A., Applegath, S.L., and Park, C.N. (1986). The precision of Daphnid (Daphnia magna Straus, 1820) static acute toxicity tests. Arch. Environ. Contam. Toxicol. 15: 741-749.

Guillot, J.P., Martini, M.C., Giauffret, J.Y., Gonnet, J.F., and Guyot, J.Y. (1982). Safety evaluation of some humectants and moisturizers used in cosmetic formulations. Int. J. Cosmetic Science 4: 67-80.

Hardin, B.D., Schuler, R.L., Burg, J.R., Booth, G.M., Hazelden, K.P., MacKenzie, K.M., Piccirillo, V., Jr, and Smith, K.N. (1987). Evaluation of 60 chemicals in a preliminary developmental toxicity test. Terat. Carcinogen. Mutagen. 7: 29-48.

Harris, M.W., Chapin, R.E., Lockhart, A.C., and Jokinen, M.P. (1992). Assessment of a short-term reproductive and developmental toxicity screen. Fundam. Appl. Toxicol. 19: 186-196.

Hess, R., Bartels, M.J., and Pottenger, L.H. (2004). Ethylene glycol: an estimate of tolerable levels of exposure based on a review of animal and human data. Arch. Toxicol. 78: 671-680.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Kurihara, A., Manabe, A., Katsuno, K., Itoh, K., Hisamitsu, H., Wakumoto, S., and Yoshida, T. (1996). Evaluation of skin irritation and sensitization of two diol solutions used as experimental dentin primers in humans and guinea pigs. Dent. Mater. J., 15: 226-232.

Lamb, J.C., IV, Maronpot, R.R., Gulati, D.K., Russel, V.S., Hommel-Barnes, L., and Sabharwa, l. P.S. (1985). Reproductive and developmental toxicity of ethylene glycol in the mouse. Toxicol. Appl. Pharmacol. 81: 100-112.

McGregor, D.B., Brown, A.G., Howgate, S., McBride, D., Riach, C., and Caspary, W.J. (1991). Responses of the L5178Y mouse lymphoma cell forward mutation assay. V: 27 coded chemicals. Environ. Mol. Mutagen. 17: 196-219.

Melnick, R.L. (1984). Toxicities of ethylene glycol and ethylene glycol monoether in Fischer 344/N rats and B6C3F1 mice. Environ. Health Perspect. 57: 147-155.

Neeper-Bradley, T.L., Tyl, R.W., Fisher, L.C., Kubena, M.F., Vrbanic, M.A., and Losco P.E. (1995). Determination of a no-observed-effect level for developmental toxicity of ethylene glycol administered by gavage to CD rats and CD-1 mice. Fundam. Appl. Toxicol. 27: 121-130.

National Toxicology Program [NTP]. (1993). Toxicology and Carcinogenesis Studies of Ethylene Glycol in B6C3F1 Mice (Feed Studies). National Toxicology Program Technical Report Series No. 413.

OECD. (2004a). SIDS Dossier on the HPV Chemical Ethylene Glycol (CAS No. [redacted]

OECD. (2004b). SIDS Initial Assessment Report on the Ethylene Glycol Category: Ethylene Glycol (CAS No. [redacted] Diethylene Glycol (CAS No. [redacted]), Triethylene Glycol (CAS No. [redacted] Tetraethylene Glycol (CAS No. [redacted] Pentaethylene glycol (CAS No. [redacted]

Pillard, D. (1995). Comparative toxicity of formulated glycol deicers and pure ethylene and propylene glycol to Ceriodaphnia dubia and Pimephales promelas. Environ. Toxicol. Chem. 14: 311-315.

Pillard, D.A. and DuFresne, D.L. (1999). Toxicity of formulated glycol deicers and ethylene and propylene glycol to lactuca sative, lolium perenne, selenastrum capricornutum, and lemna minor. Arch Environ. Contam. Toxicol. 37(1):29-35.

Price, C.J., Kimmel, C.A., Tyl, R.W., and Marr, M.C. (1985). The developmental toxicity of ethylene glycol in rats and mice. Toxicol. Appl. Pharmacol. 81: 113-127.

Robinson, M., Pond, C.L., Laurie, R.D., Bercz, J.P., Henningsen, G., and Condie L.W. (1990). Subacute and subchronic toxicity of ethylene glycol administered in drinking water to Sprague-Dawley rats. Drug Chem. Toxicol .13: 43-70.

Schuler, R.L., Hardin, B.D., Niemeier, R.W., Booth, G., Hazelden, K., Piccirillo, V., and Smith, K. (1984). Results of testing 15 glycol ethers in a short-term in vivo reproductive toxicity assay. Environ. Health Perspect. 57: 141-146.

Snellings, W.M., Corley, R.A., McMartin, K.E., Kirman, C.R., and Bobst, S.M. (2013). Oral reference dose for ethylene glycol based on oxalate crystal-induced renal tubule degeneration as the critical effect. Regul. Toxicol. Pharmacol. 65: 229-241.

Thomas, J., Haseman, J.K., Goodman, J.I., Ward, J.M., Loughran, Jr., T.P., and Spencer, P. (2007). A review of large granular lymphocytic leukemia in Fischer 344 rats as an intial step toward evaluating the implication of the endpoint to human cancer risk assessment. Toxicol. Sci. 99: 3-19.

Tyl, R.W., Ballantyne, B., Fisher, L.C., Fait, D.L., Savine, T.A., Dodd, D.E., Klonne, D.R., and Pritts, I.M. (1995a). Evaluation of the developmental toxicity of ethylene glycol aerosol in the CD rat and CD-1 mouse by whole-body exposure. Fundam. Appl. Toxicol. 24: 57-75.

Tyl, R.W., Fisher, L.C., Kubena, M.F., Vrbanic, M.A., and Losco, P.E. (1995b). Assessment of the developmental toxicity of ethylene glycol applied cutaneously to CD-1 mice. Fundam. Appl. Toxicol. 27: 155-166.

Tyl, R.W., Ballantyne, B., Fisher, L.C., Dodd, D.E., Klonne, D.R., Pritts, M., and Losco, P.E. (1995c). Evaluation of the developmental toxicity of ethylene glycol aerosol in CD-1 mice by nose-only exposure. Fundam. Appl. Toxicol. 27: 49-62.

U.S. Environmental Protection Agency [EPA]. (2017). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Waggy, G.T., Conway, R.A., Hansen, J.L., and Blessing, R.I. (1994). Comparison of 20-d BOD and OECD closed-bottle biodegradation tests. Environ. Toxicol. Chem. 13: 1277-1280.

GELATINS

This dossier on gelatins presents the most critical studies pertinent to the risk assessment of gelatins in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Gelatins

CAS RN: [redacted]

Molecular formula: Not applicable as substance is a UVCB whose specific chemical composition is dependent on formulation processes.

Molecular weight: Depending on the specific commercial use, the molecular weight can range from 72 to 132 kDaltons (i.e., 72,000 to 132,000 g/mol) (Farrugia et. al., 1998)

Synonyms: None identified.

SMILES: Not applicable.

II. PHYSICAL AND CHEMICAL PROPERTIES

Gelatin is a white to yellow, translucent powder. It is hydrolysed and partially degraded collagen obtained by acid, alkaline or enzymatic hydrolysis. It is a polypeptide. Depending on the source of collagen and the method of its manufacturing process of recovery from collagen, gelatin contains an average of the following amino acids: glycine 21%, proline 12%, hypoproline 12%, glutamic acid 10%, alanine 9%, arginine 8%, aspartic acid 6%, lysine 4%, serine 4%, leucine 3%, valine 2, phenylalanine 2%, threonine 2%, isoleucine 1%, hydroxylysine 1%, histidine <1% and tyrosine <0.5% (Gorgieva and Kokol, 2011).

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Gelatins are readily biodegradable; they are not expected to bioaccumulate or adsorb to soil.

B. Biodegradation

As a natural polymer, gelatin is expected to be readily biodegradable by most proteases when environmental conditions are adequate. While high molecular weight polymer degradation rates are generally thought to be low, the biopolymeric nature of gelatin in a variety of cross-linked forms appears to result in rapid biodegradation (e.g., 3-10 days) in the environment (Patel et. al., 2000).

Gelatin, as a rapidly biodegradable protein, is a rich source of amino acids and other nutrients such as nitrogen and carbon for bacteria and fungi. The increased bioavailability of nutrients could lead to a significant increase in biological oxygen demand (BOD) as a result of degradation of gelatin and the stimulated growth of microorganisms. High BOD will deplete local dissolved oxygen concentrations

when gelatin or its breakdown products are released into the aquatic environment in sufficient quantities relative to the volume of the receiving water body. This depletion of oxygen has the potential to place significant stress on some organisms within the aquatic environment (DoEE, 2017).

C. Environmental Distribution

Given the hydrophilic nature of gelatin it is unlikely that this biopolymer would adsorb to the soil or sediment.

D. Bioaccumulation

The potential for bioaccumulation is low. Based on the biological properties and the environmental fate of gelatin, especially the rapid biodegradation, prolonged exposure of aquatic organisms to the biopolymer will be highly unlikely (DoEE, 2017).

IV. HUMAN HEALTH HAZARD ASSESSMENT

There is no data on the human health hazard for this substance. However, based on its biopolymeric nature and uses in foods and medicines, the human health toxicity concern is expected to be very low.

NICNAS has assessed gelatin in an IMAP Tier 1 assessment and it was concluded that it poses no unreasonable risk to the environment[1]. In addition, based on an assessment of human health and environmental hazards, NICNAS also identified gelatin as a chemical of low concern to the environment (NICNAS, 2017 and DoEE, 2017). Chemicals of low concern are unlikely to have adverse environmental effects or be a concern to human health if they are released to the environment from coal seam gas operations.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Toxicological reference and drinking water guidance values have not been derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Gelatin does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

There are no aquatic toxicity studies on gelatin. However, it is expected to have low concern for aquatic toxicity since any gelatin released into aquatic ecosystems will be rapidly degraded by microorganisms through enzymatic digestion to the individual amino acids or short peptides. If sufficient quantities of gelatin were abruptly released into a water body, this could cause temporary changes in water quality for local organisms, such as reduced dissolved oxygen concentrations (DoEE, 2017).

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]2C+

B. Aquatic Toxicity

No aquatic toxicity data was available.

C. Terrestrial Toxicity

No relevant studies were available.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Gelatins are readily biodegradable; thus, it does not meet the screening criteria for persistence.

The rapid degradation and expected lability to enzymatic degradation suggests gelatins will not meet the screening criteria for bioaccumulation.

There are no aquatic toxicity studies on gelatins. It is expected to have low concern for aquatic toxicity because of its bio-composition (e.g., various amino acids and crosslinked substituents) and rapid degradation rates in the environment. Thus, gelatin does not meet the screening criteria for toxicity.

The overall conclusion is that gelatin is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

Based on the low concern of this substance, and according to the majority of notifications provided by companies to ECHA under the Classification, Labelling and Packaging of Substances and Mixtures Regulation No 1272/2008, no hazards have been classified.

X. SAFETY AND HANDLING

Based on the low concern status of this substance, no specific safety or handling precautions are relevant.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy (DoEE). (2017). Environmental risks associated with surface handling of chemicals used in coal seam gas extraction in Australia, Project report Appendices A, B, C, D, F, and G prepared by the Chemicals and Biotechnology Assessments Section (CBAS) in the Department of the Environment and Energy as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Farrugia, C.A., Farrugia, I.V. and Groves, M.J. (1998). Comparison of the Molecular Weight Distribution of Gelatin Fractions by Size-exclusion Chromatography and Light Scattering. Pharm. Pharmacol. Commun. 1998, 4: 559-562

Gorgieva, S, and Kokol V. (2011). 'Collagen- vs. Gelatine-Based Biomaterials and Their Biocompatibility: Review and Perspectives', in: Pignatello R (ed) Biomaterials applications for nanomedicine, INTECH, retrieved from http://www.intechopen.com/books/biomaterials-applications-for-nanomedicine.

Klimisch, H. J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol Pharmacol. 25:1-5.

NICNAS. (2017). Chemicals of low concern for human health based on an initial assessment of hazards, Project report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra

Patel, Rajaram dattu, Dalev, P.G., and Mark, J.E. (2000). Biodegradation of chemically modified gelatin films in lake and river waters. Journal of Applied Polymer Science 76(1):29 – 37

GLUTARALDEHYDE

This dossier on glutaraldehyde presents the most critical studies pertinent to the risk assessment of glutaraldehyde in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from NICNAS (1994) and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Glutaraldehyde

CAS RN: [redacted]

Molecular formula: $C_7H_8O_2$

Molecular weight: 100.12 g/mol

Synonyms: Pentanedial; glutaral; glutaric dialdehyde; 1,3-diformylpropane; 1,5-pentanedial; glutaric aldehyde; glutaric acid dialdehyde; dioxopentane; glutardialdehyde; 1,5-pentanedione; Algicide®C

SMILES: C(CC=O)CC=O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-Chemical Properties of Glutaraldehyde

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa*	Sweetish smelling, clear water liquid	1	ECHA
Melting Point*	-33°C (pressure not provided)	1	ECHA
Boiling Point*	101.5°C @ 98.71 kPa	1	ECHA
Density*	1,130 kg/m^3 @ 20°C	1	ECHA
Vapour Pressure*	21 Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})*	-0.36 @ 23°C and pH 7	1	ECHA
Water Solubility*	Miscible @ 20°C	2	ECHA
Flash Point*	Not measurable	1	ECHA
Auto flammability*	395°C @ ~1,000hPa	1	ECHA
Viscosity*	12.75 mm^2/s (static) at 25°C	1	ECHA
Henry's Law Constant	0.011 Pa m^3/mol at 25°C [QSAR]	2	ECHA

*ca. 50% glutaraldehyde solution (in water)
1 ppm = 4.095 mg/m3
1 mg/m3 = 0.244 ppm

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Glutaraldehyde is considered readily biodegradable. It is also expected to have a low potential for bioaccumulation. The K_{oc} values for glutaraldehyde indicate that it will have low potential for adsorption to suspended solids and sediment in water and moderate adsorption to soil. Glutaraldehyde is not expected to undergo hydrolysis in the environment. Overall, glutaraldehyde shows limited persistence in the environment.

B. Partitioning

In an OECD TG 111 test (hydrolysis as a function of pH), glutaraldehyde was hydrolytically stable at pH 4 and pH 7 but decomposed at pH 9 (ECHA) [Kl. score = 2].

Photolytic degradation of glutaraldehyde occurred in water under sensitised conditions: the half-life was 18 days when equivalent to 36 days of natural sunlight (12 hours/day; sensitised acetone system); and 49 days when equivalent to 34 days of natural sunlight (12 hours/day; sensitised acetonitrile system). There was no photodegradation of glutaraldehyde under darkness or non-sensitised conditions (ECHA) [Kl. score = 2].

C. Biodegradation

Glutaraldehyde was considered readily biodegradable in an OECD 301A (DOC die away test). Degradation was 90-100% in 28 days (ECHA) [Kl. score = 1].

In a simulation test involving aerobic sewage treatment [activated sludge units] (OECD TG 303A), glutaraldehyde degraded 97% after 73 days based on DOC removal (ECHA) [Kl. score = 1].

In an aerobic aquatic metabolism test, [^{14}C]-glutaraldehyde had a half-life of 10.6 hours in the water/sediment system. A minor transformation product was glutaric acid: the maximum yield was 18.9 to 21.5% at 12 hours, which then declined rapidly to 10.1 to 11% by 24 hours; and was not observed at the end of the study period in the aqueous phase (ECHA) [Kl. score = 1].

In an anaerobic aquatic metabolism test, [^{14}C]-glutaraldehyde was rapidly metabolised with the first-order half-life being 7.7 hours. Glutaraldehyde was transformed to 5-hydroxypentanal (ca 37% of applied radioactivity) on day 1; after that, it declined to < 10%; it was not detected at all after 30 days. The second stable transformation product was 1,5-pentanediol (35% of radioactivity on Day 1), which accounted for 70% of the radioactivity at the end of the test. A minor transformation product was a compound formed via Aldol condensation, cyclisation and dehydration. This compound accounted for about 10-20% of total radioactivity from Day 1 onwards (ECHA) [Kl. score = 1].

In an aerobic soil metabolism test, the half-life of the degradation of [^{14}C]-glutaraldehyde was calculated to be 1.7 days, indicating rapid degradation in soil by microbial biotransformation. Degradation products were measured but not identified (ECHA) [Kl. score = 1].

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

D. Environmental Distribution

The organic carbon/water partition coefficients (K_{oc}) values were determined for sediment and four types of soil. The values are as follows: 120 for sediment; 210 for sandy loam; 500 for silty clay loam; 340 for silt loam; and 460 for loamy sand (ECHA; Leung, 2001) [KI. score = 1].

Based on these K_{oc} values, glutaraldehyde is considered to be moderately mobile in soil. If released to water, based on these K_{oc} values and its water solubility, it has moderate potential for adsorption to suspended solids or sediments.

E. Bioaccumulation

Glutaraldehyde is not expected to bioaccumulate. The measured log K_{ow} at pH 5, 7 and 9 are -0.41, -0.36 and -0.80, respectively (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Glutaraldehyde has moderate-to-high acute toxicity by the oral route, low-to-moderate toxicity by the dermal route, and moderate-to-high toxicity by the inhalation route. Acute inhalation exposure may cause respiratory irritation. Glutaraldehyde is corrosive to the skin and eyes; it is also a skin and respiratory sensitiser. Repeated oral exposures via drinking water to rats have resulted in general systemic toxicity, but no target organ effects. In contrast, the upper respiratory tract, particularly the nasal cavity, is the target organ in rodents from repeated inhalation exposure. Glutaraldehyde may exhibit weak genotoxic effects in some *in vitro* tests, whereas the *in vivo* studies consistently show no genotoxic activity. Glutaraldehyde is not a reproductive toxicant; developmental toxicity can occur at maternally toxic doses, but there is no teratogenicity.

B. Toxicokinetics

Dermal Absorption

[1,5-^{14}C]-glutaraldehyde was applied to the skin of male and female F344 rats. Doses were 0.75% and 7.5%: this corresponds to approximately 6.5 and 63 mg/kg for males; and approximately 8.7 and 102 mg/kg for females. The dermal absorption data are presented in Table 2. The results indicate that glutaraldehyde has a low rate of absorption by the dermal route (ECHA).

Table 2: Dermal Absorption Data in Rats on Glutaraldehyde (ECHA)

Sex	Absorption rate constant/hr		% of applied dose	
	Low Dose	High Dose	Low Dose	High Dose
Males	1.5	0.7	0.7	1.3
Females	1.8	0.9	0.3	2.1

An *in vitro* percutaneous absorption study was conducted on glutaraldehyde using excised skin from rats, rabbits, mice, guinea pigs and humans. The skin samples were placed in a flow-through skin penetration chamber, and [^{14}C]-glutaraldehyde was added at doses of 0.75% and 7.5%. The results are presented in Table 3. Glutaraldehyde did not penetrate any of the skin samples to a significant degree, suggesting that only minimal amounts of glutaraldehyde may be available for systemic

uptake and distribution after skin exposure. The results also show that skin absorption was greater for the animal species used in toxicity tests than human skin (ECHA; Frantz et al., 1993).

Table 3: *In vitro* Percutaneous Absorption (mg/cm^2) of Glutaraldehyde (ECHA; Frantz et al., 1993)

Species	Low Dose	High Dose
Animal*	0.006	0.08
Human	0.002	0.02

*Percutaneous absorption in rats, mice, guinea pigs, mice and rabbits were similar to each other and were reported as a single value.

C. Acute Toxicity

The oral LD_{50} values are: 123 to 820 mg/kg in rats; 100 to 352 mg/kg in mice; and 50 mg/kg in guinea pigs (NICNAS, 1994).

The dermal LD_{50} values are: 640 to 2,000 mg/kg in rabbits; > 2,500 mg/kg in rats; and > 4,500 mg/kg in mice (NICNAS, 1994).

The 4-hour inhalation LC_{50} values for glutaraldehyde are listed in Table 4:

Table 4: Acute inhalation LC_{50} values for Glutaraldehyde

Test Material	LC_{50} (males) [mg/L]	LC_{50} (females) [mg/L]	LC_{50} (both sexes) [mg/L]	Reference
50% aq. aerosol	0.52	0.45	-	OECD, 1995
25% aq. aerosol	-	-	0.8	OECD, 1995
50% aq. aerosol	0.35	0.28	-	OECD, 1995
5% soln. vapour	0.096	0.164	-	OECD, 1995

During the exposure period, the animals showed signs of eye and respiratory irritation, as indicated by laboured and audible breathing, and wetness and encrustation around the nose and eyes.

D. Irritation

Glutaraldehyde is corrosive to the skin and eyes of rabbits (NICNAS, 1994; ECHA). Signs of irritation occurred at a concentration of 2% for skin and 0.2% for eyes (NICNAS, 1994). In the acute inhalation studies, rats exposed to aerosols or vapours of glutaraldehyde showed signs of eye and respiratory irritation (OECD, 1995).

E. Sensitisation

Glutaraldehyde is a skin sensitiser to guinea pigs and humans. Information on the individual studies can be found in NICNAS (1994) and in the ECHA REACH database (ECHA).

Asthmatic symptoms, such as wheezing, coughing, chest tightness, breathing difficulties and non-specific hyper-responsiveness have been reported to occur in humans occupationally exposed to glutaraldehyde (NICNAS, 1994). It is unclear whether the asthma is an allergic hypersensitivity response or a result of the aggravation of pre-existing asthma due to the irritating properties of

glutaraldehyde. Nevertheless, glutaraldehyde should be considered a respiratory sensitiser, although one of low potency.

F. Repeated Dose Toxicity

Oral

Male and female Wistar rats were given in their drinking water 0, 100, 500, or 2,000 ppm glutaraldehyde for 90 days. The approximate daily intakes were 0, 3, 15 or 53 mg/kg/day for males, and 0, 4, 19 or 72 mg/kg/day for females. There were no signs of neurotoxicity at any dose level. There was slight impairment of food consumption in the 2,000 ppm animals, as well as slight impairment of body weight and body weight gain. Impaired water consumption was seen in the 100 and 500 ppm females. The NOAEL for males is 500 ppm (15 mg/kg/day). The NOAEL for females is 100 ppm (4 mg/kg/day) since the impaired water consumption in the 100 ppm females was considered a palatability problem and not an adverse effect (ECHA) [Kl. score = 1].

Male and female F344 rats were given in their drinking water 0, 50, 250 or 1,000 ppm glutaraldehyde for 13 weeks. Additional groups of animals were given in their drinking water 0 or 1,000 ppm glutaraldehyde for 13 weeks followed by a 4-week recovery period. The approximate daily intakes were 0, 5, 25 or 100 mg/kg/day for males; and 0, 7, 35 or 120 mg/kg/day for females. Water consumption was reduced in a dose-dependent manner in the $\geq$ 250 ppm males and 1,000 ppm females, which was attributed to an aversion to the taste and/or odour of glutaraldehyde in the water. There was also a reduction in food consumption in the 1,000 ppm animals with a parallel reduction in body weights. It is unclear whether the reduction in food consumption was related to the decreased water consumption. Urine volume was decreased with an increase in specific gravity, along with a slight increase in protein and ketone concentration, in the $\geq$ 250 ppm animals, which was probably related to the decreased water consumption. There were no treatment-related changes in the haematology parameters measured. Blood urea nitrogen was increased in a dose-related manner in the $\geq$ 250 ppm females at the 6-week time point, but not at the 13-week or 17-week time points. Relative kidney weights were increased in a dose-related manner in the $\geq$ 250 ppm males and females and increased absolute kidney weights in the females. Histopathological examination showed no treatment-related effects. The NOAEL is 50 ppm (5 and 7 mg/kg/day for males and females, respectively) based on dose-related increase in kidney weights at $\geq$ 250 ppm (ECHA) [Kl. score = 2].

Male and female Wistar rats were given in their drinking water 0, 100, 500 or 2,000 ppm glutaraldehyde for 12 months. The approximate daily intakes were: 0, 6.4, 30.5, or 116.6 mg/kg/day for males; and 0. 9.6, 46, or 153 mg/kg/day for females. There was no treatment-related mortality. At 2,000 ppm, treatment-related effects included respiratory sounds (both sexes), decrease in body weight (males), decrease in body weight gain (both sexes), decrease in food consumption (both sexes), reduced water consumption (both sexes), lesions within the glandular stomach (both sexes showed erosion/ulceration of the glandular stomach), increased incidence of clear cell foci in the liver (males) and a single case of slight diffuse squamous metaplasia in the epithelium of the larynx (male). At 500 ppm, water consumption was reduced in males which was considered to be a palatability (bad taste) problem and not an adverse effect. No effects were seen in the 100 ppm animals. The NOAEL for this study is 500 ppm, which corresponds to 30.5 and 46 mg/kg/day for males and females, respectively (ECHA) [Kl. score = 1].

Male and female Fischer 344 rats were given in their drinking water 0, 50, 250 or 1000 ppm glutaraldehyde for 104 weeks. The mean glutaraldehyde consumption was 0, 4, 17 and 64 mg/kg/day for males and 0, 6, 25 and 86 mg/kg/day for females. There were no treatment-related mortalities or clinical symptoms of toxicity. In the 250 and 1,000 ppm groups, there was reduction in

body weight and body weight gain; reduction in food and water consumption; increased statistically significant incidence of nucleated erythrocytes and of large monocytes; decreases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and glutamate dehydrogenase; dose-related decrease in urine volume accompanied by a dose-related increase in osmolality; changes in absolute and relative kidney weight; gastric irritation; increases in bone marrow hyperplasia; and increased incidence of renal tubular pigmentation. The decreased water consumption was considered to be due to the bad taste, smell and/or irritancy of the test substance in the drinking water; thus, it is of no toxicological relevance. As a result of reduced water intake, there are renal physiological adaptation, such as decreased urine, increased osmolality and changes in kidney weight. The haematological and clinical chemistry parameter changes were marginal and were considered to be of no toxicological relevance. The main haematological finding seen at the end of the study, which consisted of the appearance of nucleated erythrocytes and large monocytes in all treated groups (statistically significant for the ≥250 ppm males), was related to the incidence of large granular lymphocytic leukaemia (LGLL) in the spleen. The bone marrow hyperplasia and renal tubular pigmentation are related to the occurrence/incidence of LGLL and were considered by the authors of the study as being secondary to low-grade haemolytic anaemia in animals with LGLL. The NOAEL for this study is 50 ppm which corresponds to 4 and 6 mg/kg/day for males and females, respectively (Van Miller et al., 2002) [Kl. score = 2].

Inhalation

Male and female F344 rats were exposed by inhalation to 0, 0.0625, 0.125, 0.25, 0.5 or 1.0 ppm (0, 0.26, 0.5, 1, 2 or 4.1 mg/m^3) glutaraldehyde for 6.5 hours/day, 5 days/week for 13 weeks. The study focused on the respiratory tract, using histopathology and epithelial cell labelling index as end points. Histopathological lesions in the nasal passages and turbinates were seen at ≥ 0.25 ppm. Treatment-related effects were primarily the respiratory mucosa (nasal cavity and tips of the turbinates) and the olfactory epithelium (dorsal meatus). Hyperplasia, squamous metaplasia, olfactory degeneration, squamous exfoliation (accumulation of keratin, cell debris and bacteria in the lumen of the nasal vestibule) and focal erosions were reported for both sexes, and the severity and incidence of the findings increased with increasing concentration of glutaraldehyde. The NOAEL for this study is 0.125 ppm (Gross et al., 1994) [Kl. score = 1].

Male and female B6C3F$_1$ mice were exposed by inhalation to 0, 0.0625, 0.125, 0.25, 0.5 or 1.0 ppm (0, 0.26, 0.5, 1, 2 or 4.1 mg/m^3) glutaraldehyde for 6.5 hours/day, 5 days/week for 13 weeks. The study focused on the respiratory tract, using histopathology and epithelial cell labelling index as end points. Histopathologic lesions in the nasal passages and turbinates were seen at all exposure concentrations (≥ 0.0625 ppm). Treatment-related lesions were primarily the respiratory mucosa (nasal cavity and tips of the turbinates) and the olfactory epithelium (dorsal meatus). Hyperplasia, squamous metaplasia, olfactory degeneration, squamous exfoliation (accumulation of keratin, cell debris and bacteria in the lumen of the nasal vestibule) and focal erosions were reported for both sexes, and the severity and incidence of the findings increased with increasing test concentration. Furthermore, neutrophilic inflammation was seen at ≥ 0.062 ppm, and squamous metaplasia as well as necrosis were seen in the larynx at 1 ppm. The LOAEL for this study is 0.0625 ppm; a NOAEL was not established (Gross et al*.,* 1994) [Kl. score = 1].

Male and female B6C3F$_1$ mice were exposed by inhalation to 0 or 0.1 ppm (0 or 0.41 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for 52 and 78 weeks. Survival was similar between treated and control groups. Hyperplasia of the squamous epithelium lining of the dorsal wall of the nasal passages and the lateral aspect of the atrioturbinate was seen in a greater number of exposed females than in controls. Epidermal erosion and ulceration as well as squamous and inflammatory exfoliation were also seen in the nasal lumens. All of these changes were dependent on the length of

glutaraldehyde exposure. The authors concluded that, since the induced lesions occurred in the more anterior part of the nasal passages, that they were likely the result of an irritation mechanism (Zissu et al., 1998) [Kl. score = 2].

Male and female Fischer 344 rats were exposed by inhalation to 0, 0.25, 0.5, or 0.75 ppm (0, 1, 2, or 3.1 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for two years. Survival in the mid- and high-dose females was statistically significantly decreased compared to controls. Mean body weights of all exposed males and the mid- and high-dose females were generally less than those of the controls. Non-neoplastic lesions were limited primarily to the most anterior region of the nasal cavity. Effects included hyperplasia and inflammation of the squamous epithelium; hyperplasia, goblet cell hyperplasia, inflammation and squamous metaplasia of the respiratory epithelium; and hyaline degeneration of the olfactory epithelium. The LOAEL for this study is 0.25 ppm based on hyperplasia and inflammation of the squamous epithelium of the nose in both sexes. A NOAEL was not established (van Birgelen et al., 2000) [Kl. score = 2].

Male and female B6C3F$_1$ mice were exposed by inhalation to 0, 0.0625, 0.125 or 0.25 ppm (0, 0.26, 0.5 or 1 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for two years. Survival of the treated animals was similar to controls. Mean body weights of the high-dose females were generally lower than the controls. Non-neoplastic lesions were limited primarily to the anterior region of the nasal cavity; the effects were qualitatively similar to those seen in the rats (see accompanying summary on the two-year rat study by van Birgelen et al. [2000]). Squamous metaplasia of the respiratory epithelium was observed in both sexes of mice while female mice also had inflammation and hyaline degeneration of the respiratory epithelium. The incidence and severity grade (in parentheses) of the hyaline degeneration were: 16/50 (1.4), 35/49 (1.4), 32/50 (1.3) and 30/50 (1.1) for the 0, 0.0625, 0.125 and 0.25 ppm dose groups, respectively. The LOAEL for this study is 0.0625 ppm based on hyaline degeneration of the respiratory epithelium in female mice. A NOAEL was not established (van Birgelen et al., 2000) [Kl. score = 2].

Dermal

Applications of a 50% solution of glutaraldehyde was applied to the skin of male and female SD rats for 13 weeks. The doses were 0, 50, 100 and 150 mg/kg glutaraldehyde. At the application site, there were signs of irritation (scabs, desquamation and very slight or well-defined erythema). There was no treatment-related mortality, clinical signs, body weights, feed consumption and ophthalmoscopic effects. There were no changes in the haematology and clinical chemistry parameters that were considered to be biologically or toxicologically relevant. Organ weights were similar between treated and control animals. Histopathological examination showed treatment-related effects in the skin associated with chronic irritation; no other changes were noted that were considered to be treatment-related. The NOAEL for this study is 150 mg/kg, the highest dose tested (ECHA) [Kl. score = 1].

G. Genotoxicity

In Vitro Studies

Glutaraldehyde may exhibit weak genotoxic effects in some *in vitro* tests. The bacterial reverse mutation assays have been the most consistent. Variable results have been reported for the forward gene mutation tests; and for sister chromatid exchange (SCE), chromosomal aberration and Unscheduled DNA Synthesis (UDS) tests (Vergnes and Ballantyne, 2002).

In Vivo Studies

The *in vivo* studies conducted on glutaraldehyde are presented in Table 5. All the studies show that glutaraldehyde is not mutagenic or genotoxic.

Table 5: *In Vivo* Genotoxicity Studies on Glutaraldehyde

Test System	Results*	Klimisch Score	Reference
Rat bone marrow (chromosomal aberration)	-	1	ECHA
Rat bone marrow (chromosomal aberration)	-	2	ECHA
Mouse bone marrow (micronucleus)	-	1	ECHA
Rat bone marrow (chromosomal aberration)	-	2	ECHA
Rat germ cell cytogenetic assay (alkaline elution)	-	2	ECHA
Drosophila SLRL Test	-	2	ECHA
Rat liver UDS Assay	-	1	ECHA
Rat germ cell cytogenetic assay (alkaline elution)	-	2	ECHA
Mouse peripheral blood micronucleus study	-	2	Vernes and Ballantyne (2002)
Rat liver UDS Assay	-	2	Mirsalis *et al.* (1989)

* +, positive; -, negative

H. Carcinogenicity

Oral

Male and female Fischer 344 rats were given in their drinking water 0, 50, 250 or 1,000 ppm glutaraldehyde for 104 weeks. The mean glutaraldehyde consumption was 0, 4, 17 and 64 mg/kg/day for males and 0, 6, 25 and 86 mg/kg/day for females. Mortality rates were 25-30% and 19-23% for males and females, respectively, with no dose-related increase. The major cause of death in all dose groups including the controls was LGLL. There was an increased incidence of LGLL in the liver and spleen in all treated females ($\geq$ 50 ppm). The incidence of LGLL was not significantly increased in the treated males compared to the controls. No other treatment-related increased incidence of tumours was seen (Van Miller et al., 2002) [Kl. score = 2].

Male and female Wistar rats were given in their drinking water 0, 100, 500 or 2,000 ppm glutaraldehyde for two years. The mean daily intake of glutaraldehyde was as follows: 0, 6.1, 31.9 and 120.7 mg/kg/day for males; and 0, 10.5, 48.5 and 176.4 mg/kg/day for females. In the high-dose animals, there was mortality (2 males and 9 females) from asphyxia, and mean terminal body weights were significantly decreased compared to the controls. There were no treatment-related neoplastic effects (ECHA) [Kl. score = 1].

Inhalation

Male and female $B6C3F_1$ mice were exposed by inhalation to 0 or 0.1 ppm (0 or 0.4 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for 52 and 78 weeks. No exposure-related neoplastic lesions were observed in either males or females (Zissu et al., 1998) [Kl. score = 2].

Male and female Fischer 344 rats were exposed by inhalation to 0, 0.25, 0.5 or 0.75 ppm (0, 1, 2 or 3.1 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for two years. Survival in the mid- and high-dose females was statistically significantly decreased compared to controls. Survival of the treated males was similar to controls. No exposure-related neoplastic lesions were observed in either males or females (van Birgelen et al., 2000) [Kl. score = 2].

Male and female B6C3F$_1$ mice were exposed by inhalation to 0, 0.0625, 0.125 or 0.25 ppm (0, 0.26, 0.5 or 1 mg/m^3) glutaraldehyde for 6 hours/day, 5 days/week for two years. Survival of the treated animals was similar to controls. No exposure-related neoplastic lesions were observed in either males or females (van Birgelen et al., 2000) [Kl. score = 2].

I. Reproductive Toxicity

A two-generation reproductive toxicity study was conducted in Wistar rats given 0, 100, 500 and 2,000 ppm glutaraldehyde in their drinking water. The approximately mean daily intake is 0, 12, 58 and 199 mg/kg/day for the parental males and females of the F_0 and F_1 generation during premating. There were no adverse effects on reproductive performance or fertility. Oestrous cycle data, mating behaviour, conception, gestation, parturition, lactation and weaning as well as sperm parameters, sexual organ weights, gross and histopathological findings of these organs were similar between treated and control groups. In the high-dose animals, there was decreased water and/or food consumption; and decreased body weights and/or reduced body weight gains during the premating periods in the F_0 and F_1 parental females during premating, gestation and/or lactation. The high-dose F_1 parental females also had increased the number of erosions/ulcers with microscopic erosion(s) or inflammatory oedema in the mucosa/submucosa of the glandular stomach. There were no adverse effects in the 500 ppm animals except for slight decreases in water consumption due to a palatability (bad taste) problem. Treatment-related signs of developmental toxicity were seen in the progeny of the high-dose F_0 and F_1 parental generation and included impairment in body weight and consequently in organ weights in the respective F_1 and F_2 pups. The NOAEL for reproductive toxicity is 2,000 ppm (199 mg/kg/day), the highest dose tested. The NOAEL for parental systemic toxicity is 500 ppm (58 mg/kg/day). The NOAEL for developmental toxicity is 500 ppm or 58 mg/kg/day (ECHA) [Kl. score = 1].

A two-generation reproductive toxicity study was conducted in Crj: CD(SD) rats given 0, 50, 250 and 1,000 ppm glutaraldehyde in their drinking water. Mean daily intake was not calculated. Parental body weights and body weight gains were significantly reduced at 1,000 ppm at some periods, particularly during pre-mating. Food consumption was significantly reduced at 1,000 ppm for the F_0 and F_1 parental animals during pre-mating and gestation, and F_1 females during lactation. Water consumption was reduced throughout the pre-mating period for the F_0 and F_1 250 and 1,000 ppm parental animals. There was no indication of adverse effects on reproductive performance or fertility at any dose level. For the F_1 1,000 ppm offspring, body weights were reduced from lactation days 21-28. The NOAEL for reproductive toxicity is 1,000 ppm, the highest dose tested. The NOAEL for parental systemic toxicity is 50 ppm. The NOAEL for developmental toxicity is 250 ppm (Neeper-Bradley and Ballantyne, 2000) [Kl. score = 2].

J. Developmental Toxicity

Pregnant Wistar rats were given in their drinking water 0, 50, 250 or 750 ppm (0, 5, 26 or 68 mg/kg) glutaraldehyde from GD 6 to 16. Water consumption was reduced in a dose-related manner in the $\geq$ 250 ppm dams, and was considered not to be a toxic response, but due to the palatability (bad taste) of the drinking test solution. No other maternal effects were seen in the study. There were no significant differences between treated and controls in the sex distribution, placental weights, foetal

weights, malformations or variations. The NOAEL for maternal and developmental toxicity in this study is 68 mg/kg/day, respectively (ECHA) [Kl. score = 1].

Pregnant Wistar rats were dosed by oral gavage with 0, 25, 50 or 100 mg/kg glutaraldehyde on GD 6 to 15. Mortality was significantly increased in the high-dose group (5/26); there were 2/21 deaths in the mid-dose group. Clinical signs (piloerection) occurred in all treated groups in a dose-dependent manner. Maternal body weight gain and feed consumption were significantly reduced in the high-dose dams, but not at the lower doses. The necropsy findings showed evidence of stomach irritation in almost all of the animals that died during the study and in 12/21 of the surviving dams in the high-dose group. The number of implantations per litter, resorptions and dead foetuses per litter, live foetuses per litter and incidence of post-implantation loss per litter was similar across all groups. The mean foetal body weights for male and female foetuses were significantly reduced in the high-dose group; this was attributed to the reduced food consumption of the dams during gestation rather than a direct effect of treatment. There was no evidence of a treatment-related teratogenic effect. The NOAEL for maternal and developmental toxicity is 50 mg/kg/day, respectively (Ema et al., 1992) [Kl. score = 2].

Pregnant Himalayan rabbits were dosed by oral gavage with 0, 5, 15 or 45 mg/kg glutaraldehyde on GD 7 to 19. In the high-dose group, 5/15 died on GD 9-11. Food consumption and body weight gain were also significantly reduced in the high-dose group. Clinical observations in 12/15 high-dose does included soft faces, diarrhoea and blood in the bedding. The mean gravid uterus weight was significantly reduced in the high-dose group. Post-implantation loss was greatly increased (94.3%) in the high-dose group: no viable foetuses in 9/15 of the high-dose does, only early resorptions; only one female gave four alive foetuses on the scheduled date. There were reduced placental and foetal body weights in the only four foetuses. No significant maternal or developmental effects were seen in the mid- and low-dose groups. The NOAEL for maternal and developmental toxicity in this study is 15 mg/kg/day (ECHA) [Kl. Score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for glutaraldehyde follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2011).

A. Non-Cancer

The lowest NOAEL values from key toxicity studies on glutaraldehyde are listed in Table 6.

Table 6: Lowest NOAEL Values from Key Toxicity Studies on Glutaraldehyde by the Oral Route

Species/Sex	Study Duration	mg/kg/day	Endpoint	Reference
Rats, female	90/days	4	Decreased body weights, food and water consumption	ECHA
Rats, male	13-wk (drinking water)	5	Increased kidney weights	ECHA

Species/Sex	Study Duration	mg/kg/day	Endpoint	Reference
Rats, male	12-months (drinking water)	30.5	Clinical signs; decreased body weights and food consumption; increased clear cell foci in liver	ECHA
Rats, male	2-yr (drinking water)	4	Reduced body weight, body-weight gain, and food consumption	Van Miller *et al.* (2002)
Rats	2-generation (drinking water)	58	Systemic toxicity	ECHA
Rats	GD 6-16 (drinking water)	68	Developmental toxicity	ECHA
Rats	GD 6-15 (oral gavage)	50	Developmental toxicity	Ema *et al.* (1992)
Rabbits	GD 7-19 (oral gavage)	15	Developmental toxicity	ECHA

The lowest NOAEL from these studies is 4 mg/kg/day based on reduced body weights, body weight gain and feed consumption in male rats from the two-year drinking water study (Van Miller et al., 2002). The NOAEL of 4 mg/kg/day will be used for determining the oral Reference Dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 4/(10 x 10 x 1 x 1 x 1) = 4/100 = <u>0.04 mg/kg/day</u>

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD: Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2 L (ADWG, 2011)
Drinking water guidance value = (0.04 x 70 x 0.1)/2 = 0.14 mg/L

B. Cancer

Increased incidence of large granular cell lymphatic leukaemia (LGLL) was observed in all groups of male and female Fischer 344 rats given glutaraldehyde in their drinking water, including the controls (Van Miller *et al.,* 2002). For the males, the incidence of LGLL was not statistically significantly increased. However, for the females, the incidence of LGLL was significantly increased in all treated females (≥ 50 ppm). Inhalation exposure of Fischer 344 rats to glutaraldehyde did not result in an increased incidence of tumours, including LGLL.

LGLL, also known as mononuclear cell leukaemia, is an extremely common spontaneous neoplastic disease of the ageing F344 rat (Stromberg, 1985; Ward *et al.* 1990; Thomas et al., 2007). Consistent features are splenomegaly, anaemia, thrombocytopenia and leukemic infiltration of the spleen, liver, lung, and in an advanced stage, of several other organs. The incidence is variable but has been increasing progressively with time and can exceed 70% in controls in some studies. This compares with background incidence of less than 1% in other strains of commonly used laboratory rats (Haseman et al., 1998; Thomas et al., 2007). The incidence in F344 rats is modulated by a variety of factors not clearly related to carcinogenicity. Corn oil gavage, for example, has been shown consistently to reduce the incidence of MCL in male, but not female, controls (reviewed in Thomas et al., 2007).

The neoplastic mononuclear cells appear to be derived from large granular lymphocytes (LULs) (reviewed in Thomas et al., 2007). The tumour cell is of the NK type in most, if not all, cases. LGL leukaemia, although uncommon, does occur in humans. There are two types: T-LGL leukaemia which has a chronic course characterised by neutropenia, recurrent infections, splenomegaly and accompanying rheumatoid arthritis, and the much rarer NK-LGL leukaemia which has an acute course, more pronounced splenomegaly, and thrombocytopenia. The latter type appears to resemble more closely the disease in the F344 rat than the former. The aetiology of human LGL leukaemia is unknown. There is some evidence that viral infection may play a role but no evidence that a chemically-related increased of LGLL in the F344 rat is indicative of the potential to induce LGL leukaemia in humans.

To extrapolate results from an animal model that has a clear predisposition (high spontaneous rates) to a tumour type to humans, of which this is not the case, seems inappropriate if the mechanism(s) for LGLL formation in that strain is not understood. Although that rat strain may be useful for understanding the disease process in humans, it does not seem reasonable to use the results from that rat strain for risk assessment purposes. There should be confirmation of a putative leukemogenic effect in the F344 rat in another strain before any conclusions are made about the use of this tumour type for human health risk assessment purposes.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Glutaraldehyde does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Glutaraldehyde has a moderate acute toxicity concern to fish and invertebrates, but is highly toxic to algae. It is of low toxicity concern to terrestrial invertebrates and plants. To birds, glutaraldehyde is moderately toxic on an acute basis and slightly toxic on a subacute dietary basis.

B. Aquatic Toxicity

Acute Studies

Table 7 lists the results of acute aquatic toxicity studies conducted on glutaraldehyde.

Table 7: Acute Aquatic Toxicity Studies on Glutaraldehyde

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Bluegill sunfish	96-hr LC_{50}	13	2	ECHA
Oncorhynchus mykiss	96-hr LC_{50}	10	2	ECHA
Daphnia magna	48-hr LC_{50}	14.87	2	ECHA
Daphnia magna	48-hr LC_{50}	14	2	ECHA
Scenedesmus subspicatus	72-hr EC_{50}	0.375 (biomass) 0.6 (growth rate) 0.025 (NOEC)	1	ECHA
Scenedesmus subspicatus	72-hr EC_{50}	0.92 (growth rate) 0.61(biomass) 0.33 (NOEC)	2	ECHA; Leung, 2001
Scenedesmus subspicatus	72-hr EC_{50}	0.61 (growth rate)	2	ECHA

Chronic Studies

The chronic aquatic toxicity studies conducted on glutaraldehyde are listed in Table 8.

Table 8: Chronic Aquatic Toxicity Studies on Glutaraldehyde

Test Species	Endpoint	Results (mg/L)	Kl. score	Reference
Oncorhynchus mykiss	97/day (OECD 210)	LOEC = 5 NOEC = 1.6	1	ECHA
Daphnia magna	21/day	NOEC = 5	1	ECHA

C. Terrestrial Toxicity

Table 9 lists the results of toxicity studies conducted on glutaraldehyde with earthworms, soil microorganisms and birds.

Table 9: Terrestrial Toxicity Studies on Glutaraldehyde

Test Species (method)	Endpoint	Results	Kl. score	Reference
Earthworm *Eisenia fetida* (OECD 207)	14-d LC_{50}	> 500 mg/kg soil dw	1	ECHA
Soil microorganisms* (OECD 216)	28-d EC_{50} 28-d EC_{10}	360 mg/kg soil dw 11.5 mg/kg soil dw	1	ECHA
Soil microorganisms* (OECD 217)	28-d EC_{50} 28-d EC_{10}	> 593 mg/kg soil dw 1.5 mg/kg soil dw	1	ECHA
Mallard ducks	Single-dose (oral gavage) LC_{50}	206 mg/kg	2	ECHA
Mallard ducks	5-d (dietary) NOEC	> 2,500 ppm	1	ECHA

*organic carbon content of soil = 1.34% dry weight

Glutaraldehyde has also been evaluated in a terrestrial plants test: seedling emergence and seedling growth test (OECD TG 208). The test material contained 48.9% glutaraldehyde. The results are as follows:

Avena sativa (oats): 19/day EC_{50} value is > 1,000 mg/kg soil dry weight based on emergence rate, dry weight and shoot length. The NOECs for *Avena sativa* (oats) were $\geq$ 1,000 mg/kg dry weight on all three parameters tested.

Brassica napus (rapeseed): 19/day EC_{50} is > 1,000 mg/kg soil dry weight based on emergence rate and shoot length and 994 mg/kg soil dry weight based on dry weight. The NOECs were $\geq$ 1,000, 500 and 250 mg/kg soil dry weight for emergence rate, dry matter and shoot length, respectively.

Vicia sativa (vetch): 19/day EC_{50} is > 1,000 mg/kg soil dry weight based on emergence rate and shoot length, and 901 mg/kg soil dry weight based on dry weight. The NOECs were $\geq$ 1,000, 125 and 125 mg/kg soil dry weight for emergence rate, dry matter, and shoot length, respectively (ECHA) [Kl. score = 1].

D. Calculation of PNEC

The PNEC calculations for glutaraldehyde follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (10 mg/L), *Daphnia* (14 mg/L) and algae (0.375 mg/L). Results from chronic studies are also available for all three trophic levels, with the lowest NOEC being 0.025 mg/L for algae. On the basis that the data consists of short-term and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC of 0.025 mg/L for algae. The $PNEC_{water}$ is 0.0025 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.006 mg/kg wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (3.1/1280) \times 1000 \times 0.0025$
$= 0.006$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 4.8)/1000 \times 2400]$
$= 3.1\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{0c} \times f_{oc}$
$= 120 \times 0.04$
$= 4.8$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for glutaraldehyde in sediment is 120.
F_{oc} = fraction of organic carbon suspended sediment = 0.04 [default].

PNEC soil

Experimental results are available for three trophic level. An acute LC_{50} value is available for earthworms (> 500 mg/kg). Results from long-term studies are available for two trophic levels, with the lowest NOEC or EC_{10} being 1.5 mg/kg soil dry weight for soil organisms.

The EC_{10} value is corrected for bioavailability of glutaraldehyde in soil by normalising to the fraction organic carbon matter content (Fom) in the soil using the following equation:

$EC_{10(std)} = EC_{10(exp)} \times Fom_{soil(std)}/Fom_{soil(exp)}$

Where:
$Fom_{soil(std)}$ = 1% (default soil fraction organic matter)
$Fom_{soil(exp)}$ = 1.34% (see Table 9)
$EC_{10(std)}$ = 1.5 mg/kg x 1/1.34 = 1.12 mg/kg

On the basis that the data consists of one short-term result from one trophic level and two long-term results from two additional levels, an assessment factor of 50 has been applied to the lowest reported long-term EC_{10} of 1.12 mg/kg soil dry weight [corrected for organic carbon content] for soil organisms. The $PNEC_{soil}$ is 0.02 mg/kg soil dry weight.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Glutaraldehyde is readily biodegradable and thus does not meet the screening criteria for persistence.

The log K_{ow} for glutaraldehyde at different pH values ranges from -0.36 to -0.80. Thus, glutaraldehyde does not meet the screening criteria for bioaccumulation.

The lowest NOEC value from chronic aquatic toxicity studies is < 0.1 mg/L. Thus, glutaraldehyde meets the screening criteria for toxicity.

The overall conclusion is that glutaraldehyde is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity Category 3 [oral]

Acute Toxicity Category 2 [inhalation]

Skin Corrosion Category 1B

Eye Damage Category 1

Respiratory Sensitiser 1A

Skin Sensitiser 1A

STOT Single Exposure Category 3 [respiratory irritation]

Aquatic Acute Category 1

Aquatic Chronic Category 2

The appropriate hazard statements corresponding the GHS classifications are to be added to the SDS, including the non-GHS hazard statement “AUH071: Corrosive to the Respiratory Tract”.

B. Labelling

Danger

C. Pictograms

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

First aid information was obtained from the ECHA REACH database (ECHA).

Eye Contact

Wash immediately and continuously with flowing water for at least 30 minutes. Remove contact lenses after the first 5 minutes and continue washing. Obtain prompt medical consultation, preferably from an ophthalmologist. Eye wash fountain should be located in immediate work area.

Skin Contact

Take off contaminated clothing. Wash skin with soap and plenty of water for 15-20 minutes. Call a poison control centre or doctor for treatment advice. Wash clothing before reuse. Shoes and other leather items which cannot be decontaminated should be disposed of properly. Safety shower should be located in immediate work area.

Inhalation

Move person to fresh air. If a person is not breathing, call an emergency responder or ambulance, then give artificial respiration; if by mouth-to-mouth use rescuer protection (pocket mask, etc.). Call a poison control centre or doctor for treatment advice. If breathing is difficult, oxygen should be administered by qualified personnel.

Ingestion

If the person is fully alert and cooperative, have the person rinse mouth with plenty of water. In cases of ingestion have the person drink 4 to 10 ounces (120-300 mL) of water. Do not induce vomiting. Do not attempt mouth rinse if the person has respiratory distress, altered mental status, or nausea and vomiting. Call a physician and/or transport to an emergency facility immediately. See Note to Physician. Seek medical attention immediately.

Notes to Physician

Maintain adequate ventilation and oxygenation of the patient. May cause asthma-like (reactive airways) symptoms. Bronchodilators, expectorants, antitussives and corticosteroids may be of help. Glutaraldehyde may transiently worsen reversible airways obstruction including asthma or reactive airways disease. Chemical eye burns may require extended irrigation. Obtain prompt consultation, preferably from an ophthalmologist. If the burn is present, treat as any thermal burn, after decontamination. Due to irritant properties, swallowing may result in burns/ulceration of mouth,

stomach and lower gastrointestinal tract with subsequent stricture. Aspiration of vomitus may cause lung injury. Suggest endotracheal/oesophagal control if lavage is done. Probable mucosal damage may contraindicate the use of gastric lavage. Inhalation of vapours may result in skin sensitisation. In sensitised individuals, re-exposure to very small amounts of vapour, mist or liquid may cause a severe allergic skin reaction. No specific antidote. Treatment of exposure should be directed at the control of symptoms and the clinical condition of the patient. Have the Safety Data Sheet, and if available, the product container or label with you when calling a poison control centre or doctor, or going for treatment.

Medical Conditions Aggravated by Exposure

Excessive exposure may aggravate pre-existing asthma and other respiratory disorders (e.g., emphysema, bronchitis, reactive airways dysfunction syndrome).

Emergency Personnel Protection

First Aid responders should pay attention to self-protection and use the recommended protective clothing (chemical resistant gloves, splash protection). If the potential for exposure exists, refer to Section 8 of the Safety Data Sheet for specific personal protective equipment.

B. Fire Fighting Information

Firefighting information was obtained from the ECHA REACH database (ECHA).

Extinguishing Media

Use water fog, carbon dioxide, dry chemical or foam to extinguish combustible residues of this product

Specific Exposure Hazards

This material will not burn until the water has evaporated. Residue can burn. Some components of this product may decompose under fire conditions. The smoke may contain unidentified toxic and/or irritating compounds. Combustion products may include, and are not limited to, carbon monoxide and carbon dioxide.

Special Protective Equipment for Firefighters

Wear positive-pressure self-contained breathing apparatus (SCBA) and protective firefighting clothing (includes firefighting helmet, coat, trousers, boots and gloves). Avoid contact with this material during firefighting operations. If contact is likely, change to full chemical resistant firefighting clothing with self-contained breathing apparatus. If this is not available, wear full chemical resistant clothing with self-contained breathing apparatus and fight the fire from a remote location.

C. Accidental Release Measures

Information on accidental release measures was obtained from the ECHA REACH database (ECHA).

Personal Precautions

Use appropriate safety equipment. Evacuate area. Keep upwind of the spill. Ventilate area of leak or spill. Only trained and properly protected personnel must be involved in clean-up operations.

Environmental Precautions

Spills or discharge to natural waterways is likely to kill aquatic organisms. Prevent from entering into soil, ditches, sewers, waterways and/or groundwater.

Steps to be Taken if Material is Released or Spilt

Avoid making contact with spilt material; glutaraldehyde will be absorbed by most shoes. Always wear the correct protective equipment, consisting of splash-proof mono-goggles, or both safety glasses with side shields and a wraparound full-face shield, appropriate gloves and protective clothing. A self-contained breathing apparatus or respirator and absorbents may be necessary, depending on the size of the spill and the adequacy of ventilation.

Small spills: Wear the correct protective equipment and cover the liquid with absorbent material. Collect and seal the material and the dirt that has absorbed the spilt material in polyethylene bags and place in a drum for transit to an approved disposal site. Rinse away the remaining spilt material with water to reduce odour, and discharge the rinsate into a municipal or industrial sewer.

Large spills: In the case of nasal and respiratory irritation, vacate the room immediately. Personnel cleaning up should be trained and equipped with a self-contained breathing apparatus, or an officially approved or certified full-face respirator equipped with an organic vapour cartridge, gloves, and clothing impervious to glutaraldehyde, including rubber boots or shoe protection. Deactivate with sodium bisulphite (2-3 parts [by weight] per part of active substance glutaraldehyde), collect the neutralised liquid and place in a drum for transit to an approved disposal site.

D. Storage and Handling

Information on storage and handling was obtained from the ECHA REACH database (ECHA).

General Handling

Do not get in eyes, on skin, on clothing. Avoid breathing vapour. Do not swallow. Keep container closed. Use with adequate ventilation. Wear goggles, protective clothing and butyl or nitrile gloves. Wash thoroughly with soap and water after handling. Remove contaminated clothing and wash before reuse.

Other Handling Precautions

Do not spray or aerosolise the undiluted form of the product. Full personal protective equipment (including skin covering and full-face SCBA respirator) is required for dilutions or mixtures of the product used in a spray application.

Storage

Do not store in: Aluminium. Carbon steel. Copper. Mild steel. Iron. Shelf life: Use within 12 Months.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for glutaraldehyde in Australia is 0.1 ppm (0.41 mg/m^3) as a peak limitation, with a sensitisation notation. A peak limitation is defined by Safe Work Australia as a maximum or peak airborne concentration of a substance determined over the shortest analytically practicable period of time which does not exceed 15 minutes.

The information below on exposure controls and personal protection was obtained from the Halliburton Safety Data Sheet (SDS) on ALDACIDE® G ANTIMICROBIAL (revision date: 11-Dec-2014).

Engineering Controls

Use in a well-ventilated area. Local exhaust ventilation should be used in areas without good cross ventilation. If vapours are strong enough to be irritating to the nose or eyes, the TLV is probably being exceeded, and special ventilation or respiratory protection may be required.

Personal Protection Equipment

Respiratory Protection: If engineering controls and work practices cannot keep exposure below occupational exposure limits or if exposure is unknown, wear a NIOSH-certified, European Standard EN 149, AS/NZS 1715:2009, or equivalent respirator when using this product. Selection of and instruction on using all personal protective equipment, including respirators, should be performed by an Industrial Hygienist or other qualified professional. Full Facepiece Respirator with Organic vapour cartridge with particulate pre-filter.

Hand Protection: Chemical-resistant protective gloves (EN 374). Suitable materials for longer, direct contact (recommended: protection index 6, corresponding to > 480-minute permeation time as per EN 374): Butyl rubber gloves. (>= 0.7 mm thickness). This information is based on literature references and on information provided by glove manufacturers or is derived by analogy with similar substances. Please note that in practice the working life of chemical-resistant protective gloves may be considerably shorter than the permeation time determined in accordance with EN 374 as a result of the many influencing factors (e.g., temperature). If signs of wear and tear are noticed, then the gloves should be replaced. Manufacturer's directions for use should be observed because of the great diversity of types.

Skin Protection: Butyl coated apron or clothing.

Eye protection: Splash proof chemical mono-goggles or safety glasses with side shield in conjunction with a face shield. Do NOT wear contact lenses.

Other Precautions: Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

For aqueous glutaraldehyde solutions at a concentration that is corrosive (i.e., 30% and higher):

Australia Dangerous Goods

UN3265, Corrosive Liquid, Acidic, Organic, N.O.S. (Contains Glutaraldehyde)

Class 8

Packing Group III

Environmentally Hazardous Substance

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state, and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII.REFERENCES

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

Ema, M., Itami, T., and Kawasaki, H. (1992). Teratological assessment of glutaraldehyde in rats by gastric intubation. Toxicol. Lett. 63: 147-153.

enHealth Human Risk Assessment (HHRA). (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Frantz, S.W., Beskitt, J.L., Tallant, M.J., Futrell, J.W., and Ballantyne, B. (1993). Glutaraldehyde: species comparisons of in vitro skin penetrations. J. Toxicol.-Cut. & Ocular Toxicol. 12: 349-361.

Gross, E.A., Mellick, P.W., Kari, F.W., Miller, F.J., and Morgan, K.T. (1994). Histopathology and cell replication responses in the respiratory tract of rats and mice exposed by inhalation to glutaraldehyde for up to 13 weeks. Fundam. Appl. Toxicol. 23: 348-362.

Haseman, J.K., Hailey, J.R., and Morris, R.W. (1998). Spontaneous neoplasm incidences in Fischer 344 rats and B6C3F_1 mice in two-year carcinogenicity studies: A National Toxicology Program update. Toxicol. Pathol. 26: 428-441.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology 25:1-5.

Leung, H.W. (2001). Ecotoxicology of glutaraldehyde: review of environmental fate and effects studies. Ecotoxicol. Environ. Safety 49: 26-39.

Mirsalis, J.S., Tyson, C.K., Steinmetz, K.L., Loh, E.K., Hamilton, C.M., Bakke, J.P., and Spalding, J.W. (1989). Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in vivo treatment: testing of 24 compounds. Environ. Mol. Mutagen. 14: 155-164.

Neeper-Bradley, T.L., and Ballantyne, B. (2000). Two-generation reproduction study by dosing with glutaraldehyde in the drinking water of CD rats. J. Toxicol. Environ. Health A 61: 107-129.

NICNAS. (1994). Glutaraldehyde – Full Public Report. National Industrial Chemicals Notification and Assessment Scheme (NICNAS), AGPS, Canberra, Australia.

OECD. (1995). OECD-SIDS document on Glutaraldehyde, CAS No. [redacted] UNEP Publications. Accessed at: http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=b13f2e48-0425-4a8a-b7b8-c04cfaab06e8

Stromberg, P.C. (1985). Large granular lymphocyte leukaemia in F344 rats: Model for human T lymphoma, a malignant histiocytosis and T-cell chronic lymphocytic leukaemia. Am. J. Pathol. 119: 517-519.

Thomas, J., Haseman, J.K., Goodman, J.I., Ward, J.M., Loughran, Jr., T.P., and Spencer, P.J. (2007). A review of large granular lymphocytic leukaemia in Fischer 344 rats as an intial step toward evaluating the implication of the endpoint to human cancer risk assessment. Toxicol. Sci. 99: 3-19.

van Birgelen, A.P.J.M., Chou, B.J., Renne, R.A., Grumbein, S.L., Roycroft, J.H., Hailey, J.R., and Bucher, J.R. (2000). Effects of glutaraldehyde in a 2-year inhalation study in rats and mice. Toxicol. Sci. 55: 195-205.

Van Miller, J.P., Hermansky, S.J., Losco, P.E., and Ballantyne, B. (2002). Chronic toxicity and oncogenicity study with glutaraldehyde dosed in the drinking water of Fischer 344 rats. Toxicol. 175: 177-189.

Vergnes, J.S., and Ballantyne, B. (2002). Genetic toxicology studies with glutaraldehyde. J. Appl. Toxicol. 22: 45-60.

Ward, J.M., Rehm, S., and Reynolds, C.W. (1990). Tumours of the haematopoietic system. In: Pathology of Tumours in Laboratory Animals, Vol. 1, Second Edition (Turusov, V.S., and Mohr, U., Eds.), pp. 625-657, International Agency for Research on Cancer, Lyon, France.

Zissu, D., Bonnet, P., and Binet, S. (1998). Histopathological study in B6C3F1 mice chronically exposed by inhalation to glutaraldehyde. Toxicol. Lett. 95: 131-139.

GUAR GUM

This dossier on guar gum (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the chemistry database PubChem. Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): disodium;[[[5-(6-aminopurin-9-yl)-3-hydroxyoxolan-2-yl]oxy-methoxyphosphoryl]oxy-oxidophosphoryl] hydrogen phosphate

CAS RN: [redacted]

Molecular weight: 535.15 g/mol; 200,000 to 300,000 daltons (Glickman, 1969)

Molecular formula: $C_{10}H_{14}N_5Na_2O_{12}P_3$

Synonyms: GU-052, guar flour, guaran, gum guar, slocose

SMILES:: COP(=O)(OC1C(CC(O1)N2C=NC3=C(N=CN=C32)N)O)OP(=O)([O-])OP(=O)(O)[O-].[Na+].[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Guar Gum

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Off-white to yellowish-white powder	-	PubChem
Vapour Pressure	Negligible	-	PubChem
Water Solubility	< 1 g/L @ 20°C (insoluble)	-	PubChem

III. ENVIRONMENTAL FATE PROPERTIES

Guar gum is a carbohydrate polymer consisting of D-mannose and D-galactose sugars from the guar plant or cluster bean. As a high molecular weight polysaccharide polymer, guar gum is expected to have a negligible vapour pressure. If released to air, a negligible vapour pressure indicates guar gum will exist solely in the particulate phase in the atmosphere. Particulate-phase guar gum will be removed from the atmosphere by wet and dry deposition. If released to soil, guar gum is expected to have no mobility since it is a polymer that binds strongly with soil particles. Volatilisation from moist soil surfaces is not expected to be an important fate process based upon a negligible Henry's Law constant. Likewise, guar gum is not expected to volatilise from dry soil surfaces based upon its vapour pressure. If released into water, guar gum is expected to adsorb to suspended solids and sediment (PubChem). Half-life data was not available.

Guar gum is expected to readily undergo microbial biodegradation in the environment (on the basis that it is a polysaccharide and expected to be readily biodegradable), and the potential to bioaccumulate in organisms is considered to be low (DoEE, 2017 and USEPA, 2005).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Guar gum exhibits very low acute toxicity by the oral route. It is non-irritating to the skin and minimally irritating to the eyes. Repeated dose toxicity studies in rats showed minimal toxicity from exposure to guar gum in the diet. Guar gum is not genotoxic or carcinogenic. Oral exposure to guar gum did not affect fertility in rats; nor was there any indication of developmental toxicity in either rats or mice.

NICNAS has assessed Guar Gum in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to human health[1]

B. Acute Toxicity

The oral LD_{50} in rats was reported to be 7,060 mg/kg (Graham *et al.*, 1981) [Kl. Score = 2].

C. Irritation

Guar gum is non-irritating to the skin and minimally irritating to the eyes (McCarty *et al.*, 1990). Nonetheless, ECHA warns that the substance may cause serious eye irritation.

D. Sensitisation

There were reports of workers sensitised to guar gum in a carpet-manufacturing plant. Immediate skin reactivity to guar gum was observed in 8 out of 162 employees, and 11 of 133 participants had serum IgE antibodies to guar gum. These findings are difficult to interpret since carbohydrates, such as guar gum, are generally not associated with allergenicity (Malo, 1990).

E. Repeated Dose Toxicity

<u>Oral</u>

Male and female Osborne-Mendel rats were given diets containing 0, 1, 2, 4, 7.5, or 15% guar gum for 91 days. The average daily intakes are: 0; 580; 1,187; 2,375; 4,561 and 10,301 mg/kg/day for males; and 0; 691; 1,362; 2,762; 5,770 and 13,433 mg/kg/day for females. There were no deaths during the study. Body weights were significantly decreased in the ≥1% females and the ≥7.5% males; biologically significant changes (>10%) were seen in the 7.5% females and the 15% males. Liver weights were decreased in the ≥1% dietary groups. Kidney weights were decreased in the ≥7.5% dietary groups and were borderline significant in the 4% group. The 15% group males had reduced bone marrow cellularity; although the level was within normal limits, several of the rats were at the lower end of the normal range.

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]2C+

The NOAEL for this study is 4% in the diet or 2,762 mg/kg/day based on reduced body weights in the female rats (Graham *et al.*, 1981) [Kl. Score = 2].

Male and female F344 rats and B6C3F_1 mice were given diets containing 0; 6,300; 12,500; 25,000; 50,000 or 100,000 ppm guar gum for 13 weeks. Mean body weights were decreased in the 100,000 ppm male rats and in the ≥50,000 ppm female mice. A dose-related decrease in feed consumption was observed for male and female rats; male and female mice were comparable or higher than that of controls. There were no compound-related clinical signs or histopathological effects. The NOAELs for this study are 50,000 and 25,000 ppm for rats and mice, respectively. Using the fraction of body weight that rats and mice consume per day as food (0.05 and 0.13, respectively; USEPA), the NOAELs corresponds to 2,500 mg/kg/day for rats and 3,250 mg/kg/day for mice (NTP, 1982) [Kl. Score = 2].

Male and female F344 rats and B6C3F_1 mice were given diets containing 0 ppm, 25,000 ppm or 50,000 ppm guar gum for 103 weeks. Mean body weights of the high-dose females were lower than those of the controls after week 20 for mice and week 40 for rats. No compound-related clinical signs or adverse effects on survival were observed. Feed consumption by dosed rats and mice of either sex was lower than that of controls. There were no non-neoplastic histopathological effects in either rats or mice that were treatment-related. The NOAEL for both rats and mice is 25,000 ppm. Using the fraction of body weight that rats and mice consume per day as food (0.05 and 0.13, respectively; USEPA), the NOAELs correspond to 1,250 mg/kg/day for rats and 3,250 mg/kg/day for mice (NTP, 1982) [Kl. Score = 2].

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

Guar gum was not mutagenic to *S. typhimurium* strains TA 97, TA 98, TA 100, TA 102, TA 104, TA 1535, TA 1537, and TA1538 in the presence or absence of metabolic activation (Zeiger *et al.*, 1992) [Kl. Score = 2].

In Vivo Studies

Guar gum was inactive in a rat bone marrow cytogenetic assay at doses up to 5,000 mg/kg (Johnson *et al.*, 2015) Kl. Score = 4].

In a rat dominant lethal mutation test, rats were dosed by oral gavage with either a single or multiple doses of up to 5,000 mg/kg guar gum. There was no indication of a mutagenic effect by guar gum (Lee *et al.*, 1983) [Kl. Score = 2].

G. Carcinogenicity

Male and female F344 rats were given diets containing 0 ppm, 25,000 ppm or 50,000 ppm guar gum for 103 weeks in an NTP chronic bioassay. There were increased incidences of

adenomas of the pituitary in male rats and pheochromocytomas of the adrenal medulla in female rats that were statistically significant, but these differences were considered to be unrelated to guar gum administration. When pituitary adenomas or carcinomas and when pheochromocytomas or malignant pheochromocytomas were combined, the statistical differences disappeared. NTP concluded that, under conditions of this bioassay, guar gum was not carcinogenic for F344 rats (NTP, 1982) [Kl. Score = 2].

Male and female $B6C3F_1$ mice were given diets containing 0 ppm, 25,000 ppm or 50,000 ppm guar gum for 103 weeks in an NTP chronic bioassay. Hepatocellular carcinomas occurred in treated male mice at incidences that were significantly lower than that in controls. The combined incidence of male mice with either hepatocellular adenomas or carcinomas was also significantly lower in the high-dose group. NTP concluded that, under conditions of this bioassay, guar gum was not carcinogenic for $B6C3F_1$ mice (NTP, 1982) [Kl. Score = 2].

H. Reproductive Toxicity

Oral

Male and female Osborne-Mendel rats were fed diets containing 0, 1, 3, 4, 7.5, or 15% guar gum for 13 weeks before mating, during mating and throughout gestation. The daily intakes for the female rats during gestation were 0; 700; 1,400; 2,700; 5,200 or 11,800 mg/kg/day. Fertility was unaffected by treatment. There were slightly fewer corpora lutea and implantations in the 15% dietary group, but implantation efficiency was unaffected. The NOAEL for reproductive toxicity is 5,200 mg/kg/day (Collins *et al.*, 1987) [Kl. Score = 2].

I. Developmental Toxicity

Oral

Male and female Osborne-Mendel rats were fed diets containing 0, 1, 3, 4, 7.5, or 15% guar gum for 13 weeks before mating, during mating and throughout gestation. The daily intake for the female rats during gestation were 0; 700; 1,400; 2,700; 5,200 or 11,800 mg/kg/day. There were no deaths during the study. In the 15% group, the number of viable foetuses per litter were slightly reduced but was not statistically significantly different from controls. The authors indicated that the reduction may have been an effect of the decreased number of corpora lutea because the number of resorptions was unaffected in this treatment group. There was no treatment-related effect on foetal development or sex distribution, and there were no teratogenic effects (Collins *et al.*, 1987) [Kl. Score = 2].

Pregnant female rats were dosed by oral gavage with 0, 9, 42, 200 or 900 mg/kg guar gum on GD 6 to 15. There was no maternal or developmental toxicity at any dose level. The NOAEL for maternal and developmental toxicity is 900 mg/kg/day (FDRL, 1973) [Kl. Score = 2].

Pregnant female CD-1 mice were dosed by oral gavage with 0, 8, 37, 170, or 800 mg/kg guar gum on GD 6 to 15. A significant number of deaths (6 out of 29) occurred in the 800 mg/kg dose group. There were indications of maternal toxicity in the surviving high-dose dams. There was no developmental toxicity at any dose level. The NOAELs for maternal and developmental toxicity are 170 and 800 mg/kg/day, respectively (FDRL, 1973) [Kl. Score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for guar gum follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

In a two-year NTP chronic bioassay, female rats and mice given 50,000 ppm guar gum in their feed had lower body weights. There were no treatment-related non-neoplastic lesions in either rats or mice. The NOAEL for this study is 25,000 ppm for rats and mice, which corresponds to 1,250 mg/kg/day for rats and 3,250 mg/kg/day for mice.

The NOAEL of 1,250 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

- UF_A (interspecies variability) = 10
- UF_H (intraspecies variability) = 10
- UF_L (LOAEL to NOAEL) = 1
- UF_{Sub} (subchronic to chronic) = 1
- UF_D (database uncertainty) = 1
- Oral RfD = 1,250/(10 x 10 x 1 x 1 x 1) = 1,250/100 = 13 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

- Human weight = 70 kg (ADWG, 2021)
- Proportion of water consumed = 10% (ADWG, 2021)
- Volume of water consumed = 2L (ADWG, 2021)
- Drinking water guidance value = (13 x 70 x 0.1)/2 = 46 mg/L

B. Cancer

Guar gum was not carcinogenic to rats or mice in two-year dietary studies. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Guar gum does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Guar gum is a polysaccharide polymer. It has low acute toxicity concern for fish but exhibits moderate acute toxicity to invertebrates (*Daphnia*).

B. Aquatic Toxicity

Acute Studies

The 96-hour LC_{50} for *Oncorhynchus mykiss* is 218 mg/L (Biesinger *et al.*, 1976) [Kl. Score = 2].

The 48-hour and 96-hour LC_{50} values for *Daphnia magna* are 42 mg/L and <6.2 mg/L, respectively (Biesinger *et al.*, 1976) [Kl. Score = 2].

Chronic Studies

No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for guar gum follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for two trophic levels. The acute LC_{50} values are available for fish (218 mg/L) and *Daphnia* (<6.2 mg/L). No chronic studies are available. On the basis that the data consists of acute studies from two trophic levels, an assessment factor of 1,000 has been applied to the lowest reported LC_{50} value of 6.2 mg/L for *Daphnia*. The $PNEC_{water}$ is 0.006 mg/L.

PNEC sediment

No experimental toxicity data on sediment organisms are available. The K_{ow} and K_{oc} of guar gum cannot be calculated using EPI Suite because the molecular weight of guar gum greatly exceeds the limit of 1,000. Thus, the equilibrium partition method cannot be used to determine a $PNEC_{sediment}$ and the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No experimental toxicity data on soil organisms are available. The K_{ow} and K_{oc} of guar gum cannot be calculated using EPI Suite because the molecular weight of guar gum greatly exceeds the limit of 1,000. Thus, the equilibrium partition method cannot be used to determine a $PNEC_{soil}$ and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU Reach Criteria methodology (DEWHA, 2009; ECHA, 2008).

Guar gum is a naturally occurring polysaccharide from the guar plant or cluster bean; it expected to be readily biodegradable. Thus it is not expected to meet the screening criteria for persistence.

The potential to bioaccumulate in organisms is considered to be low. Thus guar gum is not expected to meet the criteria for bioaccumulation.

There are no adequate chronic aquatic toxicity studies available on guar gum. The acute LC_{50} values for guar gum are >1 mg/L in fish and invertebrates. Therefore, guar gum does not meet the screening criteria for toxicity.

The overall conclusion is that guar gum is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Aquatic Toxicity Category 2

B. Labelling

Warning!

According to the classification provided by companies to ECHA in CLP notifications, this substance causes serious eye irritation.

C. Pictogram

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Remove contaminated clothing. Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

Notes to Physician

May cause asthma-like (reactive airways) symptoms.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus for fire fighting.

C. Accidental Release Measures

Personal Precautions

Avoid dust formation.

Environmental Precautions

No special environmental precautions required.

Steps to be Taken if Material is Released or Spilled

Sweep up and dispose in suitable, closed containers.

D. Storage And Handling

General Handling

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard specifically for guar gum.

Engineering Controls

Ensure adequate ventilation.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Handle with gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Guar gum is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Biesinger, K.E., Lemke, A.E., Smith, W.E., and Tyo, R.M. (1976). Comparative toxicity of polyelectrolytes to selected aquatic animals. J. Water Pollut. Control Fed. 48: 183-187; cited in U.S. EPA ECOTOX database.

Collins, T.F.X., Welsh, J.J., Black, T.N., Graham, S.L., and O'Donnell, M.W., Jr. (1987). Study of the teratogenic potential of guar gum. Food Chem. Toxicol. 25: 807-814.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Food and Drug Research Laboratories, Inc. [FDRL]. (1973). Teratologic evaluation of FDA 71-16 (guar gum) in mice, rats, hamsters, and rabbits. Final report prepared under DHEW contract No. FDA 71-260. Maspeth, NY. NTIS No. PB-223-819/4; cited in CIR (2015).

Glickman M. (1969). Gum technology in the Food Industry, pp. 590, Academic Press, New York; cited in Yoon *et al.* (1998).

Graham, S.L., Arnold, A., Kasza, L., Ruffin, G.E., Jackson, R.C., Watkins, T.L., and Graham, C.H. (1981). Subchronic effects of guar gum in rats. Fd. Cosmet. Toxicol. 19: 287-290.

Johnson, W., Jr., Heldreth, B., Bergfeld, W.F., Belsito, D.V., Hill, R.A., Klaassen, C.D., Liebler, D.C., Marks, J.G., Jr., Shank, R.C., Slaga, T.J., Snyder, P.W., and Andersen, F.A. (2015). Safety assessment of galactomannans as used in cosmetics. Int. J. Toxicol. 34(Suppl. 1): 35S-65S.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Lee, W.R., Abrahamson, S., Valencia, R., Von Halle, E.S., Wuergler, F.E., and Zimmering, S. (1983). The sex-linked recessive lethal test for mutagenesis in *Drosophila melanogaster*. A report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat. Res. 123: 183-279.

Malo, J.L., Cartier, A., L'Archevêque, J., Ghezzo, H., Soucy, F., Somers, J., and Dolovich, J. (1990). Prevalence of occupational asthma and immunologic sensitization to guar gum among employees at a carpet-manufacturing plant. J. Allergy Clin. Immunol. 86: 562-569.

McCarty, J.D., Weiner, M., Freeman, C., Aguinaldo, E.R., and Fletcher, M.J. (1990). Primary skin and ocular irritation studies on five food additive plant gums. J. Am. Coll. Toxicol. 1(1): 50-51.

NTP. (1982). NTP Technical Report on the Carcinogenesis Bioassay of Guar Gum (CAS No. [redacted] in F344 Rats and B6C3F_1 Mice (Feed Study), National Toxicology Program, Research Triangle Park, NC.

PubChem. PubChem open chemistry database: https://pubchem.ncbi.nlm.nih.gov

United States Environmental Protection Agency [USEPA]. (2005). Science Assessment for Hydroxypropyl Guar Gum, Lower Risk Pesticide Chemical Focus Group, Office of Prevention, Pesticides and Toxic Substances, US Environmental Protection Agency. Accessed: http://www.epa.gov/opprd001/inerts/hydroxypropyl.pdf

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1992). Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen. 21: 2-141.

HYDROCHLORIC ACID

This dossier on hydrochloric acid presents the most critical studies pertinent to the risk assessment of hydrochloric acid in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from OECD-SIDS documents (OECD, 2002a,b) and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

NICNAS has assessed hydrochloric acid in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to the environment.

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Chlorane

CAS RN: [redacted]

Molecular formula: HCl

Molecular weight: 36.46 g/mol

Synonyms: Hydrochloric acid; HCl; chlorane; hydrogen chloride; muriatic acid; chlorohydric acid

SMILES: Cl

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of hydrochloric acid

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Colourless to slightly yellow gas of fuming liquid with pungent, irritating odour.	2	ECHA
Melting Point	-114.22°C	2	ECHA
Boiling Point	-85°C	4	ECHA
Density	1.639 kg/m^3 @ 0°C (gas) 1190 kg/m^3 @ 15°C (liquid)	4	ECHA
Vapour Pressure	4,104 kPa 4,723 kPa @ 25°C	4	ECHA
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	Very soluble	4	ECHA
Viscosity	1.7 × 10^{-6} m^{2}s @ 20°C	1	ECHA

Hydrochloric acid can exist in a gaseous phase at room temperature and pressure. Hydrochloric acid is also very soluble in water and is a strong acid that dissociates completely in water to hydrogen (H^+) and chloride (Cl^-) ions.

III. ENVIRONMENTAL FATE PROPERTIES

Due to its high water solubility, hydrochloric acid will be found predominantly in the aquatic environment where it dissociates completely to hydrogen (H^+) and chloride (Cl^-) ions. Both ions are ubiquitous in the environment (UNEP, 1995).

The addition of hydrochloric acid to an aquatic ecosystem may decrease the pH depending on the buffer capacity of the receiving water. In general, the buffer capacity is regulated by the equilibria between CO_2, HCO_3^- and CO_3^{2-}:

$$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+ \ (pKa_1 = 6.35)$$
$$HCO_3^- \leftrightarrow CO_3^{2-} + H^+ \ (pKa_2 = 10.33)$$

A release of hydrochloric acid into the aquatic environment from the use of HCl could potentially increase the chloride concentration and decrease the pH in the aquatic environment. Table 2 shows the amount of hydrochloric acid that would need to be added to bicarbonate solutions to obtain pH values of 6.0 and 4.0. The UNEP (1995) study reported that the 10th percentile, mean and the 90th percentile of bicarbonate concentrations in 77 rivers in North America, South America, Asia, Africa, Europe and Oceania were 20, 106 and 195 mg/L, respectively. The data show that the decrease in pH depends on the buffer capacity (bicarbonate concentration) of the receiving water. The calculated values in Table 2 were confirmed experimentally.

Table 2: Buffer capacity to maintain the pH based on bicarbonate concentration from UNEP monitoring data (de Groot and van Dijk, 2002; taken from OECD, 2002b)

Initial concentration of HCO_3^-	Final pH	Concentration of HCl required to obtain the final pH value
		Calculated (mg/L)
20 mg/L HCO_3^- (10th percentile 77 rivers)	6.0	8.28
	4.0	11.9
106 mg/L HCO_3^- (mean value of 77 rivers)	6.0	43.9
	4.0	63.2
195 mg/L HCO_3^- (90th percentile 77 rivers)	6.0	80.7
	4.0	116.3

H^+ and Cl^- ions will not adsorb on the particulate matter or surfaces and will not accumulate in living tissues (OECD, 2002a,b).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Hydrochloric acid is a corrosive liquid. Depending on the concentration, aqueous solutions of hydrochloric acid (HCl) are either corrosive, irritating or non-irritating to the skin, eyes and gastrointestinal tract. Vapours from aqueous solutions of HCl can cause respiratory irritation. HCl is not a skin sensitiser. Subchronic inhalation studies show localised irritation to the upper respiratory tract of rats and mice, but no systemic toxicity. No repeated dose toxicity studies have been

conducted by the oral route. Positive findings have been reported in some *in vitro* genotoxicity studies, which are considered to be the result of the pH change in the test system. A lifetime inhalation study showed no carcinogenicity in rats exposed to HCl. No adequate reproductive or developmental studies have been conducted on HCl.

B. Acute Toxicity

The oral LD_{50} values in rats were reported to be 238 to 277 mg/kg and 700 mg/kg (OECD, 2002a,b) [Kl. scores = 2 and 4, respectively].

The lethal dose by dermal exposure is > 5,010 mg/kg for rabbits (OECD 2002a,b) [Kl.score=4].

The LC_{50} values in rats for HCl gas are 40,989 and 4,701 ppm for 5 and 30 minutes, respectively (ECHA) [Kl.score=2]. The LC_{50} values in rats for HCl aerosol are 31,008 and 5,666 ppm (45.6 and 8.3 mg/L) for 5 and 30 minutes, respectively (ECHA) [Kl.score=2].

C. Irritation

Application of a 37% aqueous solution of HCl for 1 or 4 hours was corrosive to the skin of rabbits (OECD, 2002a,b) [Kl.score=2]. Application of 0.5 mL of a 17% solution of aqueous solution of HCl for 4 hours was corrosive to the skin of rabbits (OECD, 2002a,b) [Kl.score=3]. Moderate skin irritation was observed in rabbits following an application of 0.5 mL of a 3.3% aqueous solution of HCl for five days; no irritation was observed with 0.5 mL of a 1% aqueous solution (OECD, 2002a,b) [Kl.score=2]. In humans, an aqueous solution of 4% of HCl was slightly irritating, while a 10% solution was sufficiently irritating to be classified as a skin irritant (OECD, 2002a,b).

Instillation of 0.1 mL of a 10% aqueous solution of HCl to the eyes of rabbits resulted in severe eye irritation (ECHA) [Kl.score=2]. Instillation of 0.1 mL of a 5% solution of HCl produced corneal opacity, iridial lesions, conjunctival redness and chemosis in 3/3 animals at 1 hour and at day one post-instillation. There was no recovery in any animal and the study was terminated on day two (ECHA) [Kl.score=1].

D. Sensitisation

Hydrochloric acid was not a skin sensitiser in a guinea pig maximisation test (ECHA) [Kl.score=2].

E. Repeated Dose Toxicity

<u>Oral</u>

No adequate studies were located.

<u>Inhalation</u>

Male and female SD rats and F344 rats were exposed by inhalation to 0, 10, 20 or 50 ppm 6 hours/day, 5 days/week for up to 90 days. Clinical signs were mainly indicative of the irritant/corrosive nature of HCl. Body weights were significantly decreased in the 50 ppm male F344 rats. There were no treatment-related effects on the haematology or clinical chemistry parameters or urinalysis. At study termination, heart, kidney and testes weights were increased in the 100 and/or 50 ppm groups; these changes were considered to be mainly related to the treatment-

related effect on body weight. Histopathological examination showed minimal to mild rhinitis in the ≥ 20 ppm dose groups of both strains of rats (both sexes). The NOAELs for systemic toxicity and localised irritation (site-of-contact) are 20 and 10 ppm, respectively (ECHA) [Kl.score=1].

Male and female $B6C3F_1$ mice were exposed by inhalation to 0, 10, 20 or 50 ppm HCl, 6 hours/day, 5 days/week for up to 90 days. Clinical signs were mainly indicative of the irritant/corrosive nature of HCl. Body weights were significantly decreased in the 50 ppm groups. At study termination, absolute liver weights were decreased in the 50 ppm males. Histopathologic examination showed only eosinophilic globules in the nasal epithelium in the 50 ppm animals. The NOAEL for this study is 20 ppm (ECHA) [Kl.score=1].

Male SD rats were exposed by inhalation to 0 or 10 ppm HCl 6 hours/day, 5 days/week for 128 weeks. Survival and body weights were similar between treated and control groups. There was a higher incidence of hyperplasia of the larynx compared to control, but no serious irritating effects of the nasal epithelium (ECHA) [Kl.score=2].

Dermal

No studies were located.

F. Genotoxicity

In vitro Studies

Table 3 presents the *in vitro* genotoxicity studies on hydrochloric acid.

Table 3: *In vitro* genotoxicity studies on hydrochloric acid

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	+	2	ECHA
Chromosomal aberration (CHO cells)	+	+	2	ECHA
Saccharomyces cerevisiae (mitotic recombination	-	-	2	ECHA
E. coli W3110 (pol A+) and P3078 (pol A-) repair assay	-	-	2	ECHA

* +, positive; -, negative

In the mouse lymphoma assay, the mutant frequency increased as the pH was lowered to 6.5 to 6.0 (from increased HCl) in the presence of metabolic activation. A decrease in pH from the addition of HCl to the medium also resulted in clastogenic effects to CHO cells in the absence or presence of metabolic activation. The positive findings in these two studies are considered to be the result of the pH change in the test media.

In vivo Studies

No adequate studies were located.

G. Carcinogenicity

Oral

No studies were located.

Inhalation

Male SD rats were exposed by inhalation to 0 or 10 ppm HCl 6 hours/day, 5 days/week for 128 weeks. Survival and body weights were similar between treated and control groups. There was a higher incidence of hyperplasia of the larynx compared to control, but no serious irritating effects of the nasal epithelium. There was no increased incidence of tumours in the HCl-treated rats compared with controls (ECHA) [Kl.score=2].

H. Reproductive Toxicity

No studies were located.

I. Developmental Toxicity

No adequate studies were located.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Repeated dose, reproductive and developmental toxicity studies by the oral route have not been conducted on hydrochloric acid. These toxicity studies would have questionable usefulness because of the corrosive/irritating nature of hydrochloric acid, which would limit the amount of absorbed HCl. Hydrochloric acid dissociates to hydrogen and chloride ions in bodily fluids, and a significant amount of these ions are already ingested in foods. Furthermore, both ions are present in the body and are highly regulated by homeostatic mechanisms. Thus, an oral toxicological reference and drinking water guidance values were not derived from hydrochloric acid.

The Australian drinking water guideline values for pH (6.5 to 8.5) and chloride (250 ppm, aesthetics) may be applicable (ADWG, 2011).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Hydrochloric acid does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The hazard of hydrochloric acid for aquatic organisms is caused by the hydrogen ion (H^+). The toxicity values in terms of mg/L are not relevant because of the varying buffering capacity of different test systems and different aquatic ecosystems.

B. Aquatic Toxicity

Acute Studies

The acute aquatic toxicity studies on hydrochloric acid are listed in Table 4.

Table 4: Acute aquatic toxicity studies on hydrochloric acid

Test Species	Endpoint	Results	Klimisch Score	Reference
Lepomis macrochirus	96-hour LC_{50}	pH 3.25 – 3.5 (20 mg/L)	2	ECHA; OECD 2002a,b
Daphnia magna	48-hour EC_{50}	pH 4.92 (0.45 mg/L)	1	ECHA
Chlorella vulgaris	72-hour EC_{50} 72-hour EC_{10}	pH 4.7 [growth rate] (0.73 mg/L) PH 4.7 (0.364 mg/L)	1	ECHA

Chronic Studies

No chronic studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

PNEC values[1] were not derived for hydrochloric acid because factors such as the buffer capacity, the natural pH and the fluctuation of the pH are very specific for a certain ecosystem.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (IChEMS, 2022; ECHA, 2023).

Hydrochloric acid is an inorganic salt that dissociates completely to hydrogen and chloride ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both hydrogen and

[1] An aquatic PNEC (mg/L) has been derived as part of the chemical assessment conducted under National Industrial Chemicals Notification and Assessment Scheme (NICNAS). However, the chronic aquatic toxicity data set used to derive the PNEC value was not available for review.

chloride ions are also ubiquitous and are present in water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Hydrogen and chloride ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated. Thus, hydrochloric acid is not expected to bioaccumulate.

No chronic toxicity data exist on hydrochloric acid. The acute EC_{50} values are > 1 mg/L in fish, < 1 mg/L for invertebrates and algae. Thus, hydrochloric acid meets the screening criteria for toxicity.

The overall conclusion is that hydrochloric acid is a PBT substance based on toxicity to invertebrates and algae.

IX. CLASSIFICATION AND LABELLING

A. Classification

For HCl concentrations of >25%:

- Metal Corrosive Category 1
- Skin Corrosive 1B
- STOT SE Category 3 [Respiratory irritant]

In addition to the hazard statements corresponding to the GHS classification for corrosive, the following non-GHS hazard statement is to be added to the SDS: AUH071: Corrosive to the Respiratory Tract.

B. Labelling

<u>Danger</u>

According to the classification provided by companies to ECHA in REACH registrations this substance causes severe skin burns and eye damage, is toxic if inhaled, may damage fertility or the unborn child, causes serious eye damage, may cause damage to organs through prolonged or repeated exposure, may be corrosive to metals and may cause respiratory irritation.

C. Pictogram

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of the body with soap and fresh water. Get medical attention immediately.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the aid of a pocket mask equipped with a one-way valve or another proper respiratory medical device. Give artificial respiration if the victim is not breathing. Get medical attention immediately.

Ingestion

Rinse mouth and lips with plenty of water if a person is conscious. Do not induce vomiting. Do not use mouth-to-mouth method if the victim ingested the substance. Obtain medical attention immediately if ingested.

Notes to Physician

Treat as corrosive due to pH of the material. All treatments should be based on observed signs and symptoms of distress in the patient.

B. Firefighting Information

Extinguishing Media

Use dry chemical, carbon dioxide, water spray or fog, or foam.

Specific Exposure Hazards

Containers may explode when heated. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following materials: halogenated compounds, may release dangerous gases (chlorine).

Special Protective Equipment for Firefighters

Structural firefighters' protective clothing provides limited protection in fire situations only; it is not effective in spill situations where direct contact with the substance is possible. Wear chemical protective clothing that is specifically recommended by the manufacturer. It may provide little or no thermal protection. Wear positive pressure self-contained breathing apparatus (SCBA). Move containers from the fire area if you can do it without risk.

C. Accidental Release Measures

Personal Precautions

Ventilate enclosed areas. Do not walk through spilt material. Do not touch damaged containers or spilt material unless wearing appropriate protective clothing. Wear appropriate personal protective equipment, avoid direct contact. Do not breath mist, vapours or spray. Do not get in eyes, on skin or on clothing.

Environmental Precautions

Prevent entry into waterways, sewers, basements or confined areas.

Steps to be Taken if Material is Released or Spilt

ELIMINATE all ignition sources (no smoking, flares, sparks or flames in immediate area). As an immediate precautionary measure, isolate spill or leak area for at least 50 meters in all directions. Keep unauthorised personnel away. Stay upwind. Keep out of low areas. Do not get water inside container.

D. Storage and Handling

General Handling

Handle and open container with care. Use only with adequate ventilation. Keep away from heat. Use caution when combining with water. DO NOT add water to corrosive liquid; ALWAYS add corrosive liquid to water while stirring to prevent the release of heat, steam and fumes. Wear appropriate personal protective equipment, and avoid direct contact. Do not breath mist, vapours or spray. Do not get in eyes, on skin or on clothing. Do not ingest. Wash thoroughly with soap and water after handling and before eating, drinking or using tobacco.

Storage

Keep contain tightly closed. Store in a cool, dry, well-ventilated place. Keep away from incompatible materials. Keep from direct sunlight. Separate from alkalis. Do not store above 49°C/120°F.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for hydrochloric acid in Australia is 5 ppm (7.5 mg/m^3 as a peak limitation, with a sensitisation notation). A peak limitation is defined by Safe Work Australia as a

maximum or peak airborne concentration of a substance determined over the shortest analytically practicable period of time that does not exceed 15 minutes.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. Use a properly fitted, air-purifying or air-fed respirator complying with an approved standard if a risk assessment indicates this is necessary. Respirator selection is based on known or anticipated exposure levels, the hazard of the product and the safe working limits of the selected respirator.

Hand Protection: Chemical-resistant, impervious gloves complying with an approved standard should be worn at all times when handling chemical products if a risk assessment indicates this is necessary. Considering the parameters specified by the glove manufacturer, check during use that the gloves are still retaining their protective properties. It should be noted that the time to breakthrough for any glove material may be different for different glove manufacturers. In the case of mixtures, consisting of several substances, the protection time of the gloves cannot be accurately estimated.

Skin Protection: Personal protective equipment for the body should be selected based on the task being performed and the risks involved and should be approved by a specialist before handling hydrochloric acid.

Eye Protection: Wear chemical splash goggles and face shield.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Australian Dangerous Goods

UN 1789 (HYDROCHLORIC ACID)

Class: 8

Packing Group: II or III

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

Australian Drinking Water Guidelines [ADWG]. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council. Updated September 2022. https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines

de Groot, W.A., & van Dijk, N.R.M. (2002). Addition of hydrochloric acid to a solution with sodium bicarbonate to a fixed pH. Solvay Pharmaceuticals, Study No. A SOL.S.027; cited in OECD 2002a and 2002b.

European Chemicals Agency [ECHA]. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances.

European Chemicals Agency [ECHA]. (2023). Chapter R.11: vPvB assessment. In *Guidance on information requirements and chemical safety assessment*. Version 4.0. https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

Industrial Chemicals Environmental Management Standard [IChEMS]. (2022). Australian Environmental Criteria for Persistent, Bioaccumulative and/or Toxic Chemicals. https://www.dcceew.gov.au/sites/default/files/documents/australian-pbt-criteria.pdf

Klimisch, H.J., Andreae, M., & Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol., 25*, 1–5.

Organisation for Economic Co-operation and Development [OECD]. (2002a). IUCLID Data Set for Hydrogen chloride (CAS No. [redacted] UNEP Publications.

Organisation for Economic Co-operation and Development [OECD]. (2002b). Screening Information Dataset (SIDS) Initial Assessment Report for Hydrogen chloride (CAS No. [redacted] UNEP Publications.

UN Environment Programme [UNEP]. (1995). Water quality of world river basins. UNEP Environment Library No. 14, Nairobi, Kenya; cited in OECD, 2002a and 2002b.

ISOPROPANOL

This dossier on isopropanol presents the most critical studies pertinent to the risk assessment of isopropanol in its use in coal seam gas extraction activities. It does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Propan-2-ol

CAS RN: [redacted]

Molecular formula: C_3H_8O

Molecular weight: 60.1 g/mol

Synonyms: Isopropanol, isopropyl alcohol, 2-propanol, *sec*-propyl alcohol, dimethylcarbinol

SMILES: CC(C)O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Isopropanol

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colourless liquid	2	ECHA
Melting Point	-88.5°C; -89.5°C[1]	2	ECHA
Boiling Point	82.5°C; 82.3°C @ 101.3 kPa	2	ECHA
Density	800 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	4,400 Pa @ 20°C; 6,002 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	0.05 @ 25°C	2	ECHA
Water Solubility	Miscible	2	ECHA
Viscosity	2.038 mPa s @ 25°C	2	ECHA

[1] No information on the atmospheric pressure reported.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Isopropanol is readily biodegradable. It is not expected to bioaccumulate. Isopropanol has a low tendency to bind to soil or sediment.

B. Partitioning

Isopropanol is miscible in water. Volatilisation from water surfaces or moist soil surfaces is expected to be an important fate process based upon this compound's estimated Henry's Law constant of 0.821 Pa m^3/mole. It is also expected to volatilise from dry soil surfaces based upon its vapour pressure (Pub Chem).

C. Biodegradation

Aerobic biodegradation of isopropanol has been shown to occur rapidly under non-acclimated conditions, based on a result of 49% biodegradation from a 5-day BOD test (Bridie et al., 1979). Additional biodegradation data developed using standardised test methods show that isopropanol is readily biodegradable in both freshwater and saltwater media (72 to 78% biodegradation in 20 days) (Price et al., 1974).

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

D. Environmental Distribution

No experimental data are available for isopropanol. Using KOCWIN in EPI Suite™ (USEPA, 2017), the estimated K_{oc} value from log K_{ow} is 3.478 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 1.53 L/kg.

E. Bioaccumulation

Bioconcentration of isopropanol in aquatic organisms is not expected to occur based on a measured log K_{ow} of 0.05 (ECHA). Based on this estimated value, the substance is expected to have very high mobility in soil. If released to water, based on this value and its water solubility, it is also not expected to adsorb to suspended solids and sediment.

Volatilisation from water surfaces is expected with half-lives for a model river and model lake of 86 hours and 29 days, respectively (PubChem).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of isopropanol is low by the oral, dermal and inhalation routes. At high exposure levels, isopropanol is irritating to the eyes, nose and throat and may cause transient central nervous system depression. It is not a skin sensitiser, but in some individuals, there may be an allergic contact dermatitis due to cross-sensitisation to other alcohols, such as ethanol. Repeated high exposures cause reversible narcotic effects, consistent with other short-chain alcohols. Isopropanol is not genotoxic. Lifetime inhalation studies in rodents showed no carcinogenic effects. The weight-of-evidence indicates that

isopropanol is not a reproductive toxicant. In a two-generation reproductive toxicity study, the male mating index was affected by isopropanol exposure; the significance of this effect is, however, unclear. Developmental toxicity can occur at maternally toxic doses; but it is not a teratogen. Isopropanol also does not affect neurobehavioral development.

B. Acute Toxicity

The acute oral LD_{50} of isopropanol has been reported as 4,700 mg/kg, 5,300 mg/kg, 5,500 mg/kg and 5,400 mg/kg in rats; 4,500 mg/kg in mice; and 5,030 mg/kg, 7,800 mg/kg and 7,900 mg/kg in rabbits (ECHA) [KI Score = 2].

The acute dermal LD_{50} in rabbits has been reported to be 12,900 mg/kg (ECHA) [KI Score = 2].

The acute inhalation 8-hour LC_{50} in rats was 19,000 ppm in females and 22,500 ppm in males (ECHA) [KI Score = 2]. Exposure of rats to 16,000 ppm for 8 hours resulted in four deaths out of six animals (ECHA) [KI Score = 2].

In an acute neurotoxicity study, male and female F344 rats were exposed to 0, 500, 1,500, 5,000 or 10,000 ppm isopropanol for 6 hours. A spectrum of behavioural effects indicative of narcosis, defined as a generalised loss of neuromotor and reflex function, was observed in animals of the 10,000 ppm group and to a lesser extent in the 5,000 ppm animals. Recovery from these effects was observed by 24 hours for the 10,000 ppm animals and by 6 hours for the 5,000 ppm animals. A concentration-dependent decrease in motor activity was observed for the 1,500 ppm males and the 5,000 ppm females. The results show that exposure of rats to isopropanol vapour produces transient, concentration-related narcosis and/or central nervous system sedation. The NOAEL for acute neurotoxicity is 500 ppm (ECHA) [KI Score = 2].

C. Irritation

Isopropanol applied to the intact or abraded skin of rabbits and guinea pigs produced negligible irritation. Liquid isopropanol is moderately irritating to the eyes of rabbits. Isopropanol produced little irritation when tested on the skin of six human subjects (ECHA) [KI Score = 1].

D. Sensitisation

There have been reports of isolated cases of dermal irritation and/or skin sensitisation. Except for three case reports, the positive reactions were observed on patch testing patients with contact dermatitis due to ethanol. These patients also had a positive reaction to ethanol.

E. Repeat Dose Toxicity

<u>Oral</u>

In a drinking water study, rats ingested 0.5 to 10% of isopropanol for 27 weeks and showed decreased body weight gain but no gross or microscopic tissue abnormalities (ECHA) [KI score = 3]. Increased formation of hyaline droplets in the proximal tubules was reported in male rats given 1–4% isopropanol in drinking water for 12 weeks (ECHA) [KI Score = 3].

A two-generation reproductive toxicity study has been conducted in rats given isopropanol by oral gavage. Pre-mating exposures were for at least 10 weeks for both generations. The results from this study are presented in the Reproductive Toxicity section (ECHA) [KI Score = 2].

Inhalation

F344 rats and CD-1 mice (both sexes) were exposed to 0, 100, 500, 1,500 or 5,000 ppm isopropanol for 6 hours/day, 5 days/week for 13 weeks. There were no deaths during the study. During and immediately following exposure to 5,000 ppm, ataxia, narcosis, hypoactivity and a lack of startle reflex were observed in some rats and mice. Narcosis was not observed in rats during exposure following week 2, suggesting some adaptation to isopropanol. During exposures to 1,500 ppm, narcosis, ataxia, and hypoactivity were observed in some mice, whereas only hypoactivity was observed in rats. Immediately following exposures, ataxia and/or hypoactivity were observed in a few rats or mice exposed to 5,000 ppm. Overall, the 1,500 and 5,000 ppm rats and the 5,000 ppm female mice showed increased body weights and/or body weight gain during the study. Liver weights relative to body weight were observed in rats of both sexes and the 5,000 ppm female mice; however, no corresponding microscopic changes were noted in the liver. Histopathological evaluation showed a slight increase in the size and frequency of hyaline droplets in the kidneys of the isopropanol-exposed rats. Excluding the clinical signs of CNS depression, the NOAEL for this study is 5,000 ppm (ECHA) [KI Score = 1].

In a subchronic neurotoxicity study, male and F344 rats were exposed by inhalation to 0, 100, 500, 1,500 or 5,000 ppm for 13 weeks. Neurobehavioural evaluations included a functional observation battery (FOB), motor activity and neuropathology. Effects of narcosis were observed in the 5,000 ppm groups only. There were no changes in FOB, but increased motor activity was noted in 5,000 female rats at weeks 9 and 13. Neuropathological examination revealed no exposure-related lesions in the nervous system. The NOAEL for acute effects is 500 ppm, and the NOAEL for subchronic neurotoxicity is 1,500 ppm (ECHA) [KI Score = 1].

An additional subchronic neurotoxicity study was conducted to clarify the increased motor activity findings. Female F344 rats were exposed to 0 or 5,000 ppm of isopropanol vapour for 6 hours/day, 5 days/week. Half of the animals in each group were exposed for 9 consecutive weeks and the other half for 13 consecutive weeks. After 9 weeks of exposure, the motor activity effect was reversible within 2 days after the last exposure. Subtle differences in the shape of the motor activity versus test session time curve were noted in both the 9-week and the 13-week exposed animals, although it was unclear whether these changes were treatment-related. Complete reversibility of these changes did not occur until 1 and 6 weeks after the last exposure in the 9 and 13 week exposure groups, respectively (ECHA) [KI Score = 2].

Male and female CD-1 mice were exposed by inhalation to 0, 500, 2,500 or 5,000 ppm isopropanol vapour 6 hours/day, 5 days/week for 18 months. An additional group of mice (all exposure levels) were assigned to a recovery group which were exposed to isopropanol for 12 months and then retained until study termination at 18 months. Survival was similar across all groups. Clinical signs were noted in the 5,000 ppm animals and included hypoactivity, lack of a startle reflex, ataxia, prostration and narcosis. Some of the animals in the 2,500 ppm group also showed hypoactivity, lack of a startle reflex and narcosis. Ataxia was the only exposure-related clinical sign that was noted for the 5,000 ppm animals

following exposure. There was a concentration-related increase in body weights and body weight gain in both the 2,500 and 5,000 ppm animals (both sexes). There were no exposure-related changes in the hematological parameters at the 12- and 18-month time points. At study termination, there was a concentration-related increase in liver weights in the females, with the 5,000 ppm females being statistically significant. Nonneoplastic lesions were limited to the testes (males) and the kidney. In the testes, enlargement of the seminal vesicles occurred in the absence of associated inflammatory or degenerative changes. The kidney effects included tubular proteinosis and/or tubular dilatation. The incidence of testicular and kidney effects was not increased in the isopropanol-exposed recovery animals. The NOAEL is 500 ppm (ECHA) [KI Score = 2].

Male and female Fischer 344 rats were exposed to 0, 500, 2,500 or 5,000 ppm isopropanol vapour 6 hours/day, 5 days/week for 24 months. The mortality rates for all male rats were 82, 83, 91 and 100% for the 0, 500, 2,500 and 5,000 ppm groups, respectively. The corresponding values for the female rats were 54, 48, 55 and 69%. The main cause of death for the 5,000 ppm rats (both sexes), as well as for much of the mortality of the 2,500 ppm male rats, was chronic progressive nephropathy. Clinical signs were seen in the 5,000 ppm animals and included hypoactivity, lack of a startle reflex and narcosis. Some of the 2,500 ppm animals also showed a lack of a startle reflex. Body weight of the 5,000 ppm animals showed an initial decrease; from Weeks 6-72, body weights and body weight gain were increased. A similar pattern was seen in the 2,500 ppm males. Liver weights were increased in the ≥2,500 ppm male at 18 months, in the 2,500 ppm males at 24 months and in the 5,000 ppm females at 24 months. Kidney weights were increased in the 5,000 ppm males at 18 months and in the 5,000 ppm females at 24 months. Isopropanol exposure resulted in impaired kidney function, as indicated by various urine chemistry changes in male (2,500 and 5,000 ppm) and female (5,000 ppm) rats. Animals in these groups also exhibited histopathological effects in the kidneys which appeared to be an exacerbated form of chronic progressive nephropathy. The NOAEL is 500 ppm (ECHA) [KI Score = 1].

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on isopropanol are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Isopropanol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* TA98, TA100, TA1535, TA1537)	-	-	2	ECHA
Bacterial reverse mutation (*S. typhimurium* TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, TA1538)	-	-	2	ECHA
Sister Chromatid Exchange (V79 cells)	-	-	2	ECHA
Mammalian cell gene mutation (CHO/HGPRT)	-	-	1	ECHA

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Adenovirus (SA7) cell transformation (Syrian hamster embryo cells)	NA	-	2	ECHA

*+, positive; -, negative; NA, not applicable

In Vivo Studies

Male and female ICR mice were given a single intraperitoneal injection of 0, 350, 1,173 or 2,500 mg/kg isopropanol. There were no increases in micronuclei in the bone marrow polychromatic erythrocytes at the 24, 48 or 72-hour post-dosing time points at any dose level (ECHA) [KI Score = 1].

G. Carcinogenicity

Oral

No studies are available.

Inhalation

The carcinogenic potential of isopropanol was evaluated via inhalation using three strains of mice. Male mice were exposed to 7.5 ppm of isopropanol for 3 to 7 hours/day, 5 days/week for 5 to 8 months. Animals were killed at either 8 or 12 months. There was no significant increase in the number of lung tumours observed (ECHA) [KI Score = 3].

Male and female CD-1 mice were exposed by inhalation to 0, 500, 2,500 or 5,000 ppm isopropanol vapour for 6 hours/day, 5 days/week for 18 months. An additional group of mice (all exposure levels) were assigned to a recovery group which were exposed to isopropanol for 12 months and then retained until study termination at 18 months. There was no increased frequency of neoplastic lesions in any of the isopropanol-exposed animals (ECHA) [KI Score = 1].

Male and female Fischer 344 rats were exposed to 0, 500, 2,500 or 5,000 ppm of isopropanol vapour for 6 hours/day, 5 days/week for 24 months. The mortality rates for all male rats were 82, 83, 91 and 100% for the 0, 500, 2,500 and 5,000 ppm groups, respectively. The corresponding values for the female rats were 54, 48, 55 and 69%, respectively. The main cause of death for the 5,000 ppm rats (both sexes), as well as for much of the mortality of the 2,500 ppm male rats, was chronic progressive nephropathy. The only neoplastic lesion noted was increased interstitial (Leydig) cell adenomas in male rats. The frequency of these tumours, although elevated above the control animals, was within the historical control range of the testing facility and within the range reported for control animals from the National Toxicology Program carcinogenicity studies (ECHA) [KI Score = 1].

H. Reproductive Toxicity

In a two-generation reproductive toxicity study, Sprague–Dawley rats were dosed by oral gavage with 0, 100, 500 or 1,000 mg/kg isopropanol. There were seven parental deaths that were considered treatment-related: two high-dose F_0 females, two F_1 high-dose females,

one mid-dose F_0 female, and two low-dose F_1 males. Lactation body weight gain was increased in the 500 and 1,000 mg/kg females in both generations, and liver and kidney weights were increased in the 500 and 1,000 mg/kg groups in both sexes. Centrilobular hepatocyte hypertrophy was noted in some 1,000 mg/kg F_1 males. There were some kidney effects in the 500 and 1,000 mg/kg F_0 males and in all treated F_1 male rats. The kidney effects were characterised by an increased number of hyaline droplets in the convoluted proximal tubular cells, epithelial degeneration and hyperplasia, and proteinaceous casts. Increased mortality occurred in the high-dose F_1 offspring during the early postnatal period; no other clinical signs of toxicity were observed in the offspring from either generation. Offspring body weight, however, in the 1,000 mg/kg group was reduced during the early postnatal period. There was significant mortality in the F_1 weanlings (18/70) before the selection of the F_1 adults. A statistically significant reduction was observed in the F_1 male mating index of the 1,000 mg/kg group (73 versus 97% in the controls). There were no other treatment-related effects on reproduction, including fertility and gestational indices, or histopathology of the reproductive organs. A benchmark dose level of 420 mg/kg/day was calculated (lower bound on dose associated with a 5% response rate) for the decrease in the male mating index (ECHA) [KI Score = 1].

In a one-generation reproductive/embryotoxicity study, male and female Wistar rats were given 0, 0.5, 1.0 or 2.0% isopropanol in their drinking water. The calculated intakes for males were 383, 686 and 1,107 mg/kg/day (pre-mating) and 347, 625 and 1,030 mg/kg/day (18 weeks of treatment). The calculated intakes for females were 456, 835 and 1,206 mg/kg/day (premating); 668, 1,330 and 1,902 mg/kg/day (gestation); and 1,053, 1,948 and 2,768 mg/kg/day (postpartum). An immediate, statistically significant dose-dependent decrease occurred in water intake in the male rats. Intake was reduced ~5-14% (1% group; premating period) and ~30% (2% group; days 7-11 to end of study). Overall mean feed consumption was significantly lower in treated versus control animals. Male body weights (2% only) were reduced throughout the study. Water consumption was initially reduced in the 1% and 2% females, but the 2% group recovered to only ~70% of the control values (premating); it continued to be reduced during the gestation and lactation period. Mean maternal body weights were reduced (all treated groups) at the start of gestation, with partial recovery during the gestation period except for the 2% group. Overall weight gain during gestation in these groups were similar to the controls. Following parturition from PND 4 onward, the 2% dams had significantly lower body weights. There were no infertile males in any group, and no treatment-related effect on female fertility or on length of gestation. The number of pups/litter on GD 1 was reduced in the 2% group; because it was not replicated in the embryotoxicity portion, an increase in pup mortality during parturition or GD 0, followed by cannibalism of the dead pups by the dam was suggested. No macroscopic abnormalities were seen in females; nor was there any treatment-related histopathological changes seen in the reproductive tissue in the 2% parental animals. Absolute kidney weight and relative kidney, liver and spleen weights were increased in the 2% F_0 males; increased absolute liver and kidney weights and relative liver weights in the 2% F_0 females. In the embryotoxicity portion, there was a statistically significant increase in the total number of pre-implantation losses in the 2% animals. Whole body oedema was seen in 40% of the foetuses in 3/8 litters in the 2% group. No macroscopic abnormalities of the viscera of these foetuses were detected, and the incidence of oedema was not related to gender. In the one-generation portion, postnatal pup survival and in the average pup weight (by PND 7) were decreased in the 2% group. F_1 generation animals of both sexes showed increased relative liver weights at all dose levels, and the 2% males had higher relative kidney weights. A slight but significant decrease in absolute brain weight and increase in relative empty cecum weights in both sexes of the 2% F_1 generation group was observed. No treatment-related gross

abnormalities were observed in the F_1 generation animals at necropsy. The NOAEL for reproductive toxicity is 2% in drinking water, the highest dose tested (ECHA) [KI Score = 1]. The effects of isopropanol (2.5% in drinking water) on the reproduction and growth of rats were assessed in a multigenerational study. No reproductive toxicity was observed. The NOAEL for reproductive toxicity is 2.5% isopropanol in drinking water (ECHA) [KI Score = 4].

Isopropanol was administered as a 3% solution in drinking water to Wistar rats. Reduced parental body weight gain, food, and water consumption were observed in the treated animals compared with the controls. Fertility, litter size and pup weights at postnatal days 4 and 21 were reduced in treated animals compared with the controls. In the second generation, the isopropanol concentration was reduced to 2%, and there were essentially no effects (ECHA) [KI Score = 4].

I. Developmental Toxicity

Oral Studies

Isopropanol was given at concentrations of 0, 0.5, 1.25 or 2.5% in the drinking water to female Wistar rats on GD 6 to 16. The calculated intakes of isopropanol during GD 6-16 were 596, 1,242 and 1,605 mg/kg/day. There was an immediate reduction in water intake in the 2.5% dose group, and this was statistically significant throughout the treatment period when compared to controls. A smaller reduction in water intake was also seen in the 1.25% females (statistically significant during GD 6-9), with no change in the 0.5% females. Palatability of the drinking water may have been the problem since water intake significantly increased the first day following the end of the treatment period for all dose groups. Feed consumption patterns paralleled the water consumption during and after treatment in the mid- and high-dose groups. Overall, mean body weights of the 2.5% females were lower than the controls from GD 7 to termination. Effects on weight gain in the 0.5% and 1.25% females were limited to a failure to gain weight during the first (0.5%) and second (1.25%) day of treatment. There were no treatment-related effects in post-implantation loss, mean number of implantation sites or live foetuses. There was a slight dose-dependent decrease in mean litter weight and a significant decrease in mean foetal weight in the 1.25% and 2.5% groups. A statistically significant increase in variations was observed, indicative of a lower degree of ossification in the treated animals. There was a dose-dependent decrease in the number of foetuses with the 4th sacral arch and a dose-dependent increase in the number of foetuses with less than 2 caudal arches. The sternum also showed reduced ossification because there were increased numbers of foetuses with small, absent or incompletely ossified sternebrae. The NOAEL for maternal and developmental toxicity is 596 mg/kg/day (ECHA) [KI Score = 1].

In a rat developmental study, female Sprague–Dawley rats were dosed by oral gavage with either 0, 400, 800 or 1,200 mg/kg of isopropanol during gestational days 6 to 15. Two dams (8%) died at 1,200 mg/kg and one dam (4%) died at 800 mg/kg. At 1,200 mg/kg, maternal body weights were reduced throughout gestation (GS 0-20; 89.9% of control value), associated with reduced gravid uterine weight. There were no other treatment-related effects on the dams. Foetal body weights per litter were also significantly reduced at the 800 and 1,200 mg/kg dose levels, but there were no teratogenic effects. The NOAEL for maternal and developmental toxicity is 400 mg/kg/day, respectively (ECHA) [KI Score = 1]. In a rabbit developmental study, female New Zealand white rabbits were dosed by oral gavage with either 0, 120, 240 or 480 mg/kg of isopropanol during gestational days 6 to 18. At 480 mg/kg, isopropanol was unexpectedly toxic to pregnant female rabbits, resulting in the deaths of four does (26%). Maternal body weights were significantly reduced during

treatment (gestational days 6–18) and were associated with reduced maternal food consumption during this period. Profound clinical signs were noted at 480 mg/kg and included flushed and/or warm ears, cyanosis, lethargy and laboured respiration. No adverse maternal effects were noted at 120 or 240 mg/kg. There were no developmental or teratogenic effects at any dose tested. The NOAELs for maternal and developmental toxicity are 240 and 480 mg/kg/day, respectively (ECHA) [KI Score = 1].

Isopropanol was given by oral gavage to Sprague–Dawley rats from gestational days 6 to 21 in doses of 0, 200, 700 or 1,200 mg/kg. The dams were allowed to deliver, litters were culled on postnatal day (PND) 4, pups were weaned on PND 22, and their dams were killed. Weaned pups were assessed for day of testes descent or vaginal opening, motor activity, auditory startle and active avoidance. The pups were killed on PND 68. Some of the pups were taken from each dose group and were perfused in situ for pathological examination of the central nervous system. There were no biologically significant findings in the behavioural tests, no changes in organ weights and no pathological findings of note. Thus, there was no evidence of developmental neurotoxicity from isopropanol exposure (ECHA) [KI Score = 1].

Inhalation Studies

Pregnant female Sprague Dawley rats were exposed to 0, 3,500, 7,000 or 10,000 ppm isopropanol for 7 hours/day during gestational days 1–19. The animals showed unsteady gait and narcotisation during initial exposures in the mid- and high-dose groups; reduced food consumption and reduced weight gain were also noted in both the mid- and high-dose groups. Foetal body weights per litter were reduced in all dose groups. Exposure to 10,000 ppm also resulted in failure of implantation, fully resorbed litters, increased resorptions per litter and increased incidence of cervical ribs. The NOAEL for maternal toxicity is 3,500 ppm. The LOAEL for developmental toxicity is 3,500 ppm; a NOAEL was not established (ECHA) [KI Score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for isopropanol follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-cancer

Oral

The repeated-dose toxicity studies on isopropanol by the oral route are inadequate for the purposes of risk assessment. There is, however, a well-conducted two-generation reproductive toxicity study, in which rats were dosed by oral gavage up to 1,000 mg/kg/day (Bevan et al., 1995). Allen et al. (1998) calculated a benchmark dose level of 420 mg/kg/day (lower bound on dose associated with a 5% response rate for the decrease in the male mating index). The Point of Departure (POD) of 420 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 10
UF_D (database uncertainty) = 1
Oral RfD = 420/(10 x 10 x 1 x 10 x 1) = 420/1000 = 0.4 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (0.4 x 70 x 0.1)/2 = 1.4 mg/L

B. Cancer

Isopropanol was not carcinogenic to rats or mice in chronic inhalation studies. Therefore, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Isopropanol is a flammable liquid.

Isopropanol does not exhibit the following physico-chemical properties:

- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL EFFECTS SUMMARY

A. Summary

Isopropanol is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on isopropanol.

Table 3: Acute Aquatic Toxicity Studies on Isopropanol

Test Species	Endpoint	Results	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	9,640 mg/L	2	ECHA
Daphnia magna	24-hour EC_{50}	> 10,000 mg/L	2	ECHA

Chronic Studies

Table 4 lists the results of chronic aquatic toxicity studies on diethanolamine.

Table 4: Chronic Aquatic Toxicity Studies on Isopropanol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Daphnia magna	16-day NOEC	141 mg/L	4	ECHA
Daphnia magna	21-day NOEC	30 mg/L	4	OECD, 1977a,b
Scenedesmus quadricauda	7-day NOEC	1,800 mg/L	2	ECHA

C. Terrestrial Toxicity

An EC_{50} value of 2,100 mg/L was determined from a lettuce seed germination test (Reynold, 1977) [Kl score = 2].

D. Calculation of PNEC

The PNEC calculations for isopropanol follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for two trophic levels. Acute $E(L)C_{50}$ values are available for fish (9,640 mg/L) and invertebrates (> 10,000 mg/L). Results from chronic studies are available for invertebrates (16- and 21-day NOECs for *Daphnia* are 141 and 30 mg/L, respectively). On the basis that the data consists of acute studies from two trophic levels and a chronic study from one trophic level, an assessment factor of 100 has been applied to the lowest reported NOEC of 30 mg/L for invertebrates. The $PNEC_{water}$ is 0.3 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.2 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.87/1280) \times 1000 \times 0.3$
$= 0.2$ mg/kg

Where:

$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water}$ = 0.8 + [0.2 x Kp_{sed})1000 x BD_{solid}]
= 0.8 + [0.2 x 0.14/1000 x 2400]
= 0.87 m^3/m^3

Where:

Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
Kp_{sed} = K_{oc} x f_{oc}
= 3.478 x 0.04
= 0.14 L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for isopropanol calculated from EPI Suite™ using Log K_{ow} is 3.478.
f_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.014 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil}$ = (Kp_{soil}/BD_{soil}) x 1000 x $PNEC_{water}$
= (0.07/1500) x 1000 x 0.3
= 0.014 mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
Kp_{soil} = K_{oc} x f_{oc}
= 3.478 x 0.02
= 0.07 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for isopropanol calculated from EPI Suite™ using K_{ow} is 3.478 L/kg.
f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Isopropanol is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of 0.05 and a calculated BCF of 1, isopropanol does not meet the screening criteria for bioaccumulation.

The chronic toxicity data on isopropanol show a NOEC of > 0.1 mg/L. The acute E(L)C_{50} values for isopropanol are > 1 mg/L. Thus, isopropanol does not meet the screening criteria for toxicity.

The overall conclusion is that isopropanol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable Liquid Category 2

Eye Irritant Category 2

STOT Single Exposure Category 3 [Narcosis]

B. Labelling

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. If respiratory irritation, dizziness, nausea or unconsciousness occurs, seek immediate medical assistance. Give artificial respiration if victim is not breathing. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

If ingested, material may be aspirated into the lungs and cause chemical pneumonitis. Treat appropriately.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide. Do not use straight streams of water.

Specific Exposure Hazards

Highly flammable. Vapours are flammable and heavier than air. Vapours may travel across the ground and reach remote ignition sources causing a flashback fire danger. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. All equipment used when handling the material must be grounded. A vapour suppressing foam may be used to reduce vapours. Use clean non-

sparking tools to collect absorbed material. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Prevent exposure to ignition sources (i.e., use non-sparking tools and explosion-proof equipment). Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation. Use proper bonding and/or ground procedures. However, bonding and grounds may not eliminate the hazard from static accumulation. Peroxides may form upon prolonged storage. Exposure to light, heat or air significantly increases peroxide formation. If evaporated to a residue, the mixture of peroxides residue and material vapour may explode when exposed to heat or shock.

Storage

Keep container tightly closed. Store in a cool, well-ventilated area away from heat and light. Storage containers should be grounded and bonded. Fixed storage containers, transfer containers and associated equipment should be grounded and bonded to prevent accumulation of static charge. See SDS for suitable materials and coatings.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for isopropanol in Australia is 400 ppm as an 8-hour TWA and 500 ppm as a 15-min STEL.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN 1219 (Isopropanol)

Class 3

Packing Group II

XI. DISPOSAL

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Allen, B; Gentry, R; Shipp, A; Van Landingham, C. (1998). Calculation of benchmark doses reproductive and developmental toxicity observed after exposure to isopropanol. Regul Toxicol Pharmacol 28: 38-44. http://dx.doi.org/10.1006/rtph.1998.1226

Bevan C., Tyler T.R., Gardiner T.H., Kapp Jr. R.W., Andrews L. and Beyer B.K. (1995). Two generation reproductive toxicity study with isopropanol in rats. J. Appl. Toxicol. 15(2):117-123.

Bridie, A.L., Wolff, C.J.M., and Winter, M. (1979). BOD and COD of some petrochemicals. Water Res. 13: 627-630.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

OECD. (1997a). IUCLID Data Set for 2-Propanol (CAS No. [redacted] UNEP Publications.

OECD. (1997b). Screening Information Dataset (SIDS) Initial Assessment Report for 2-Propanol (CAS No. [redacted] UNEP Publications.

Price, K.S., Waggy, G.T., and Conway, R.A. (1974) Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollut. Contr. Fed., 46: 63-77.

PubChem. National Institutes of Health. National Library of Medicine National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/

Reynold, T. (1977). An anomalous effect of isopropanol on lettuce germination. Plant Sci. Lett. 15: 25-28.

USEPA. (2017). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

MAGNESIUM SILICATE HYDRATE (TALC)

This dossier on magnesium silicate hydrate (talc) presents the most critical studies pertinent to the risk assessment of this substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): dioxosilane; oxomagnesium; hydrate

CAS RN: [redacted]

Molecular formula: $H_2Mg_3O_{12}Si_4$

Molecular weight: 379.27 g/mol

Synonyms: Talcum, oxosilanediol, trimagnesium; dioxido(oxo)silane; hydroxy-oxido-oxosilane, dioxosilane; oxomagnesium; hydrate

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Magnesium Silicate Hydrate (Talc)

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White solid odorless powder	2	ECHA
Melting Point	1,500°C @ 101.3 kPa	2	ECHA
Boiling Point	This substance is a solid that melts above 300°C	-	-
Density	2700 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	0 Pa at 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-9.4 @ 25°C	2	ECHA
Water Solubility	0.0001 g/L @ 25°C; insoluble in water	2	ECHA
Flash Point	ND	-	-
Auto flammability	ND	-	-
Viscosity	Not applicable as substance is a solid.	2	ECHA
Dissociation constant	ND because the substance is insoluble in water	-	ECHA

ND – not determined

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Magnesium silicate hydrate (talc) is an inorganic substance for which biodegradation is irrelevant. Moreover, it will not bioaccumulate and has a low potential to adsorb to soil.

B. Biodegradation

As an inorganic substance, magnesium silicate hydrate (talc) will not biodegrade. Soil and sediment degradation studies are not considered to be applicable as the test material is essentially insoluble in water and consists of materials which occur naturally in these compartments (ECHA).

C. Environmental Distribution

Magnesium silicate hydrate (talc) is insoluble in water. The log K_{OC} of was estimated to be 1.5027 which is equal to a K_{OC} value of 31.82 L/kg using the KOCWIN v2.00 QSAR method (ECHA). Based on this K_{oc} value, if released to soil, magnesium silicate hydrate (talc) is expected to have a low potential for adsorption. If released into water, the substance has a low potential for adsorption to sediment or suspended solids.

D. Bioaccumulation

There is no potential for bioaccumulation. Due to its inherent chemical-physical properties, such as absence of lipophilicity as well as the capability of the organism to excrete absorbed SiO_2 components, bioaccumulation can be disregarded. Magnesium is widespread in living cells and does not bioconcentrate in aquatic organisms (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Talc is a mineral composed of hydrated magnesium silicate. Talc is essentially non-toxic by the oral and dermal routes. Talc is non-irritating to the eyes and skin. There was no toxicity or carcinogenic effects in rats. Talc is not genotoxic. No developmental toxicity was reported in pregnant female rats, mice or rabbits given oral doses of talc.

B. Basic Toxicokinetics

Inhalation

To determine the deposition, distribution and clearance of talc, 44 female Syrian golden hamsters received a single 2-hour nose-only exposure to a neutron-activated talc aerosol and sub-groups of 4 animals were then killed at 11 different intervals from 15 minutes to 132 days after exposure.

The talc tested was a commercial baby powder. Nine unexposed control animals were used; four were killed on the day the test animals were exposed and five were killed on the final day of the study. The aerosol exposure system had 7 tiers of exposure ports, and the talc aerosol was passed through a cyclone elutriator to remove particles that were larger than ~10 µm in diameter; the activity median aerodynamic diameter was 6.4-6.9 µm. The mean aerosol concentration was 40 and 75 µg/L at the 15 to 30 and 60 to 90-minute sampling periods, respectively. In the presentation of the results, the γ-ray counts from the controls were expressed as µg talc equivalent, and the γ-ray counts of the exposed animals were not corrected for control values.

Variations among animals killed at the same time were attributed to variations in aerosol concentration at different tiers. The mean pulmonary talc content in the lungs of test animals at various time intervals was 33.08 µg (15 minutes after exposure), 24.08 µg (100 minutes), 42.70 µg (4 hours), 18.75 µg (21 hours), 21.30 µg (2 days), 21.03 µg (after 4 days), 13.85 µg (after 8 days) and 8.95 µg (after 18 days); the mean for the Day 0 control animals was 1.78 µg. The biological half-life

of the talc deposited in the lungs was 7 to 10 days. At the time of termination of the final group, i.e., 132 days, there was no statistically significant difference in the talc burden of the lungs of test (3.70 µg) and control (2.30 µg) animals. The amount of talc in the liver, kidneys and lungs was also determined; the only statistically significant differences compared to controls in any of these organs were found in the liver. There was a decrease at 4 hours compared to day 0 controls, an increase at Day 36 compared to both Day 0 and Day 132 controls, and an increase on Day 68 compared to Day 132 controls.

Analysis of the data using the Kruskal-Wallis test showed that there were no significant differences among the mean talc burden values for the liver, kidneys and ovaries, including the control values, and that there was no significant trend, indicating there was no translocation of talc to these tissues.

As noted, no translocation from the respiratory tract to other tissues was found in this study, and the clearance of talc from the lungs was complete within 4 months after exposure.

Oral

In one study, six female Syrian golden hamsters (outbred Ela:ENG strain) were dosed by gavage with 1 mL neutron-activated talc suspended in physiological saline containing 0.6% (w/w) 1% methyl cellulose, and the animals were killed 24 hours after dosing. The talc used was a commercial baby powder.

Four hamsters were dosed similarly with a non-irradiated talc solution. The neutron-activated talc was exposed to an integrated neutron flux of 7 x 1,016 n/cm^2 30 days prior to dosing. The skinned carcass, gastrointestinal (GI) tract, lungs, liver, kidneys and excreta were analysed for isotopes 60 Co and 46 Sc by gamma-ray spectrometry, and the gamma-ray counts were compared with those of four hamsters that were not dosed with talc.

The γ-ray counts of the tissue and excreta of the dose animals were equivalent to a total of 2.94 mg talc. Based on γ-ray counts, 74.5% of the neutron-activated talc was recovered in the faeces and 23.5% was recovered in the GI tract, while 1.91% was recovered in the skinned carcass, 0.09% in the urine, 0.04% in the kidneys and 0.02% in the liver. The amount found in the urine of the hamsters given irradiated talc was statistically significantly increased compared to the controls. No talc was recovered in the lungs (ECHA) [Kl score = 2].

In a second oral study, four LACA female mice were given a single oral dose of 40 mg/kg [3H] talc. Two mice were killed at 6 hours and two at 24 hours after dosing. In the mice killed 6 hours after dosing, 95 and 96% of the radioactivity was recovered in the large intestines and faeces, 9 and 7% was recovered in the small intestines and stomach, and 0.7 and 0% in the urine of each mouse. In the two mice killed 24 hours after dosing, 99 and 101% of the radioactivity was recovered in the large intestines and faeces, 4 and 6% was recovered in the small intestines and stomach, and 1.3 and 1.5% in the urine of each mouse. Less than 0.005% of the radioactivity was found in the carcass of any of the mice (ECHA) [Kl score = 2].

In a third oral study, three male Wistar albino rats were given a single oral dose and three rats were given six daily oral doses by gavage of 50 mg/kg body wt [3H] talc. After the last dose, urine and faeces were collected every 24 hours for 4 days and on Day 10; the rats were then killed. Within 24 hours after administration of the single dose, approximately 75% of the radioactivity was recovered in the faeces and only 1% was recovered in the urine. After 96 hours, a total of 95.8% of the dose was excreted in the faeces and 1.7% in the urine, with a total excretion of 97.5% of the dose. No radioactivity was recovered in the liver or kidneys 10 days after a single dose of talc. On Day 10 in

the rats given six daily doses of [3H] talc, there was no radioactivity found in the faeces or livers, and there was a trace of radioactivity (< 0.02%) in the kidneys of these rats (ECHA) [Kl score = 2].

C. Acute Toxicity

Oral

A single oral dose of 5,000 mg/kg of talc prepared as an 18.3% (w/v) suspension in saline was administered to 10 male rats. All animals survived, and there were no signs of toxicity. In conclusion, the median lethal dose of Talc (Mg3H2(SiO3)4) after a single oral administration to male rats, observed over a period of 14 days is: LD50 > 5,000 mg/kg body weight (ECHA) [Kl Score = 2].

Inhalation

Groups of 5 male and female Wistar rats were treated with magnesium hydroxide as aerosol during 4 hours. No mortality or other relevant adverse effects were observed. An inhalatory LC_{50} (4-hour) value for magnesium hydroxide exceeding 2.1 mg/L was determined, being the maximum feasible concentration that could be tested (ECHA) [Kl Score = 2].

Dermal

An OECD Guideline 402 (Acute Dermal Toxicity) was performed. Five males and five female Wistar rats were dermally exposed to a single talc dose of 2,000 mg/kg.

Approximately 24 hours before the test, the fur was removed from the dorsal area of the trunk using an electric clipper. Care was taken to avoid abrading the skin, and only animals with healthy intact skin were used. No less than 10% of the body surface was cleared for the application.

The test item was applied at a single dose, uniformly over an area which was approximately 10% of the total body surface. The test item was held in contact with the skin throughout a 24-hour period. At the end of the exposure period the residual test item was not removed.

Under the conditions of this study, single dermal application of the test item magnesium chloride hexahydrate to rats at a dose of 2,000 mg/kg body weight was associated with no mortality. The dermal LD_{50} was determined to be > 2,000 mg magnesium chloride hexahydrate/kg body weight (ECHA) [Kl Score = 2].

Dermal

No studies were available.

D. Irritation

Skin

An *in vitro* skin irritation test was carried out with the reconstituted three-dimensional human skin model EPISKIN-SM™ (Skinethic). This skin model consists of normal (non-cancerous), adult human-derived epidermal keratinocytes (NHEK) which have been cultured to form a multilayered, highly differentiated model of the human epidermis. The NHEK are cultured on chemically modified, collagen-coated cell culture inserts. A highly differentiated and stratified epidermis model is

obtained after a 13-day culture period and is comprised of the main basal, supra basal, spinous and granular layers and a functional stratum corneum.

The test item showed no irritant effects. The mean relative tissue viability (% negative control) was ≥ 50% (112.9%) after 15-minute treatment and 42-hour post incubation. The controls confirmed the validity of the study. The mean OD550 of the three negative control tissues was ≥ 0.6. The mean relative tissue viability (% negative control) of the positive control was ≤ 30% (22.6%). The standard deviation of replicate tissues of all dose groups was ≤ 30% (1.4% - 9.4%). It can be concluded that talc is non-irritating to skin (ECHA) [KI Score = 2].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) study was performed using magnesium chloride hexahydrate as a surrogate substance for talc. A dose of 0.1 g of the test item was applied at a single dose in the conjunctival sac of one eye of each test animal after pulling the lower lid away from the eyeball. The lids were then gently held together for about 1 second in order to prevent loss of the material. The untreated contralateral eye served as control. Observations of the eye were made at 1, 24, 48 and 72 hours and 4 to 6 days.

Under the conditions of the study, single ocular instillation of the test item magnesium chloride hexahydrate to rabbits at a dose of 0.1 g produced irritant effects, which were fully reversible. Neither mortalities nor significant clinical signs of toxicity were observed. The test item is deemed to be non-irritating to eyes (ECHA) [KI Score = 2].

E. Sensitisation

No experimental data are available on the Talc ($Mg_3H_2(SiO_3)_4$) powder and silicates; however, there is long experience in humans. Data collected from industrial hygiene surveillance over the last 50 years do not indicate any potential for skin sensitisation. Despite the widespread cosmetic use of talc and special studies in volunteers (BIBRA, 1991) there are no indications of any allergenic effect (ECHA) [KI score = 3].

F. Repeated Dose Toxicity

Oral

A study equivalent or similar to OECD Guideline 452 (Chronic Toxicity Studies) was performed using male and female Wistar rats. Wistar rats (16 male and 16 female) were exposed to talc in feed which resulted in an amount taken up of 100 mg/kg/day. After feeding had been carried out for 101 days, the animals were observed until death and subsequently examined histopathologically.

One of the animals treated with talc showed a leiomyosarcoma of the stomach. Sarcomas, which were not associated with the talc treatment, were found in the uterus of two animals. No chronic pathological effect was associated with oral administration of talc over 5 months. No adverse effects were seen on general toxicity endpoints. Under the condition of this study, for a period of 101 days for male and female rats, the NOAEL of talc in a feeding study was 100 mg/kg/day (ECHA) [KI score = 2].

Inhalation

A study equivalent or similar to OECD Guideline 452 (Chronic Toxicity Studies) was performed using male and female Wistar rats. The Wistar rats (12 male and 12 female) were exposed whole body to aerosolised talc at a mean respirable dust concentration of 10.8 mg/m^3 for 7.5 hours per day, 5 days a week for 6 or 12 months.

Ten days after the end of each exposure period, 6 rats per group were killed; 12 rats per group died and 2 rats per group were unaccounted for. The remaining 4 rats per group were killed one year after the end of the exposure period. Minimal fibrosis was observed. Talc exposure led to distinct fibrosis that was comparable with that after exposure to chrysotile in the parallel group. A lung adenoma was detected in 1 of 24 animals treated with talc. In rats exposed by inhalation to 10.8 mg/m^3 Italian talc (grade 00000; ready milled; mean particle size, 25 µm) for 3 months, minimal fibrosis was observed, the degree of which did not change during the observation period after exposure. Animals that were exposed for 1 year had minimal to slight fibrosis, the degree of which had increased to moderate within 1 year after cessation of exposure.

A no observed adverse effect concentration (NOAEC) of 10.8 mg/m^3 was determined (ECHA) [KI Score = 2].

Dermal

No adequate studies for human health risk assessment are available.

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on talc are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Talc

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Mammalian cell gene mutation (rat pleural mesothelial cells (RPMC)).	-*	ND	2	ECHA

*+, positive; -, negative
ND – not determined

Talc did not cause a statistically significant increase in sister chromatid exchanges (SCEs) and was not clastogenic. The test substance is non-mutagenic under the given experimental conditions (ECHA) [KI Score = 2].

In Vivo Studies

A study equivalent or similar to OECD Guideline 478 (Genetic Toxicology: Rodent Dominant Lethal Test) was performed per a rat dominant lethal assay on Sprague Dawley rats. Groups of 10 male rats were dosed by gavage with a single dose or once daily for 5 days with 30, 300, 3,000 or 5,000 mg/kg talc.

There were no dose-response or time trend patterns; talc did not induce dominant lethal mutations in this assay. Therefore, talc was not genotoxic in a rat dominant lethal assay (ECHA) [KI Score = 2].

H. Carcinogenicity

Oral

An OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) was performed. In a feeding study of 16 male and 16 female Wistar rats, talc was added to the diet; this resulted in a dosage rate of 100 mg/kg/day. After feeding had been carried out for 101 days, the animals were observed until death (approximately 614 days) and subsequently examined histopathologically. One of the animals treated with talc showed a leiomyosarcoma of the stomach. Sarcomas, which were not associated with the talc treatment, were found in the uterus of two animals.

However, no differences in tumour incidence were noted between treated animals and 8 male and 8 female control animals fed basal diet throughout (average survival, 641 days).

Inhalation

In a lifetime experiment, three groups of 50 male and 50 female Syrian golden hamsters, 4 weeks of age, were exposed (whole body) by inhalation to an aerosol of talc baby powder that was prepared from Vermont talc by flotation (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite and rutile) for 3, 30 or 150 minutes per day, 5 days a week for 30 days. The mean aerosol concentration was 37.1 mg/m^3, with a measurable respiratory fraction of 9.8 mg/m^3 and a MMAD of 4.9 µm. A placebo exposed group comprised 25 males and 25 females. Two further groups of hamsters, 7 weeks of age, were exposed to talc aerosol for 30 or 150 minutes per day for 300 days. The mean aerosol concentration was 27.4 mg/m^3, with a measurable respiratory fraction of 8.1 mg/m^3 and a MMAD of 6.0 µm. Another placebo-exposed group comprised 25 males and 25 females. The survivors of the last two talc-exposed groups were killed at the age of 20 months.

No clinical signs of toxicity to talc were observed. The type, incidence and severity of lesions indicated no trend toward a dose-response and no statistically significant differences between exposed and control groups. The incidence of focal alveolar cell hyperplasia (25% in treated groups; 10% in controls) appeared to be affected by treatment, but a two-way weighted analysis showed no significant association. Thus, exposure of hamsters to talc via inhalation did not produce carcinogenic effects (ECHA) [KI Score = 2].

I. Reproductive Toxicity

An OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) was performed. Groups of 12-15 gravid Dutch-belted female rabbits were dosed orally with 9, 42, 195 or 900 mg/kg bw talc in corn oil on Days 6-18 of gestation. Eight gravid negative controls were given only vehicle and nine gravid positive controls were dosed with 2.5 mg/kg bw of 6-aminonicotinamide on Day 9 of gestation. The dams were killed on Day 29 of gestation. A total of 1/8, 4/15, 2/12, 5/15 and 2/13 dams of the negative control, 9, 42, 195 and 900 mg/kg bw dose groups, respectively, died or aborted before Day 29 of gestation, and the number of live litters for these groups was 6/7, 10/11, 8/10, 10/10 and 7/11, respectively. Details on Results (PO): Administration of up to 900 mg/kg bw talc on Days 6-18 of gestation had no discernible effect on nidation or on maternal survival.

The number of abnormalities did not differ between test and control animals.

Details on Results (F1): Administration of up to 900 mg/kg bw talc on days 6-18 of gestation had no discernible effect on nidation or on foetal survival. The number of abnormalities did not differ between test and control animals.

The NOAEL was considered to be 900 mg/kg bw/day for reproduction toxicity study. A NOAEL of > 900 mg/kg/day was determined for reproduction (ECHA) [KI Score = 2].

J. Developmental Toxicity

A GLP compliant study was performed. Groups of 20-22 gravid albino CD-1 mice and groups of 20-24 gravid Wistar rats were dosed by gavage with 0, 16, 74, 350 or 1,600 mg/kg bw talc as an anhydrous corn oil suspension on days 6-15 of gestation. The mice were killed on Day 17 and the rats on Day 20 of gestation and the number of implantation sites, resorptions sites, and live and dead foetuses, and the live pup body weights were recorded.

Maternal Toxicity: The administration of up to 1,600 mg/kg bw talc in corn oil had no effect on maternal endpoints.

Embryotoxic / Teratogenic Effects: The administration of up to 1,600 mg/kg bw talc in corn oil had no effect on developmental parameters and had no effect on foetal survival.

The NOAEL was considered to be 1,600 mg/kg bw/day for developmental toxicity (ECHA) [KI score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for talc follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

<u>Oral</u>

The NOAEL of 100 mg/kg/day from a chronic feeding study in rats was used to determine the oral RfD and drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

- UF_A (interspecies variability) = 10
- UF_H (intraspecies variability) = 10
- UF_L (LOAEL to NOAEL) = 1
- UF_{Sub} (subchronic to chronic) = 1
- UF_D (database uncertainty) = 1
- Oral RfD = 100/(10 x 10 x 1 x 1 x 1) = 100/100 = 1 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (1 x 70 x 0.1)/2 = 3.5 mg/L

B. Cancer

The carcinogenicity studies suggest talc is not a carcinogen. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Talc does not exhibit the following physico-chemical properties:

- Flammability
- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Talc is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Table 3 lists the results of the acute aquatic toxicity studies on magnesium silicate hydrate (talc).

Table 3: Acute Aquatic Toxicity Studies on Talc

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Fish (species unnamed)	96-hour LC_{50}	89,581 mg/L (QSAR)	2	ECHA
Daphnid	48-hour LC_{50}	36,812 mg/L (QSAR)	2	ECHA
Algae (species unnamed)	96-hour LC_{50}	7,203 mg/L	1	ECHA

<u>Chronic Studies</u>

No data are available. Short term aquatic toxicity tests reported in the literature on fish (LC_{50} *Brachydanio rerio* (Zebra fish) >100,000 mg/L/24 hr; for talc) show this substance is not toxic to aquatic life. On this basis the need for long term aquatic testing is waived (ECHA).

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

PNEC calculations for talc follow the methodology discussed in DEWHA (2009).

PNEC water

Acute experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (89,581 mg/L), *Daphnia* (36,812 mg/L), and algae (7,203 mg/L). By applying an assessment factor of 100 to the lowest E(L)C_{50} value of 7,202 mg/L from the acute studies, the $PNEC_{water}$ for talc is 72 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Moreover, the low K_{ow} indicates that talc is not expected to partition to sediments. Therefore, a $PNEC_{sed}$ was not calculated.

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Moreover, talc is biodegradable and due to its low K_{ow}, is not expected to partition to soil. Therefore, a $PNEC_{soil}$ was not calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Magnesium silicate hydrate (talc) is an inorganic substance and thus, biodegradation is not relevant. For the purposes of this PBT assessment, the persistent criteria are not considered applicable for this substance.

No data are available on bioaccumulation. However, based on the low log K_{ow}, and the inherent chemical-physical properties of magnesium silicate hydrate (talc), bioaccumulation is not expected. Thus, magnesium silicate hydrate (talc) does not meet the screening criteria for bioaccumulation.

Chronic aquatic toxicity data is not available. The E(L)C_{50} values from the acute aquatic toxicity studies on magnesium silicate hydrate (talc) are > 1 mg/L. Thus, magnesium silicate hydrate (talc) does not meet the criteria for toxicity.

Therefore, magnesium silicate hydrate (talc) is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H332- Harmful if inhaled.

B. Labelling

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Rinse out mouth then drink plenty of water. Get medical attention.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Magnesium oxide, silicon oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Avoid dust formation. Avoid breathing vapours, mist of gas. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

No specific environmental precautions required.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage and Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light. Store in cool place. Keep container tightly closed in a dry and well-ventilated place.

E. Exposure Controls/Personal Protection

Occupational Exposure Standards

Workplace Australia has established an occupational exposure standard for exposure to talc of an 8 hour time weighed average (TWA) exposure limit of 2.5 mg/m^3 (containing no asbestos fibres).

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to

maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products, as well as before eating, smoking and using the lavatory and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Talc is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council

BIBRA. (1991). The British Industrial Biological Research Association (BIBRA) Toxicity Profile – Talc. BIBRA, Carshalton, GB.

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

European Chemicals Agency [ECHA] (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

METHANOL

This dossier on methanol presents the most critical studies pertinent to the risk assessment of methanol in its use in coal seam gas extraction activities. It does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained primarily from the OECD-SIDS documents on methanol (OECD, 2004a,b), and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Methanol

CAS RN: [redacted]

Molecular formula: CH_4O

Molecular weight: 32.04 g/mol

Synonyms: Methyl alcohol, carbinol, wood spirits, wood alcohol, methylol, wood, columbian spirits, colonial spirit, columbian spirit, methyl hydroxide, monohydroxymethane, pyroxylic spirit, wood naphtha.

SMILES: CO

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Physico-Chemical Properties of Methanol

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colourless liquid	2	ECHA
Melting Point	-97.8°C @ 101.3 kPa	2	ECHA
Boiling Point	64.7°C @ 101.3 kPa	2	ECHA
Density	790 kg/m^3@ 20 °C	2	ECHA
Vapour Pressure	16927 Pa @ 25 °C	2	ECHA
Partition Coefficient (log P_{ow})	-0.77	2	ECHA
Water Solubility	>1,000 g/L [miscible]	2	ECHA
Flash Point	9.7°C	2	ECHA
Auto flammability	455°C @ 101.3 kPa	2	ECHA
Viscosity	0.544 – 0.59 mPa s (dynamic)	2	ECHA
Henry's Law Constant	0.461 Pa m^3/mol @ 20 °C	2	ECHA

Methanol is a highly flammable liquid.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Methanol is readily biodegradable. It has a low adsorptive capacity to soils and is unlikely to bioaccumulate.

B. Biodegradation

Methanol is readily biodegradable. In a closed bottle test using seawater, there was 84% and 95% degradation after 10 and 20 days, respectively (Price et al., 1974; ECHA). [Kl. score = 2]

In a soil test using [^{14}C]-methanol, there was 53.4% degradation under aerobic conditions after 5 days, as measured by CO_2 evolution; and 46.3% degradation under anaerobic conditions after 5 days, as measured by CO_2 evolution (Scheunert et al., 1987; ECHA). [Kl. score = 2]

If a chemical is found to be readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

The adsorption of methanol was investigated in three different soil types at 6°C (Lokke, 1984; ECHA). There was slight adsorption with the sandy soils tested (percentage organic matter of 0.09% and 0.1% in the samples) and with the clay soil (percentage organic matter was 0.22%). Methanol solutions of concentrations of 0.1, 1.0, 9 and 90 mg/L were used in one-hour exposure adsorption studies; the K_{oc} values were between 0.13 and 0.61 for all soil types and at all concentrations.

Based upon these K_{oc} values, if released to soil, methanol is expected to have very high mobility. If released into water, due to its high water solubility and low K_{oc}, methanol is not expected to adsorb to suspended solids and sediment in water.

D. Bioaccumulation

The BCF of methanol in *Cyprinus carpio* was determined to be 1.0 (Gluth et al. 1985); in *Leuciscus idus*, the BCF was < 10 (Hansch and Leo, 1985; Freitag et al. 1985). Therefore, the potential for bioaccumulation is low.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Methanol has low acute oral, dermal and inhalation toxicity in experimental animals but moderate to high acute oral and dermal toxicity in humans. Methanol is metabolised to formate, which is considered to be the ultimate toxicant in acute methanol intoxication in humans. Acute methanol toxicity in humans is characterised by CNS depression, followed by acidosis and ocular injury. Methanol is not irritating to the skin, but it is slightly irritating to the eyes. It is not a skin sensitiser. Repeated exposures by the oral and inhalation routes have not resulted in any systemic toxicity to rodents. In primates, adverse health effects on brain, kidney and heart were observed in chronic inhalation studies. Methanol is not genotoxic or carcinogenic. Conflicting results have been obtained concerning the effect of methanol on reproductive and developmental toxicity in experimental animals. However, it is not considered to have reproductive or developmental toxicity in humans.

B. Toxicokinetics and Metabolism

Several reviews on the metabolism and pharmacokinetics of methanol are available (Kavet and Nauss, 1990; Liesivuori and Savolainen, 1991; Tephly, 1991; IPCS, 1997; OECD, 2004a, b). Methanol is first oxidised to formaldehyde. This initial metabolic step involves different enzymes in rats than in primates and humans, although the rates are similar. A catalase–peroxidase system is primarily responsible for the initial step in rats, whereas alcohol dehydrogenase plays a major role in humans and monkeys. Methanol oxidation can also occur via hepatic microsomal oxidation involving the cytochrome P450 system.

Formaldehyde is converted to formic acid, which is converted to formate and a hydrogen ion. Conversion to formic acid is a two-step process, the second step is irreversible. In the first reaction, formaldehyde combines with reduced glutathione (GSH) to form S-formylglutathione. This is mediated by an NAD-dependent formaldehyde dehydrogenase. In the second reaction, thiolase catalyses the hydrolysis of S-formylglutathione to form formic acid and GSH. A folate-dependent pathway in the liver is responsible for formate metabolism in both rats and primates. Formate first forms a complex with tetrahydrofolate (THF) that is sequentially converted to 10-formyl-THF (by formyl-THF synthetase) and then to CO_2 (by formyl-THF dehydrogenase). THF is derived from folic acid in the diet and is also regenerated in the folate pathway. Although the folate pathway metabolises formate in both rats and monkeys, rats use the pathway more efficiently.

The dermal uptake rate of liquid methanol applied to the forearm of human volunteers was 11.5 mg/cm^2/hr (Dutkiewicz et al., 1980). The dermal flux for methanol in human skin (epidermis) *in vitro* is 8.29 mg/cm^2/hr (Schueplein and Blank, 1971). When 12 human volunteers immersed one hand into a vessel containing neat methanol for up to 16 minutes, the maximum methanol concentration in blood reached 1.9 ± 1.0 hr after exposure. Delivery rates from the skin into blood lagged exposure by 0.5 hours, and methanol continued to enter the blood for 4 hours following exposure. The average derived dermal absorption rate absorption rate was 8.1 $\pm$ 3.7 mg/cm^2/hr. The authors calculated that the maximum concentration of methanol in blood following immersion of one hand in methanol for approximately 20 minutes is comparable to that reached following inhalation exposures to 200 ppm methanol (Batterman and Franzblau, 1997).

C. Acute Toxicity

The acute oral LD_{50} for rats range from 6,200 to 13,000 mg/kg (Kimura et al., 1971; Welch and Slocum, 1943; Deichman and Mergard, 1948; Smyth et al., 1941). The acute dermal LD_{50} for rabbits was reported to be 20 mL/kg (Rowe and McCollister, 1982). The inhalation 4- and 6-hour LC_{50} values in rats are 128.2 and 87.5 mg/L, respectively (BASF, 1980a,b). Sublethal doses, however, produce CNS effects and ocular injury that may result in blindness. This effect has been seen in primates, but not in rodents, and has been attributed to the differences in blood levels of the metabolite, formic acid.

Methanol is metabolised to formate, which is considered to be the ultimate toxicant in acute methanol intoxication in humans. Acute methanol toxicity in humans is characterised by CNS depression, followed by acidosis and ocular injury. Generally, transient CNS effects appear above methanol levels of 200 mg/L and serious ocular symptoms appear above 500 mg/L (OECD, 2004a). This blood concentration can transiently be achieved in an adult person (70 kg) by ingestion of 0.4 mL methanol/kg (approximately 0.32 mg/kg). The minimal acute methanol dose to humans that can result in death is considered to be 300 to 1,000 mg/kg by ingestion, and fatalities have occurred in untreated patients with initial methanol blood levels in the range of 1,500-2,000 mg/L (OECD,

2004a). However, such high blood methanol levels able to cause death are not likely to be achieved through inhalation exposure.

D. Irritation

Methanol is not irritating to the skin of rabbits (BASF, 1975), but it is slightly irritating to the eyes of rabbits (BASF, 1975).

E. Sensitisation

Methanol was not considered a skin sensitiser to guinea pigs (BASF, 1979).

F. Repeated Dose Toxicity

Oral

Male and female Sprague–Dawley rats were dosed by oral gavage with 0, 100, 500 or 2,500 mg/kg of methanol for 90 days. There were no differences in body weight gain and food consumption between treated and control animals. Brain weights were decreased in both sexes in the 2,500 mg/kg dose group. Elevated serum glutamic pyruvate transaminase and alkaline phosphatase were noted in the 2,500 mg/kg dose group, but there were no adverse treatment-related effects in the gross pathology and histopathological evaluation. The NOAEL is 500 mg/kg/day (USEPA, 1986).

Sprague-Dawley rats were given in their drinking water 0, 500, 5,000 or 20,000 ppm methanol for 104 weeks, and then the animals were maintained until natural death. The study was conducted by the Ramazzini Foundation which uses its testing guideline for carcinogenicity studies and not an internationally accepted guideline. Treatment with methanol did not decrease survival. However, there was considerable early mortality; by 18 months, 30% of the male controls had died. In females, there were no differences in survival between controls and treated groups. There was still more early mortality in the females than expected, but it was less pronounced than the males. There was no obvious effect of methanol exposure on water consumption. The 20,000 ppm males and females weighed more than the controls (up to 14% and 7%, respectively) throughout the study. The 5,000 ppm females also weighed more (4%) than the controls at 24 months, but not at earlier time points. There were no body weight differences between the remaining treatment groups and the controls. The calculated methanol doses based on water intake were: 0, 55, 542 and 1,840 mg/kg/day for males; and 0, 67, 630 and 2,250 mg/kg/day for females. Nearly all rats in all dose groups had some pathology in the lung. The finding of lung pathology was consistent regardless of the age at death (not an old age response). The lung pathology included inflammation, dysplasia or tumours. Lung pathology was present in 70-100% of the first 10% of deaths in each group, including controls (70, 80, 80, 100% in males; and 90, 90, 100, 100% in females at 0, 500, 5,000 and 20,000 ppm, respectively). The degree of inflammation in the lungs is difficult to assess because no other lung information was recorded for the rats when a neoplasm in the lung was recorded (Soffritti et al., 2002; Cruzan, 2009; USEPA, 2013a) [Kl. score = 3].

Inhalation

Cynomolgus monkeys or Sprague–Dawley rats were exposed by inhalation to 0, 500, 2,000 or 5,000 ppm (0, 660, 2,620 or 6,552 mg/m^3) methanol for 6 h/day, 5 days/week for 4 weeks. There was no mortality and no clinical signs of toxicity among the monkeys, but there were a few signs of eye and nose irritation in the rats. No differences were seen between treated and control groups in body weight gain and organ weights, with the exception being decreased absolute adrenal weight in the 5,000 ppm female monkeys and increased relative spleen weights in the 2,000 ppm female rats.

These changes were not considered by the authors to be of biological significance. There were no treatment-related effects on the ophthalmoscopy, gross pathology or histopathology. The NOAEL for this study is 5,000 ppm (6,552 mg/m^3) (Andrews et al., 1987) [Kl. score = 4].

Groups of four male rats were exposed by inhalation to 0, 200, 2,000 or 10,000 ppm (0, 262, 2,621 or 13,104 mg/m^3) methanol for 6 hours/day, 5 days/week for 1, 2, 4 or 6 weeks. Additional groups of animals were exposed for 6 weeks followed by a 6-week recovery period. Evaluation of a number of parameters including lung weights, surfactant levels and enzyme activities did not reveal any adverse effects on the lung. No histopathological examinations were performed (White et al. 1983) [Kl score = 2].

Male and female F344 rats were exposed by inhalation to 0, 10, 100 or 1,000 ppm methanol 19.5 hours/day, 7 days/week for 104 weeks. The average methanol doses were: 0, 3.7, 37 and 369 mg/kg/day in males; and 0, 5.9, 60 and 599 mg/kg/day for females. There were no treatment-related clinical signs and no effect on survival or food consumption. Lower body weights were seen in the 1,000 ppm females beginning around Day 259, but after Day 574, there was no difference from controls. Body weights in males were similar across all groups. There were no treatment-related effects on urinalysis, hematology or clinical biochemistry. Nor were there any treatment-related effects on organ weights or gross lesions. Histopathologic examination showed no statistically significant differences between treated and control animals (NEDO, 1985a) [Kl score = 2].

Male and female B6C3F1 mice were exposed by inhalation to 0, 10, 100 or 1,000 ppm methanol 19.5 hours/day, 7 days/week for 78 weeks. The average methanol doses were: 0, 9.8, 95 and 947 mg/kg/day in males; and 0, 8.1, 106 and 1,071 mg/kg/day for females. There were no treatment-related clinical signs and no effect on survival or body weight. Food consumption was decreased slightly between months 7 and 12 in the 1,000 ppm females. Urinalysis, hematology and clinical biochemistry were similar across all groups. No differences were seen in organ weights, gross lesions or histopathology between treated and control mice (NEDO, 1985b) [Kl score = 2].

Dermal

No studies were identified.

G. Genotoxicity

In Vitro Studies

Methanol was not mutagenic to *Salmonella* strains TA97, TA98, TA100, TA1535, TA1537 and TA1538 in *in vitro* bacterial mutation assays with or without metabolic activation (De Flora et al., 1984a,b; Florin et al., 1980; Gocke et al.,1981). Equivocal results were obtained with *Salmonella* strain TA102 in the presence of metabolic activation (De Flora et al., 1984b). Methanol was not mutagenic in a DNA-repair test using various strains of *Escherichia coli* WP2 (De Flora et al., 1984a) and in a forward mutation assay using *Schizosaccharomyces pombe* (Abbondandolo et al., 1980).

Methanol did not induce micronuclei in Chinese hamster lung V79 cells in vitro (Lasne et al., 1984). Methanol was mutagenic in the mouse lymphoma assay in the presence of metabolic activation (McGregor et al., 1985), but it was not mutagenic in a Basc test or in a Drosophila, sex-linked, recessive lethal mutation assay (Gocke et al., 1981). Treatment of primary cultures of Syrian golden hamster embryo cells with methanol did not lead to cell transformation (Heidelberger et al., 1983).

In Vivo Studies

Male C57BL/6J mice were exposed by inhalation to 0, 800 or 4,000 ppm methanol, 6 hours/day for five days. There were no increased frequencies of micronuclei in blood cells; sister chromatid exchanges, chromosomal aberrations, or micronuclei in lung cells; or synaptosomal complex damage in spermatocytes (Campbell et al., 1991).

Normal or folate-deficient mice were given four daily intraperitoneal injections of up to 2,500 mg/kg of methanol. There was no increase in micronucleated erythrocytes in the treated mice compared to the controls (O'Loughlin et al., 1992).

Male and female NMRI mice were given a single intraperitoneal injection of 0, 1,920, 3,200 or 4,480 mg/kg methanol. There was no increase in micronuclei observed in the bone marrow at any dose level (Gocke et al., 1981).

H. Carcinogenicity

The carcinogenicity studies conducted on methanol were reviewed by Cruzan (2009) and by the USEPA (2013a).

Oral

Male and female SD rats were given in their drinking water 0, 500, 5,000 or 20,000 ppm methanol for 104 weeks. This study was conducted by the Ramazzini Foundation, which uses a unique methodology and not the standardised international testing guidelines. There was excessive early mortality, and lung pathology (inflammation, dysplasia, or tumours) was present in 87 to 94% of those dying anytime during the study. An increase in lympho-immunoblastic lymphomas was reported (Soffritti et al., 2002; Cruzan, 2009; USEPA, 2013a) [KI score = 3].

Inhalation

Male and female F344 rats were exposed by inhalation to 0, 10, 100 or 1,000 ppm methanol 19.5 hours/day, 7 days/week for 104 weeks. The average methanol doses were: 0, 3.7, 37 and 369 mg/kg/day in males; and 0, 5.9, 60 and 599 mg/kg/day for females. There was no increase in tumours in the methanol-exposed rats and mice (NEDO, 1985a) [KI score = 2].

Male and female B6C3F1 mice were exposed by inhalation to 0, 10, 100 or 1,000 ppm methanol 19.5 hours/day, 7 days/week for 78 weeks. The average methanol doses were: 0, 9.8, 95 and 947 mg/kg/day in males; and 0, 8.1, 106 and 1,071 mg/kg/day for females. There was no increase in tumours in the methanol-exposed mice (NEDO, 1985b) [KI score = 2].

I. Reproductive and Developmental Toxicity

Based on the data available, methanol is not considered to have reproductive or developmental toxicity in humans (NICNAS, 2013).

The reproductive and developmental toxicity studies were reviewed by the NTP Centre for Evaluation of Risks to Human Reproduction (NTP-CERHR, 2003). Conflicting results have been obtained concerning the effect of methanol on testicular hormones in rats; nevertheless, methanol does not appear to be a male reproductive toxicant. The primate data indicates that methanol is unlikely to be a reproductive hazard in females. Methanol causes developmental effects at very high

exposure levels in both rats (≥ 10,000 ppm) and mice (≥ 2,000 ppm); there is also some evidence that it is a developmental neurotoxicant in rodents, but not in primates.

Blood methanol concentrations associated with serious teratogenic effects and reproductive toxicity are in the range associated with formate accumulation, which is likely to result in metabolic acidosis, and visual and clinical effects in humans (NTP-CERHR, 2003). Other effects (such as subtle, not yet definitive neurological effects observed in primates) may be exhibited at lower inhalation doses and lower methanol blood levels (OECD, 2004).

The limited data available in humans do not show an association of reproductive and developmental toxicity with methanol (NTP-CERHR, 2003). Based on the studies reviewed by the NTP (2003), it concluded that there is evidence to suggest that women with low folate levels may be more susceptible to the adverse developmental effects of methanol, but more information is necessary to clarify this issue (NICNAS, 2013).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for methanol follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

USEPA has derived an oral reference dose (RfD) by using exposure-response data from candidate principal inhalation studies of mice (Rogers et al., 1993) and rats (NEDO, 1987) and route-to-route extrapolation with the aid of the USEPA physiologically based pharmacokinetic (PBPK) model. The decision to use inhalation rather than oral study data is due to limitations in the database of oral studies, including the limited reporting of noncancer findings in the subchronic and chronic oral studies of rats, the determination that developmental effects are the most sensitive effects of methanol exposure. The RfD of 2 mg/kg/day was estimated from the Rogers et al. (1993) study for extra cervical rib incidence in mice (USEPA, 2013a). This RfD will be used for determining the drinking water guidance value.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD: Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2 L (ADWG, 2021)
Drinking water guidance value = (2 x 70 x 0.1)/2 = 7 mg/L

B. Cancer

Methanol was not carcinogenic to rats or mice in chronic inhalation studies. Increased tumours from methanol in drinking water were reported by Soffritti et al. (2002); however, there are methodological problems with this study and questions have been raised about the validity of the results. No cancer reference value was derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Methanol is a highly flammable liquid.

Methanol does not exhibit the following physico-chemical properties:

- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Methanol exhibits a low toxicity concern for aquatic organisms, terrestrial invertebrates and plants.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies conducted on methanol.

Table 2: Acute Aquatic Toxicity Studies on Methanol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Bluegill	96-hour LC_{50}	15,400	1	Poirer et al. 1986
Salmo gairdneri	96-hour LC_{50}	20,100	1	Call et al., 1983
Pimphales promelas	96-hour LC_{50}	28,100	1	Call et al., 1983
Daphnia magna	96-hour EC_{50}	18,260	2	Dom et al., 2012; ECHA
Daphnia magna	48-hour EC_{50}	>10,000	2	Kuehn et al., 1989
Selenastrum capricornutum	96-hour EC_{50}	~22,000	2	Cho et al., 2008; ECHA
Chlorella pyrenoidosa	10 to 14-day EC_{50}	28,400	2	Stratton and Smith, 1988

Chronic Studies

No adequate chronic studies were identified. Reported studies were either invalid or their reliability was questionable. Methanol belongs to the category of organic chemicals exerting toxicity for aquatic organisms with a non-specific mode of action. The acute and chronic toxicity may be estimated for such kind of chemicals using QSAR methods. The ECOSAR model (version 1.11, US EPA, July 2012) predicts for methanol a chronic toxicity value of about 450 mg/L (equivalent to a NOEC) for *Pimephales promelas* and a value of 208 mg/L for *Daphnia magna* (REACH) [Kl. score = 1].

C. Terrestrial Toxicity

The terrestrial toxicity studies on methanol are listed in Table 3.

Table 3: Terrestrial Toxicity Studies on Methanol

Test Species (Method)	Endpoint	Results (mg/kg soil dw)	Klimisch score	Reference
Earthworm *Eisenia fetida* (OECD 222)	35-day EC_{50} 63-day EC_{50}	17,199 26,646	2	ECHA
Folsomia candida (OECD 232)	28-day EC_{25} 28-day NOEC* (reproduction)	2,842 1,000	1	ECHA
Hordeum vulgare (OECD 208)	14-day EC_{50} 14-day NOEC* (seedling emergence)	15,492 12,000	1	ECHA
	14-day EC_{25} 14-day NOEC* (shoot dry mass)	2,538 1,555		
	14-day EC_{25} 14-day NOEC* (root dry mass)	2,823 2,592		
	14-day EC_{25} 14-day NOEC* (shoot length)	4,885 2,592		
	14-day EC_{25} 14-day NOEC* (root length)	5,752 4,320		

* Since only EC_{25} values were available from the test results, NOECs were derived graphically from the representing treatment means.

D. Calculation of PNEC

The PNEC calculations for methanol follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (15,400 mg/L), *Daphnia* (> 10,000 mg/L) and algae (22,000 mg/L). There are no well-conducted long-term studies on methanol. Therefore, an assessment of 1,000 has been applied to the lowest reported effect concentration of 10,000 mg/L for *Daphnia*. The $PNEC_{water}$ is 10 mg/L.

PNEC sediment

There are no adequate toxicity studies on sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 6.3 mg/kg wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.81/1280) \times 1000 \times 10$
$= 6.3$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{soilid}]$
$= 0.8 + [0.2 \times 0.02/1000 \times 2400]$
$= 0.81\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 0.61 \times 0.04$
$= 0.02$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for methanol is 0.61 L/kg.
f_{oc} = fraction of organic carbon suspended sediment = 0.04 [default].

PNEC soil

Experimental results from chronic studies are available for three trophic levels. The lowest NOEC is 1,000 mg/kg soil dry weight for the arthropod *Folsomia candida*. On the basis that the data consists of long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported long-term NOEC of 1,000 mg/kg soil dry weight. The $PNEC_{soil}$ is 100 mg/kg soil dry weight.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009 and ECHA, 2008).

Methanol is readily biodegradable and thus it does not meet the screening criteria for persistence.

Based on an experimental BCF of < 10 in fish, methanol does not meet the criteria for bioaccumulation.

There are no adequate chronic toxicity studies on methanol. Predicted toxicity based on QSAR methods indicates chronic values > 0.1 mg/L for fish and invertebrates. The acute EC_{50} values of methanol in fish, invertebrates and algae is >1 mg/L; thus, it does not meet the screening criteria for toxicity.

The overall conclusion is that methanol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable Liquid Category 2

Acute Toxicity Category 3 [Oral]

Acute Toxicity Category 3 [dermal]

Acute Toxicity Category 3 [inhalation]

STOT SE Category 1 [optic nerve, central nervous system]

In the EU, there are concentration limits for the STOT SE classification of methanol. This may or may not apply to GHS classifications for Australian SDS.

Concentration range (%):

>10	STOT SE Category 1
>3 and <10	STOT SE Category 2

B. Labelling

Danger

C. Pictograms

The health hazard pictogram is omitted if the STOT SE classification for methanol does not apply (i.e., concentration of methanol is below the concentration limits).

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

Note: Methanol is used in the drilling mud product ALDACIDE® G ANTIMICROBIAL at a concentration of 0.1% to 1%. The safety and handling of methanol at this concentration in ALDACIDE® G ANTIMICROBIAL will be provided in the dossier on glutaraldehyde, the major constituent of ALDACIDE® G ANTIMICROBIAL.

<u>Occupational Exposure Standards</u>

The workplace exposure standard for methanol in Australia is 200 ppm (262 mg/m^3) as an 8-hour TWA and 250 ppm (328 mg/m^3) as a 15-minute STEL. There is also a skin notation indicating that absorption through the skin may be a significant source of exposure.

A. Transport Information

Methanol is used in drilling mud product ALDACIDE® G ANTIMICROBIAL at a concentration of 0.1 to 1%. The transportation information for ALDACIDE® G ANTIMICROBIAL will be provided in the dossier on glutaraldehyde, the major constituent of ALDACIDE® G ANTIMICROBIAL.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

Abbondandolo, A. et al. (1980). Mutat. Res. 79: 141 – 150.

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Andrews, L.S., Clary, J.J., Terrill, J.B., and Bolte, H.F. (1987). Subchronic inhalation toxicity of methanol. J. Toxicol. Environ. Health 20: 117-124.

BASF AG. (1975). Unpublished data, (XXIV 436), 03 July 1975; cited in OECD-SIDS SIAR on Methanol.

BASF AG. (1979). Unpublished data, (78/333), 11 April / 11 July 1979; cited in OECD-S SIDS SIAR on Methanol.

BASF AG. (1980a). Unpublished report, (80/158), 07 Aug. 1980; cited in OECD-SIDS SIAR on Methanol.

BASF AG. (1980b). Unpublished report, (80/158), 20 Nov. 1980; cited in OECD-SIDS SIAR on Methanol.

Batterman, S.A., and Franzblau, A. (1997). Time-resolved cutaneous absorption and permeation rates of methanol in human volunteers. Int. Arch. Occup. Environ. Health 70: 341-351.

Call, D.J., L.T. Brooke, N. Ahmad, J.E. Richter. (1983). Toxicity and metabolism studies with EPA priority pollutants and related chemicals in freshwater organisms, EPA-600/3-83-095, PB83-263665.

Campbell, J.A., Howard, D.R., Backer, L.C., Allen, J.W. (1991). Evidence that methanol does not induce chromosome damage in mice. Mutat. Res. 260 : 257-264.

Cho, C. W., Y-C. Jeon, T.P.T. Pham, K. Vijayaraghaven, Y-S. Yun. (2008). The ecotoxicity of ionic liquids and traditional organic solvents on microalga Selenastrum capricornutum. Ecotoxicol. Environ. Saf. 71: 166-171.

Cruzan, G. (2009). Assessment of the cancer potential of methanol. Crit. Rev. Toxicol. 39: 347-363.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Deichman, W.B., and Mergard, E.G. (1948). J. Ind. Hyg. Toxicol. 30: 373 – 378.

Dom, N., M. Penninck, D. Knapen, R. Blust. (2012). Discrepancies in the acute versus chronic toxicity of compounds with a designated narcotic mechanism. Chemosphere 87: 742-749.

Dutkiewicz, B., Korczalik, H., and Karwacki, W. (1980). Int. Arch. Occup. Environ. Health 47: 47: 81-88.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment (HHRA). (2012). Environmental Health RiskAssessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

De Flora, S., Zanacchi, A., Camoirano, A., Bennicelli, C. and Badolati, G.S. (1984a). Mutat. Res. 133(3) : 161 – 198.

De Flora, S., Zanacchi, A., Camoirano, A., Bennicelli, C. and Badolati, G.S. (1984b). Mutat. Res. 134 : 159 – 165.

Florin, I., Rutberg, L., Curvall, M. and Enzell, C.R (1980). Toxicol. 18 : 219 – 232.

Freitag, D., Lay, P. and Korte, F. (1985). Environmental Hazard Profile of Organic Chemicals: An experimental method for the assessment of the behaviour of organic chemicals in the ecosphere by means of simple laboratory tests with 14C labelled chemicals. Chemosphere, 14: 1589-1616.

Gluth, G., D. Freitag, W. Hanke, F. Korte. (1985). Accumulation of pollutants in fish. Comp. Biochem. Physiol., 81C: 273 – 277.

Gocke, E., M.-T. King, K. Eckhardt, D. Wild. (1981). Mutagenicity of cosmetic ingredients licensed by the European Communities. Mutat. Res. 90: 91 – 109.

Hansch, C. and Leo, A.J. (1985). Medchem. Project Issue No.26, Claremont CA, Pomona College.

Heidelberger, C. Freeman A., Pienta R.J., Sivak A., Bertram J.S., Casto B.C., Dunkel V., Francis M.W., Kakunaga T., Little J.B., Schechtman L.M. (1983). Mutat. Res. 114 : 283 – 385.

IPCS. (1997). Environmental Health Criteria on Methanol 196, WHO, Geneva.

Kavet , R., and Nauss, K.M. (1990). The toxicity of inhaled methanol vapors. CRC Crit. Rev. Toxicol. 20: 21 – 50.

Kimura, E.T., Ebert, D.M., and Dodge, P.W. (1971). Toxicol. Appl. Pharmacol. 19: 699 – 703.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Kuehn, R., et al. (1989). Water Research, 23: 495-499.

Lasne, C., et al. (1984.) Mutat. Res. 130: 273 – 282.

Liesivuori, J., and Savolainen, H. (1991). Pharmacol. Toxicol. 69: 157 – 163.

Lokke, H. (1984). Leaching of ethylene glycol and ethanol in subsoils. Water, Air, and Soil Pollution 22: 373-387.

McGregor, D.B et al. (1985). Environ. Mutagen. 7(Suppl. 3), A10.

NEDO. (1985a). 24-month inhalation carcinogenicity study on methanol in Fischer 344 rats (test no.: 5A-268), Report dated September 30, 1985, 10 volumes. Mitsubishi Kasei Institute for Toxicological and Environmental Sciences, Tokyo.

NEDO. (1985b). 18-month inhalation carcinogenicity study on methanol in B6C3F1 mice (test no.: 4A-223), Report dated March 30, 1985, 9 volumes. Mitsubishi Kasei Institute for Toxicological and Environmental Sciences, Tokyo.

NEDO. (1987). Toxicological research of methanol as a fuel for power station: summary report on tests with monkeys, rats and mice. Tokyo, Japan.

NICNAS. (2013). IMAP Single Assessment Report for Methanol: Human Health Tier II Assessment. May 17, 2013. Available at: https://www.industrialchemicals.gov.au/sites/default/files/Methanol_Human%20health%20tier%20II%20assessment.pdf

NTP-CERHR. (2003). NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Methanol, Center for the Evaluation of Risks to Human Reproduction, National Toxicology Program, U.S. Department of Health and Human Services, NIH Publication, No. 03-4478.

OECD. (2004a). IUCLID Data Set for Methanol (CAS No. [redacted] Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=39B5D34A-2F5D-4D53-B000-E497B3A3EE89

OECD. (2004b). Screening Information Dataset (SIDS) Initial Assessment Report for Methanol (CAS No. [redacted] Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=39B5D34A-2F5D-4D53-B000-E497B3A3EE89

O'Loughlin, K. et al. (1992). Environ. Mutagen Soc. 47 (Abstr.).

Poirer S.H., Knuth, L.M., Anderson-Buchou, C.D,. et al. (1986). Comparative toxicity of methanol and N,N-dimethylformamide to freshwater fish. Bull. Environ. Contam. Toxicol., 37: 615-621.

Price, K.S., G.T. Waggy, R.A. Conway. (1974). Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollution Control Fed. 46: 63-77.

Rogers, JM; Mole, ML; Chernoff, N; Barbee, BD; Turner, CI; Logsdon, TR; Kavlock, RJ. (1993). The developmental toxicity of inhaled methanol in the CD-1 mouse, with quantitative dose-response modeling for estimation of benchmark doses. Teratology 47: 175-188. http://dx.doi.org/10.1002/tera.1420470302.

Rowe, K., and McCollister, S.B. (1982). In: Patty's Industrial Hygiene and Toxicology, 3rd rev. ed. (G. D. Clayton and F. E. Clayton, eds.), pp. 4527-4708, Wiley, New York.

Scheunert, I., D. Vockel, J. Schmitzer, F. Korte. (1987). Biomineralization rates of 14C-labelled organic chemicals in aerobic and anaerobic suspended soil. Chemosphere 16: 1031-1041.

Schuelplein, R.J., and Blank, I.H. (1971). Physiol. Rev. 51: 702-747.

Smyth, H.F., Seaton, J., and Fisher, L. (1941). J. Ind. Hyg. Toxicol. 23: 259 – 268.

Soffritti, M., Belpoggi, F., Cevolani, D., Guarino, M., Padovani, M., and Maltoni, C. (2002). Results of long-term experimental studies on the carcinogenicity of methyl alcohol and ethyl alcohol in rats. In: M.A. Mehlman (Ed.), Carcinogenesis bioassays and protecting public health: commemorating the lifework of Cesare Maltoni and colleagues, pp. 46-69, Bologna, Italy: Ann. N.Y. Acad. Sci.

Stratton, G.W., and Smith, T.M. (1988). Interaction of organic solvents with the green alga Chlorella pyrenoidosa, Bull. Environ. Contam. Toxicol., 40: 736-742.

Tephly, T.R. (1991). The toxicity of methanol. Life Sci. 48: 1031 – 1041.

USEPA. (1986). Rat Oral Subchronic Study on Methanol, U.S. Environmental Protection Agency, Washington, DC. Cited in the U.S. Integrated Risk Information System (IRIS) database for methanol (https://www.epa.gov/iris).

USEPA. (2013a). Toxicological Review of Methanol (Noncancer) (CAS No. [redacted] in Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-11/00FA U.S. Environmental Protection Agency, Washington, DC. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0305tr.pdf

USEPA. (2013b). Integrated Risk Information System (IRIS) Chemical Assessment Summary: Methanol (CASRN [redacted] Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0305_summary.pdf

Welch, H., and Slocum, G.G. (1943). J. Lab. Chem. Med. 28: 1440.

White, L.R., Marthinsen, A.B.L., Ricchard, R.J., Eik-Nes, K.B., and Nilsen, O.G. (1983). Biochemical and cytological studies of rat lung after inhalation of methanol vapor. Toxicol. Lett. 17: 1-5.

ETHYLENE DIAMINETETRAACETIC ACID TETRASODIUM SALT [NA_4EDTA]

This dossier on ethylene diaminetetraacetic acid tetrasodium salt (Na_4EDTA) presents the most critical studies pertinent to the risk assessment of Na_4EDTA in its use in coal seam gas extraction activities It does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained primarily from the EU Risk Assessment Report on Na_4EDTA, and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Tetrasodium{[2-bis-carboxymethyl-amino)-ethyl]-carboxymethyl-amino}-acetate

CAS RN: [redacted]

Molecular formula: $C_{10}H_{12}N_2O_8Na_4$

Molecular weight: 380.2 g/mol

Synonyms: Tetrasodium ethylenediaminetetraacetate; ethylenediaminetetraacetic acid tetrasodium salt; ethylene dinitrilotetraacetic tetrasodium salt; Edetic acid tetrasodium salt; Na_4EDTA or Na_4EDTA tetrasodium; Edetate sodium or Sodium ededate; N,N'-1,2-Ethanediylbis[N-(carboxymethyl)glycine]tetrasodium salt; tetrasodium 2,2',2'',2'''-(ethane-1,2-diyldinitrilo)tetraacetate

SMILES: C(CN(CC(=O)[O-])CC(=O)[O-])N(CC(=O)[O-])CC(=O)[O-].[Na+].[Na+].[Na+].[Na+]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Na_4EDTA

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White powder	2	ECHA
Melting Point	> 150°C; > 300°C; decomposition may occur at > 150°C (pressure not provided)	2	ECHA
Boiling Point	-	-	-
Density	1670 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	-	-	-
Partition Coefficient (log K_{ow})	-	-	-
Water Solubility	500 g/L @ 20°C	2	ECHA
Auto flammability	> 200 °C @ 101.3 kPa	2	ECHA

The most important property of Na_4EDTA is that it forms complexes (usually 1:1-complexes) with multivalent metal ions (EU, 2004).

III. ENVIRONMENTAL FATE SUMMARY

A. Summary

Na_4EDTA is not readily biodegradable, but it can under certain conditions (i.e., alkaline pH), which is realistic under environmental surface water conditions, be degraded. Therefore, it can be concluded that EDTA is ultimately biodegradable under such environmental conditions (REACH). It is not expected to adsorb to soil or sediment. Na_4EDTA has a low potential for bioaccumulation.

B. Partitioning

Na_4EDTA is typically released to the environment in its complexed form (Nowack et al., 2001). The speciation of metal complexes is determined by the complex released, and metal exchange reactions mediated by its interactions with the chemistry of the receiving water compartment (Nowack, 2002; EU, 2004). However, complexes of Na_4EDTA with iron(III) are often detected in river water due to the ubiquity of iron(III) and the slow kinetics of relevant metal exchange reactions (half-life approximately 20 days) (Nowack, 2002).

Partitioning of complexed EDTA between water and sediment compartments is dependent on the metal ion complexed. For example, EDTA complexed with cobalt(III) and iron(III) partitions predominately to the water compartment, while lead(II) EDTA complexes adsorb strongly to sediment (Nowack, 2002).

Na_4EDTA is resistant to hydrolysis. However, EDTA is photolytically unstable when complexed with iron(III) ions. The complex is reported to have a half-life of 5 hours in central Europe in summer, with a worst-case half-life of 20 days (EU, 2004).

C. Biodegradation

There have been many degradation tests conducted on Na_4EDTA; in most cases, the acid or the sodium salt was tested, but not Na_4EDTA in its complexed form. Na_4EDTA is not readily biodegradable (EU, 2004). In a 28-day Sturm test, there was only 10% degradation (measured as CO_2) after 28 days (EU, 2004). In a Closed Bottle test, degradation was 3% and 0% of TOD after 28 days in two separate tests (EU, 2004). Inherent biodegradability tests have shown variable results, ranging from 0 to 37% biodegradation rates (EU, 2004). If a chemical is found to be not readily or inherently biodegradable, it is categorised as Persistent since its half-life is greater than 60 days (DoEE, 2017).

Na_4EDTA can be degraded under alkaline conditions. A Closed Bottle test was conducted to investigate the potential of samples from a river, a ditch and a lake to degrade $CaNa_2EDTA$ (8 mg/L) at pH values 6.5 – 8.0. There was little to no biodegradation (2-12%) at pH 6.5 within the first 28 days and 60-83% after 49 days. At pH 8, rates of 53, 62 and 72% were seen after 28 days and 75-89% after 35 days (van Ginkel et al., 1999). The pH values of lakes and river water range from 7.7 to 8.5; however, Na_4EDTA is preferably complexed with heavy metal ions (EU, 2004).

Na_4EDTA can be biodegraded in soil under aerobic conditions. After four weeks, biodegradation of Na_4EDTA between 4.8 and 7.9% at 30°C was determined in agriculture soil of mid-Michigan (EU, 2004). Another study showed primary degradation of 53 to 60% after 173 days at 22°C. An additional 39% of the substance was assumed to be eliminated by sorption and abiotic degradation (EU, 2004).

D. Environmental Distribution

Environmental transport of Na_4EDTA will be determined by the metal ions it is complexed with. Most studies investigating the transport of Na_4EDTA complexes compare this to transport of the uncomplexed metal. Generally, Na_4EDTA is found to decrease adsorption of metals and therefore increase its potential for transport in the environment. For instance, the mobility of Na_4EDTA in soil was investigated by eluting solutions of H_4EDTA and ZnEDTA through cores of two various surface soils. H_4EDTA was slightly adsorbed and moved quite readily through both soils. The Na_4EDTA from ZnEDTA also moved readily through the soils (EU, 2004). Therefore, due to the ionic structure of Na_4EDTA, no adsorption to the organic fraction of soils is expected under environmental relevant pH conditions and the substance is expected to be mobile.

If released to water, Na_4EDTA will not evaporate from the water surface into the atmosphere and, based on its high water solubility value and ionic structure noted above, is likely to remain in water and not adsorb to sediment.

E. Bioaccumulation

BCF values of 1.8 (0.08 mg/L Na_4EDTA) and 1.1 (0.76 mg/L Na_4EDTA) were determined in a 28-day bioaccumulation test on *Lepomis macrochirus* (EU, 2004). These measured values indicate a low potential for bioaccumulation.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Na_4EDTA exhibits low acute toxicity by the oral route. It is irritating to the eyes. Data on other sodium salts of EDTA show that these substances are not skin sensitizers. Exposures of sodium EDTA salts to rats in their diet for up to two years showed no systemic effects. No systemic effects were seen in rats exposed by inhalation to a sodium EDTA salt for 13 weeks, although there were some localised (site-of-contact) effects seen in the respiratory tract. Sodium EDTA salts are not considered to be genotoxic or carcinogenic. It is not a reproductive or developmental toxicant.

B. Acute Toxicity

Oral

For Na_4EDTA, the oral LD_{50} values in rats from three different studies range from 1,700 to 1,913 mg/kg; two additional limit studies reported the oral LD_{50} values to be > 2,000 mg/kg (EU, 2004).

Inhalation

No acute inhalation studies have been conducted on Na_4EDTA. In a study on Na_2EDTA (CAS No. [redacted] male Wistar rats were exposed nose-only to an aerosol of 0, 30, 300 or 1,000 mg/m^3 for 6 hours on five consecutive days. Exposure to 1,000 mg/m^3 for one day (6 hours) resulted in deaths of 6 out of 20 animals (ECHA) [KI score = 1].

Dermal

No dermal toxicity studies on Na_4EDTA are available.

C. Irritation

Application of 0.5 g (in 80% water) of Na_2EDTA to the skin of rabbits for 4 hours under occlusive conditions was not irritating. The mean of the 24, 48, and 72-hour erythema scores was 0.4. The mean of the 24, 48, and 72-hour oedema scores was 0 (ECHA) [KI score = 1]. Application of a 40% solution of Na_4EDTA in water (CAS No. [redacted] with a pH 11 to the skin of rabbits for up to 20 hours under occlusive conditions was not irritating (ECHA) [KI score = 2].

Instillation of 50 mg of Na_4EDTA into the eyes of rabbits was irritating. The mean 24 and 72-hour scores were: 1.25 for corneal lesions; 1.75 for conjunctival redness; 1.25 for chemosis; and 0 for iridial lesions (ECHA) [KI score = 2].

D. Sensitisation

No sensitization studies have been conducted on Na_4EDTA. Na_3EDTA was not a dermal sensitizer in a guinea pig sensitization study (ECHA) [KI score = 2].

Na_2EDTA was not a dermal sensitizer in a guinea pig maximisation test. The intradermal injection was 0.5% in corn oil; the topical applications were 30% in corn oil, and the challenge dose was 30% in corn oil (ECHA) [KI score = 1].

E. Repeated Dose Toxicity

Oral

Male Holtzman rats were fed in their diet 0, 1, 5, or 10% (0, 500, 2,500 or 5,000 mg/kg/day) Na_2EDTA for 90 days. There was mortality in the mid- and high-dose groups: 20% and 60%, respectively. Body weights and food consumption were significantly lower in the mid- and high-dose groups compared to controls. The animals in these two groups also had diarrhea and were emaciated, and water consumption was increased. The 10% group showed intermittent decreases in hematocrit and haemoglobin levels, and the livers appeared pale when examined at necropsy. Histopathologic evaluation showed no treatment-related effects. The NOAEL is 500 mg/kg/day (Wynn et al., 1970; ECHA) [KI score = 2].

Male and female F344 rats were fed in their diet 0, 3,750 or 7,500 ppm (0, 248 or 495 mg/kg/day) Na_3EDTA. There were no clinical signs; survival and body weights were similar between treated and control groups throughout the study. There was no evidence of adverse effects in the gross necropsy and histopathologic examinations. The NOAEL is 495 mg/kg/day (EU, 2004) [KI score = 2].

Male and female B6C3F1 mice were fed in their diet 0, 3,750 or 7,500 ppm (0, 469 or 938 mg/kg/day) Na_3EDTA. There was no clinical signs and survival was similar across all groups. Body weights in the high-dose males showed a significant decrease in body weights throughout the study. There was no evidence of adverse effects in the gross necropsy and histopathologic examinations. The NOAEL is 938 mg/kg/day (NCI, 1977) [KI score = 2].

Inhalation

Male and female Wistar rats were exposed nose-only to 0, 0.5, 3 or 15 mg/m^3 Na_2EDTA (as an aerosol dust) 6 hours/day, 5 days/week for 13 weeks. The MMAD of the particles for the respective groups were: 2.3 - 2.8 µm, 2.0 – 2.4 µm and 2.3 – 2.5 µm, respectively. There were no clinical signs of toxicity or any effects on the haematology and clinical chemistry parameters. Histopathological examination showed some effects on the larynx in the 15 mg/m^3 females, but no evidence of

systemic toxicity. The NOAEC for systemic toxicity in this study is 15 mg/m^3. The NOAEC for localized (site-of-contact) effects is 3 mg/m^3 (ECHA) [KI score = 1].

Dermal

No dermal studies are available.

F. Genotoxicity

In Vitro Studies

There are no *in vitro* genotoxicity studies on Na_4EDTA; however, studies have been conducted on Na_2EDTA and Na_3EDTA (Table 2).

Table 2: In Vitro Genotoxicity Studies on Na_2EDTA and Na_3EDTA

Test System	Test Substance	Results*		Klimisch Score	Reference
		-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	Na_3EDTA	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	Na_2EDTA	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	Na_3EDTA	-	-	2	ECHA
Chromosomal aberration (CHO cells)	Na_3EDTA	-	-	2	ECHA
Cell transformation assay (Syrian hamster embryos)	Na_2EDTA	N/A	-	1	ECHA
Cell transformation assay (Syrian hamster embryos)	Na_3EDTA	N/A	-	2	ECHA

*+, positive; -, negative; N/A, not applicable.

In Vivo Studies

There are no *in vivo* genotoxicity studies on Na_4EDTA. Studies conducted on other sodium salts of EDTA are summarised below.

Male NMRI mice were dosed by oral gavage with 0, 500, 1,000 or 2,000 mg/kg Na_2EDTA once daily for two consecutive days. There were no increased frequencies of micronuclei in the normochromatic erythrocytes of the bone marrow in the treated animals compared to controls (ECHA) [KI score = 1].

Male Balb/c mice were given a single intraperitoneal injection of 0, 93 or 186 mg/kg Na_2EDTA and the spermatocytes were examined 6 hours and 5 days later for aneuploidy. There were no significant increases in aneuploidy in the primary and secondary spermatocytes at both time points (Zordan et al., 1990; ECHA) [KI score = 2].

Male Balb/c mice were given a single intraperitoneal injection of 0 or 186 mg/kg Na_2EDTA, and the frequency of micronuclei was analysed in the Golgi and Cap phase, which represents the two earliest phases of spermatid development. The sampling time points were 24 and 48 hours post-dosing.

Micronuclei were induced in the Golgi phase spermatids at both time points; there was no increase in micronuclei in the Cap phase (Russo and Lewis, 1992; ECHA) [KI score = 2].

No chromosomal aberrations were noted in male Balb/c mouse spermatogonia following a single intraperitoneal dose of 186 mg/kg Na_2EDTA (Russo and Lewis, 1992; ECHA) [KI score = 2].

In summary, Na_2EDTA did not induce genotoxicity in bone marrow cells in mice. In germ cells of mice, Na_2EDTA did not induce chromosomal aberrations in spermatogonia, aneuploidy in primary and secondary spermatocytes, but micronuclei were induced at a specific phase of spermatogenesis. The dose of Na_2EDTA used to induce micronuclei in these spermatids is an extremely high dose; given that the induction of aneuploidy is based on a threshold mode-of-action, it is unlikely that this effect will occur in humans exposed to sodium salts of EDTA. Overall, the sodium salts of EDTA are not genotoxic (EU, 2004).

G. Carcinogenicity

Oral

No studies are available on Na_4EDTA.

Male and female F344 rats were fed in their diet 0, 3,750 or 7,500 ppm (0, 248 or 495 mg/kg/day) Na_3EDTA. There were no clinical signs; survival and body weights were similar between treated and control groups throughout the study. Tumour incidences were similar across all groups, indicating no evidence of carcinogenicity from chronic exposure to Na_3EDTA (NCI, 1977) [KI score = 2].

Male and female B6C3F1 mice were fed in their diet 0, 3,750 or 7,500 ppm (0, 469 or 938 mg/kg/day) Na_3EDTA. There was no clinical signs and survival was similar across all groups. Body weights in the high-dose males showed a significant decrease in body weights throughout the study. Tumour incidences were similar across all groups, indicating no evidence of carcinogenicity from chronic exposure to Na3EDTA (NCI, 1977) [KI score = 2].

No inhalation or dermal carcinogenicity studies were located.

H. Reproductive Toxicity

No studies are available on Na_4EDTA.

Male and female Wistar rats were given in their feed 0, 50, 125 or 250 mg/kg/day CaNa2EDTA (CAS No. [redacted] for two years. The study included reproductive and lactation components in four successive generations. There were no significant differences between treated and controls groups in behaviour, clinical signs, survival, body weight gain in any generation. The high-dose group showed no treatment-related organ weight changes or histopathologic effects in any of the organs examined, including the testes. There were no consistent treatment-related effects on reproductive performance or developmental effects in any of the four generations examined. The NOAEL for reproductive toxicity is 250 mg/kg/day, the highest dose tested (Oser et al., 1963; ECHA) [KI score = 2].

I. Developmental Toxicity

Pregnant female rats were dosed by oral gavage with 0 or 1,000 mg EDTA/kg during GD 7-14. The salts of EDTA (Na_2EDTA, Na_3EDTA, $CaNa_2EDTA$ and Na_4EDTA were also included in this study and were tested on an equimolar basis. For Na_4EDTA, the dose is 1,374 mg/kg/day which was given as

equally divided doses twice daily. There was diarrhea in 90% of the dams after each daily dosing and which disappeared after the last day of dosing. There was also reduced feed intake and reduced weight gain during the treatment period; both recovered during the post-treatment period. There was no developmental toxicity in any of the treatment groups compared to controls. The NOAEL for maternal and developmental toxicity for Na_4EDTA is 1,374 mg/kg/day (Schardein et al. 1981; ECHA).

The toxicity and teratogenicity of Na_2EDTA were studied in pregnant female CD rats following different routes of administration during GD 7-14. When Na_2EDTA was administered in the diet at 3% (average dose of 954 EDTA/kg/day), the dams had reduced feed intake, severe diarrhea and severe weight loss. There was a significant proportion of foetal deaths (~33% resorptions/litter), significantly lower average foetal weight and gross external, internal and skeletal malformations in about 71% of the surviving foetuses. When Na_2EDTA was administered by oral gavage at doses of 1,250 or 1,500 mg EDTA/kg/day, there was severe toxicity to the dams: 3/8 and 7/8 deaths in the 1,250 and 1,500 mg/kg/day groups, respectively; significantly reduced weight gain and diarrhea in the 1,250 mg/kg/day group. There was a significantly higher proportion of malformed surviving foetuses. When administered subcutaneously with 375 mg EDTA, the dams showed signs of severe pain (vocalisations and shock) and 24% of them died; there was also a significant reduction in body weight and feed intake. Foetal toxicity included about 32% resorptions/litter and significant reduction of foetal body weight, and about a 4% malformed survivors/litter (Kimmel, 1977; ECHA).

Pregnant female CD rats were given in their diet 0, 2, or 3% Na_2EDTA; in addition, a group was fed 3% Na_2EDTA supplemented with 1,000 ppm zinc (Zn). Exposures were as follows: 2% (GD 0-21), 3% (GD 0-21, GD 6-14, or GD 6 to 21); 3% + Zn (GD 6-21). The dietary doses of 2% and 3% Na_2EDTA correspond to approximately 1,000 and 1,500 mg/kg/day, respectively. All of the dams had moderate to severe diarrhea. In the 2% Na_2EDTA group, all rats had living young at term; the litter size was normal; the young were slightly small than controls, and 7% of the foetuses were malformed. In the 3% Na_2EDTA (GD 0-21), reproduction was severely disturbed, and none of the females had grossly visible implantation sites. In the 3% Na_2EDTA (GD 6-14 and 6-21), almost all females had implantation sites; half of the sites had dead or resorbed foetuses; 100% of the foetuses were malformed in the GD 6-21 group. In the 3% Na_2EDTA + Zn group, there was a normal reproduction, and none of the young was malformed. It was suggested by the study authors that the congenital abnormalities caused by EDTA were due specifically to zinc deficiency (Swenerton et al., 1977).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Toxicological reference values were not derived for Na_4EDTA.

The Australian drinking water guidance value for EDTA is 0.25 mg/L (ADWG, 2021).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Na_4EDTA does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Details on the aquatic toxicity studies on Na_4EDTA and its sodium salts can be found in the EU Risk Assessment Report (RAR) on Na_4EDTA (EU, 2004). The mode-of-action of Na_4EDTA in aquatic systems involves disturbances of metal metabolism; hence, the complex formation properties of Na_4EDTA need to be taken into account. In general, complexed and non-complexed EDTA have a low toxicity concern for fish and invertebrates. EDTA is highly toxic to algae in tests using standard media; the effect is probably caused by nutritional deficiency. If nutrient metal concentrations are increased, then EDTA has a low toxicity concern for algae; this is the more likely scenario in the environment.

B. Aquatic Toxicity

Uncomplexed Na_4EDTA will only be present in the test media of aquatic toxicity studies when present in an excess amount relative to the calcium and magnesium ions, as well as some level of heavy metal ions, which are present mainly as trace nutrients. Complexes with the heavy metals are predominant because the formation constants are several orders of magnitude higher than those of the calcium and magnesium ions. After addition of Na_4EDTA (as an acid or sodium salt), the concentration of uncomplexed trace metals will decrease considerably, and if there is a surplus of Na_4EDTA, there will also be complexing with the calcium and magnesium ions.

Na_4EDTA and its sodium salts appear to be more toxic in an uncomplexed form in the acute toxicity studies. Most of the acute fish studies have LC_{50} values that are much greater than 100 mg/L, with the exception of two studies tested with H_4EDTA in soft and very soft water: the LC_{50} values were 41 and 59.8 mg/L, respectively. It is thought that there was an excess of uncomplexed Na_4EDTA in the test media of these two studies due to the low levels of magnesium and calcium ions in soft water; this, however, is an unlikely scenario in the environment.

The EU RAR (EU, 2004) considered the most relevant chronic fish toxicity study to be an early-life stage test on zebrafish; the NOEC was > 26.8 mg/L H_4EDTA ($CaNa_2EDTA$ was the test substance) (EU, 2004).

The acute toxicity tests on *Daphna magna* reported 24-hour EC_{50} values of 480 to 790 mg/L (EU, 2004). The 21-day NOEC from a *Daphnia* reproduction test was 22 mg/L (EU, 2004).

Essential trace metal bioavailability seems to be the critical factor in algal toxicity from Na_4EDTA exposure. The ratio of the Na_4EDTA concentration to the metal cations is a critical element to algal growth and not the absolute Na_4EDTA concentration. H_4EDTA concentrations up to 310 mg/L will not cause any effect on algal growth if there is sufficient trace metals present. Since there is a considerable amount of metal ions present in the environment, Na_4EDTA is not expected to have an intrinsic toxic effect on plants. In a study with *Scenedesmus subspicatus*, an EC_{10} value of 0.37 mg/L was obtained (EU, 2004). The EU RAR considered that the effect was probably due to nutrient deficiency because essential metals (Cu, Zn, Co) are largely complexed to the Na_4EDTA, resulting in considerably reduced concentrations. In another study with *Pseudokirchnerella subcapitata* conducted according to OECD TG 201, the ECb_{50} and ECr_{50} of Fe(III)EDTA were > 100 mg/L; the NOEC values were 79.4 and 48.4 mg/L, respectively, when based on mean measured concentrations.

C. Terrestrial Toxicity

No relevant studies are available. The only test results that are available are those that have investigated the decrease of heavy metal toxicity caused by Na_4EDTA.

D. Calculation of PNEC

The PNEC calculations for Na_4EDTA follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Results from chronic studies are also available for all three trophic levels, with the lowest NOEC being 22 mg/L for algae (EU, 2004). On the basis that the data consists of short-term and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported long-term NOEC of 22 mg/L for invertebrates. The $PNEC_{water}$ is 2.2 mg/L.

PNEC sediment

No experimental toxicity data on sediment organisms are available. The equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$ because Na_4EDTA is not expected to adsorb to sediment. The assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No experimental toxicity data on soil organisms are available. The equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$ because Na_4EDTA is not expected to adsorb to soil. The assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Na_4EDTA is not readily biodegradable; thus, it meets the screening criteria for persistence.

The experimental BCF of Na_4EDTA in fish is 1.1 – 1.8. Thus, Na_4EDTA does not meet the criteria for bioaccumulation.

The lowest NOEC from chronic aquatic toxicity studies is > 0.1 mg/L. Na_4EDTA and its sodium salts appear to be more toxic in an uncomplexed form in the acute toxicity studies. Acute EC_{50} values in fish, invertebrates and algae are > 1 mg/L. Thus, Na_4EDTA does not meet the screening criteria for toxicity.

The overall conclusion is that Na_4EDTA is not a PBT substance.

IX. CLASSIFICATION AND LABELING

A. Classification

Acute Toxicity Category 4 [oral]

Acute Toxicity Category 4 [inhalation]

Eye Damage Category 1

B. Signal Word

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon monoxide, carbon dioxide, nitrogen oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical protective clothing.

C. Accidental Release Measures

Personal Precautions

Use personal protective clothing. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust. Wear respiratory protection if ventilation is inadequate. Avoid contact with skin, eye, and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways, or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessarily provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust. Take precautionary measures against static discharges by bonding and grounding equipment.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for Na_4EDTA.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Na_4EDTA is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

EU. (2004). European Union Risk Assessment Report for Tetrasodium ethylenediamineacetate (CAS No. [redacted] Volume 51. Available at: https://echa.europa.eu/documents/10162/415c121b-12cd-40a2-bd56-812c57c303ce

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Kimmel, C.A. (1977). Effect of route of administration on the toxicity and teratogenicity of EDTA in the rat. Toxicol. Appl. Pharmacol. 40: 299-306.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

National Cancer Institute [NCI]. (1977). Bioassay of Trisodium Ethylenediamininetetraacetate trihydrate (EDTA) for Possible Carcinogenicity (CAS No. [redacted] NCI-CG-TR-11, DHEW Publication No. (NIH) 77-811. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

Nowack, B. (2002). 'Environmental chemistry of aminopolycarboxylate chelating agents', Environmental Science and Technology, vol. 36(19), pp. 4009-4016.

Nowack, B., Kari, F.G., Krüger, H.G. (2001)., 'The remobilization of metals from iron oxides and sediments by metal-EDTA complexes', Water, Air and Soil Pollution, vol. 125, pp. 243-257.

Oser, B.L., Oser, M., and Spencer, H.C. (1963). Safety evaluation studies of calcium EDTA. Toxicol. Appl. Pharmacol. 5: 142-162.

Russo, A., and Levis, A.G. (1992). Further evidence for the aneuploidogenic properties of chelating agents: Induction of micronuclei in mouse male germ cells by EDTA. Environ. Mol. Mutagen. 19: 125-131.

Schardein, J.L., Sakowski, R., Petrere, J., and Humphrey, R.R. (1981). Teratogenesis studies with EDTA and its salts in rats. Toxicol. Appl. Pharmacol. 61: 423-428.

Swenerton, H., and Hurley, L.S. (1971). Teratogenic effects of a chelating agent and their prevention by zinc. Science 173: 62-64.

van Ginkel C.G., Kester H., Stroo C.A., van Haperen A.M. (1999). Biodegradation of EDTA in pulp and paper mill effiuent by activated sludge. Appl Water Sci 8:111 (1999)

Wynn, J.E., van Riet, B., and Borcelleca, J.F. (1970). The toxicity and pharmacodynamics of EDTA: Oral administration to rats and comparison with EDTA. Toxicol. Appl. Pharmacol. 16: 807-817.

Zordan, M., Russo, A., Costa, R., Bianco, N., Beltrame, C., and Levis, A.G. (1990). A concerted approach to the study of the aneuoploidogenic properties of two chelating agents (EDTA and NTA) in the germ and somatic cell lines of Drosophila and the mouse. Environ. Mutagen. 15: 205-213.

POLY(OXY-1,2-ETHANEDIYL), ALPHAHEXYL-OMEGA-HYDROXY-
(ETHYLENE GLYCOL-N-MONOHEXYL ETHER)

This dossier on poly(oxy-1,2-ethanediyl), alphahexyl-omega-hydroxy or ethylene glycol-n-monohexyl ether (EGMHE) does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies pertinent to the risk assessment of EGMHE in its use in in coal seam gas extraction activities. The majority of information presented in this dossier was obtained from the OECD-SIDS documents on a well-defined surrogate ethylene glycol monobutyl ether (EGBE) (CAS RN [redacted] and from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-hexoxyethanol

CAS RN: [redacted]

Molecular formula: $C_8H_{18}O_2$

Molecular weight: 146.23 g/mol

Synonyms: Poly(oxy-1,2-ethanediyl), alpha-hexyl-omega-hydroxy-; ethylene glycol monohexyl ether; EGHE; alpha-Hexyl,omega-hydroxypoly(oxy-1,2-ethanediyl); hexyl alcohol, ethoxylated

SMILES: CCCCCCOCCO

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of EGBE (CAS No. [redacted]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	A colourless liquid. Odour is mild, ether-like, and slightly rancid.	2	ECHA
Melting Point	-74.8°C @ 101.3 kPa	2	ECHA
Boiling Point	171 – 171.5°C @ 101.3 kPa	2	ECHA
Density	900 kg/m^3 @ 20°C	2	ECHA
Vapour Pressure	80 Pa @ 20°C	2	ECHA
Partition Coefficient (log K_{ow})	0.81 (temperature not available)	1	ECHA
Water Solubility	900 g/L @ 20°C (fully soluble)	2	ECHA
Flash Point	67°C	2	ECHA
Auto flammability	230°C	2	ECHA
Viscosity	3.642 mm^2/s (3.28 mPa.s)	2	ECHA
Henry's Law Constant	0.041 Pa.m^3/mol	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

EGBE is readily biodegradable. It is not expected to bioaccumulate. EGBE has a low tendency to bind to soil or sediment.

B. Biodegradation

EGBE was considered readily biodegradable in an OECD 301B test. Degradation was 90.4% after 28 days; the 10-day window was met (ECHA) [KI score = 2]. Results from another OECD 301B test showed 63% and 74-75% degradation after 10 and 28 days, respectively (ECHA) [KI score = 2]. An OECD 301 D test showed 67-75% degradation after 15 days and 73-77% after 28 days (ECHA) [KI score = 2]. In a Zahn-Wellen (OECD 302B test), degradation of EGBE was 95% after 8 days, measured as DOC removal (ECHA) [KI score = 2].

C. Environmental Distribution

No experimental data are available for EGBE. Using KOCWIN in EPI Suite™ (U.S. EPA, 2017), the estimated K_{oc} value from log K_{ow} is 7.624 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 2.823 L/kg.

D. Bioaccumulation

No bioconcentration studies have been conducted on EGBE. EGBE is not expected to bioaccumulate based on the experimental log K_{ow} of 0.81 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

EGBE has low-to-moderate acute toxicity by the oral route. Species vary greatly in their susceptibility to acute toxicity by the dermal route, with the rabbit being the most sensitive species showing moderate toxicity, with the rat and guinea pig showing low toxicity (in descending order). EGBE is a skin and eye irritant; it is not a skin sensitiser. The major target organ effect of EGBE from exposure (regardless of the route of exposure) is the red blood cell (RBC). Animal studies show a hemolytic anemia (haemolysis of RBCs) from acute and chronic exposure to EGBE, resulting in effects in the kidney, liver and spleen. The hemolytic effect of EGBE is caused by the acid metabolite, 2-butoxyacetic acid (BAA). A number of species, including humans and guinea pigs, are relatively insensitive to the hemolytic effects of EGBE. Lifetime rodent studies by the inhalation route showed no carcinogenic effects in rats; however, liver tumours and hemangiosarcomas of the liver were seen in male mice, and forestomach tumours were seen in female mice. These tumours are thought to occur by a non-genotoxic mode-of-action and are only likely to occur in humans, if at all, at unrealistically high exposures (primarily because of kinetic/dynamic differences between mice and humans). Animal studies show that EGBE can cause reproductive and developmental toxicity, but only exposures that also cause parental or maternal toxicity.

B. Toxicokinetics/Metabolism

The toxicokinetics and metabolism of EGBE have been extensively studied and are reviewed in the EU Risk Assessment Report (EU, 2006) and in the U.S. EPA IRIS Toxicological Review of EGBE (U.S. EPA, 2010).

The major metabolite of EGBE is 2-butoxyacetic acid (BAA). EGBE is metabolised to butoxyaldehyde (BAL) by alcohol dehydrogenases, which is then further metabolised to BAA by aldehyde dehydrogenases. The metabolism of EGBE to BAA appears to be a saturable process. The other metabolites of EGBE are (in order of magnitude): the glucuronide conjugate of EGBE (a competing pathway to BAA formation and whose percentage increases relative to dose), the sulfate-conjugate of EGBE and ethylene glycol. Elimination is rapid and occurs mainly by urinary excretion. EGBE does not accumulate in tissues, and the metabolic profile does not change after repeated exposures compared to acute exposures.

Physiologically-based pharmacokinetic (PBPK) models has been developed for EGBE (Corley et al., 1994, 1997, 2005).

C. Acute Toxicity

The oral LD_{50} values for EGBE are presented in Table 2.

Table 2: Acute Oral LD_{50} Values for EGBE

Species	Results (mg/kg)	Klimisch Score	Reference
Rat	1,746 (fasted) 1,746 (fed)	1	ECHA
Rat	880 (male) 614 (female)	2	ECHA
Rat	1,480	2	ECHA
Rat	~1,900	2	ECHA
Rat	2,420	2	ECHA
Rat	2,100 (male) 1,850 (female)	2	ECHA
Mouse	1,519 (fasted) 2,005 (fed)	1	ECHA
Guinea pig	1,414	1	ECHA
Guinea pig	1,200	2	ECHA

The acute inhalation LC_{50} values for EGBE are presented in Table 3.

Table 3: Acute Inhalation LC_{50} Values for EGBE

Species	Exposure	Results (mg/L)	Klimisch Score	Reference
Rat	4-hour LC_0	2.4 (males) 2.2 (females)	1	ECHA
Rat	1- to 3-hour LC_0	> 29	2	ECHA

Species	Exposure	Results (mg/L)	Klimisch Score	Reference
Rat	3-hour LC_0 8-hour LC_{100}	1.44 4.25	2	ECHA
Rat	7-hour LC_{50}	> 4.26	2	ECHA
Rat	4-hour LC_{50} 8-hour LC_{50}	> 3.9 ~3.9	2	ECHA
Rabbit	7-hour LC_{50}	~400 ppm	2	ECHA
Guinea pig	1-hour LC_0	> 3.4 (males) > 3.1 (females)	2	ECHA
Guinea pig	7-hour LC_0	>400 ppm	2	ECHA

The dermal LD_{50} values for EGBE are presented in Table 4.

Table 4: Acute Dermal LD_{50} Values for EGBE

Species	Results (mg/kg)	Klimisch Score	Reference
Rabbit	> 2,000	1	ECHA
Rabbit	> 2,000	1	ECHA
Rabbit	612 (abraded)	2	ECHA
Rabbit	405	2	ECHA
Rabbit	567	2	ECHA
Rat	> 2,000	1	ECHA
Rat	2,275	2	ECHA
Guinea pig	> 2,000	1	ECHA
Guinea pig	0.23 mL/kg (intact) 0.30 mg/kg (abraded)	2	ECHA
Guinea pig	7.3 mL/kg	2	ECHA

D. Irritation

Application of 0.5 mL EGBE to the skin of rabbits for 4 hours under occlusive conditions was irritating. The mean of the 24, 48 and 72-hour erythema scores was 1.7. The mean of the 24, 48 and 72-hour oedema scores were 0.13. The erythema was not fully reversible within 14 days observation period (ECHA) [KI score = 2]. Another study showed an irritating response to rabbit skin following a 24-hour exposure under occlusive conditions (ECHA) [KI score = 2].

Instillation of 0.1 mL EGBE into the eyes of rabbits was irritating. The 24, 48 and 72-hour mean scores were: 0.89 for corneal opacity; 0.56 for iridial lesions; 2.6 for conjunctival redness; and 1.8 for chemosis. All effects were reversible within the 21-day observation period (ECHA) [KI score = 1].

E. Sensitisation

EGBE was not considered to be a skin sensitiser in the guinea pig maximisation test (ECHA) [KI score = 1].

F. Repeated Dose Toxicity

Oral

Male CR, COBS, CD-BR rats were dosed by oral gavage with 0, 222, 443 or 885 mg/kg EBGE, 5 days/week for 6 weeks. Bloody urine, which persisted through the third week of treatment, was observed in all of the ≥ 443 mg/kg animals; only one 222 mg/kg rat had bloody urine, which disappeared after the week 3 of exposure. Lethargy, unkempt hair coats, piloerection, rates, slight weakness and inactivity were also seen in these animals. Body weights and feed consumption were significantly reduced in the 885 mg/kg animals. Haematological effects were seen in the 885 mg/kg animals and included decreased haemoglobin, total red blood cells (RBCs), and increased MCH in all dose groups and showing a dose-related response. MCHC was decreased and MCV was increased in the ≥ 443 mg/kg animals. Alkaline phosphatase levels were elevated in the ≥ 443 mg/kg animals; and SGPT and glucose levels were increased in the 885 mg/kg group. Absolute and relative spleen and liver weights were increased in the ≥ 443 mg/kg animals. Relative liver weights were also increased in the 222 mg/kg animals. Enlarged, dark spleens were seen in the ≥ 443 mg/kg animals at gross necropsy. Histopathological examination showed stomach hyperkeratosis/acanthosis and splenic congestion in virtually all treated animals at all dose levels. Extramedullary haematopoiesis was observed in the spleens of treated animals. Liver effects were also seen in treated animals and included hepatocytomegally (885 mg/kg only), anisokaryosis (22 and 443 mg/kg), and hemosiderin deposition (≥ 443 mg/kg). Kidney effects were also seen in the treated animals and included hyaline droplet degeneration, proteinaceous casts and hemosiderin in the proximal tubules. The latter two effects were seen in the ≥ 443 mg/kg animals and were considered compound-related; the hyalaine droplets were seen in the controls and its significance is uncertain. The LOAEL for this study was considered 222 mg/kg/day based on adverse effects on the RBC and splenic congestion (it is difficult to discern what were primary effects, and what were secondary to the hemolytic effects); a NOAEL was not established (ECHA) [KI score = 2].

Male and female F344/N rats were given in their drinking water 0, 750, 1,500, 3,000, 4,500 or 6,000 ppm EGBE for 13 weeks. Based on water consumption, the average daily intake was 0, 69, 129, 281, 367 or 452 mg/kg/day for males and 0, 82, 151, 304, 363 or 470 mg/kg/day for females. Supplemental groups were included for hematology and clinical chemistry observations at weeks 1 and 3. There was no mortality and no clinical signs of toxicity. Reduced body weight gain was seen in the ≥ 4,500 ppm animals, particularly in the females. Water consumption was also reduced in the higher dose groups, particularly for females. At each time point, there was a noticeable macrocytic and mildly hypochromic anemia. Reticulocyte counts were moderately increased in weeks 1 and 13; and erythrocyte counts were decreased at all time points in the ≥ 3,000 ppm males and the ≥ 1,500 ppm males. Thrombocytopenia was consistently observed at all time points in ≥ 4,500 ppm males and females; it also occurred in the 3,000 ppm females at week 13. Alkaline phosphatase was increased in the 6,000 ppm group on week 1 and in the ≥ 4,500 ppm groups on week 13. BUN and creatinine were increased, along with mild decreases in total protein and albumin, occurred at weeks 3 and 13; these changes were considered to be consistent with decreased feed intake. Absolute thymus weight were reduced in the ≥ 4,500 ppm groups. All other organ weight changes were considered secondary to body weight changes. Histopathological effects were seen in the liver, spleen and bone marrow of both male and female rats. The liver changes were primarily centrilobular hepatocellular degeneration and centrilobular Kupffer cell pigmentation. These changes were present in the majority of dosed rats, but they were more prevalent in the ≥ 3,000 ppm animals and were slightly more severe in

females. In addition, the cytoplasm of hepatocytes of treated rats was more eosinophilic and lacked the ampholytic-to-basophilic granularity typical of the controls. In the spleen, there was an increase in haematopoiesis and deposition of hemosiderin. In bone marrow there was an hyperplasia characterised by an increase of hematopoietic cells and decrease in marrow fat cells. All of these lesions were present in the majority of dosed rats, but they were more prominent in the ≥ 3,000 ppm animals. The LOAEL for this study is 750 ppm (69 and 82 mg/kg/day for males and females, respectively) based on the effects seen in the liver. A NOAEL was not obtained (NTP, 1993) [Kl score = 1].

Male and female B6C3F_1 mice were given in their drinking water 0, 750, 1,500, 3,000, 4,500 or 6,000 ppm EGBE for 14 weeks. Based on water consumption, the average daily intake was estimated to be 0, 118, 223, 553, 676 or 694 mg/kg/day for males and 0, 185, 370, 676, 861 or 1,306 mg/kg/day for females. There was no mortality and no significant clinical signs of toxicity. Reduction in body weight gain was seen in the ≥ 3,000 ppm males and females. Water consumption did not appear to be affected by treatment. Organ weight changes were considered secondary to body weight gain reduction. No treatment-related gross or microscopic lesions in male or female mice were observed. The NOAEL for this study is 223 and 370 mg/kg/day for males and females, respectively. However, this study did not include hematology measurements (NTP, 1993) [Kl score = 1].

Inhalation

Male and female F344 rats were exposed by inhalation to 0, 5, 25 or 77 ppm (0, 24, 121 or 372 mg/m^3) EGBE 6 hours/day, 5 days/week for 90 days. Effects were more pronounced in females than males. In females, there was a slight hemolytic anemia, which was indicated by a minimal depression of RBC counts, haemoglobin and hematocrit; with a slight increase in MCH that was noted at week 2 and at the end of the exposure period. The haematological effects were non-progressive in that there was no increase in severity over time. Reduced body weight gain was seen at week 2, but not at the end of the study. No effects were seen in the males. The NOAECs for males and females were 77 ppm and 25 ppm, respectively (Dodd et al., 1983; ECHA).

Male and female F344/N rats were exposed by inhalation to 0, 31, 62.5, 125, 250 or 500 ppm EGBE 6 hours/day for 14 weeks. Six female rats were found moribund and killed during the study: five in the 500 ppm group and one in the 250 ppm group. Clinical signs were mainly in the ≥ 125 ppm animals and included abnormal breathing, pallor, red urine stains, nasal and eye discharge, lethargy and either increased salivation or lacrimation. All 500 ppm females developed alternating blue and white bands on their tails, particularly during the first two weeks of treatment, that caused them to self-mutilate and loose the distal portion of their tails. The mean final body weights and body weight gains were significantly reduced in the 500 ppm females. There was a persistent and exposure-related macrocytic, normochromic, responsive anemia, characterised by decreased haematocrit, hemoglobin concentrations, and erythrocyte counts in the ≥ 125 ppm males and ≥ 31 ppm females. The anemia was dose-related and statistically significant; at the lower doses, the effect was small (~5% in the 31 ppm females). Increases in reticulocyte and nucleated erythrocyte counts were seen in the ≥ 125 ppm males and the ≥ 62.5 ppm females, which are indicative of a erythropoietic response. Kidney weight increased in the 500 ppm males and the ≥ 125 ppm females. Liver weights were increased in the ≥ 250 ppm males and the ≥ 125 ppm females. Thymus weights were decreased in the 500 ppm females. There were histopathological changes in the surviving rats. Bone marrow necrosis and infarcts were found in the tails of all surviving 500 ppm females. Minimal hematopoietic cell proliferation of the spleen was seen

in the ≥ 62.5 ppm females and ≥ 250 ppm males. Bone marrow hyperplasia was increased in the ≥ 62.5 ppm females and ≥ 250 ppm males. Increased pigmentation of Kupffer cells in the liver was seen in the ≥ 62.5 ppm females and ≥ 125 ppm males. Renal tubule pigmentation was noted in most of the 250 ppm males, in all of the 500 ppm males, and all of the ≥ 125 ppm females. Minimal forestomach inflammation and hyperplasia were noted in a few of the ≥ 250 ppm males. Epithelial hyperplasia of the forestomach were noted in one female each in the ≥ 250 ppm groups. The NOAEC for males is 62.5 ppm based on haematological changes. The LOAEC for females is 31 ppm based on haematological changes; a NOAEC was not established (NTP, 2000) [Kl score = 1].

Male and female B6C3F_1 mice were exposed by inhalation to 0, 31, 62.5, 125, 250 or 500 ppm 6 hours/day for 14 weeks. There was mortality in the 500 ppm exposure group: two males and two females died; two males and two females were found moribund and were killed. Clinical findings were limited to the 500 ppm males and females that died or were killed. By study termination, body weight gains were significantly reduced in the ≥ 125 ppm males. There was a persistent and exposure-related normocytic (unlike rats), normochromic, responsive anemia, characterised by decreased haematocrit, hemoglobin concentrations, and erythrocyte counts in the ≥ 125 ppm males and ≥ 31 ppm females. The anemia was dose-related and statistically significant; at the lower doses, the effect on erythrocyte count and haemoglobin was small (1.8% and 2.2% in the 31 and 62.5 ppm females). The normocytic and normochromic erythrocytes were demonstrated by the lack of change in the mean cell volumes and mean cell haemoglobin concentrations, respectively. Relative, but not absolute, liver weighs were increased in the 250 ppm males. At 500 ppm, there were increased relative liver weights (both sexes), absolute liver weights (males), and relative kidney and heart weights (females). The livers of the 500 ppm males and ≥ 250 ppm females showed hemosiderin deposition in the Kupffer cells. Hemosiderin pigmentation was also seen in the kidney tubular cells of the 500 ppm animals (both sexes). Extramedullary hematopoietic cell proliferation (primarily erythroid) was seen in the ≥ 125 ppm males and ≥ 250 ppm females. In the forestomach, increased incidence of inflammation was seen in the ≥ 250 ppm females and epithelial hyperplasia in the ≥ 125 ppm females. The NOAEC for males is 62.5 ppm based on haematological changes. The LOAEC for females is 31 ppm based haematological changes; a NOAEC was not established (NTP, 2000) [Kl score = 1].

Male and female F344/N rats were exposed by inhalation to 0, 31, 62.5 or 125 ppm (0, 151, 302 or 604 mg/m^3) EGBE vapour for 6 hours/day, 5 days/week for 104 weeks (NTP, 2000). For haematological and bone marrow analyses, additional groups of animals were exposed to 0, 62.5 or 125 ppm for evaluation at 3, 6 and 12 months; and to 31.2 ppm for 3 months (haematological examination only) and 6 months. Survival was similar across all groups, and there were no treatment-related clinical signs. Body weights of the 125 ppm females were generally lower than the controls from week 17 until study termination. There was a persistent and treatment-related macrocytic, normochromic, responsive anemia, characterised by decreased haematocrit, hemoglobin concentrations and erythrocyte counts at 3, 6 and 12 months in the 62.5 ppm females and the 125 ppm males. Some anemia also occurred at 3 and 6 months in the 31 ppm females and at 12 months in the 62.5 ppm males. In females, the anemia was characterised by a dose-related and significant fall in haematocrit, hemoglobin and erythrocyte count and an increase in MCV. The changes at 31 ppm were small (< 5%). Circulating reticulocyte and nucleated erythrocyte counts are indicative of an erythropoietic response to the anemia. There was about 15-35% decrease in the myeloid/erythroid ratio in the bone marrow of the 125 ppm rats (both sexes), particularly in the females. Significant changes in the ratio were also seen in the 125 ppm males and the 62.5 ppm females, but at only one time point. The severity of the response

was dose-related. Non-neoplastic changes occurred in the nose, liver and spleen. The incidence of hyaline degeneration of the olfactory epithelium were significantly increased in the ≥ 31 ppm males and in the ≥ 62.5 ppm females. The severity was minimal and did not change with increasing exposure concentration. The incidence of Kupffer cell pigmentation of the liver increased significantly in all exposed male and in the ≥ 31 ppm males and in the ≥ 62.5 ppm females; the severity increased in the 135 ppm of both sexes. The incidences of fibrosis in the spleen were significantly increased in the ≥ 62.5 ppm males, but not in females. The LOAEC for males is 31 ppm based on hematology and Kupffer cell pigmentation in the liver. The LOAEC for females is 31 ppm based on Kupffer cell pigmentation in the liver. A NOAEC for either sex was not established (NTP, 2000) [KI score = 2].

Male and female B6C3F_1 mice were exposed by inhalation to 0, 62.5, 125 or 250 ppm (0, 302, 604 or 1,208 mg/m^3) EGBE vapour for 6 hours/day, 5 days/week for 104 weeks (NTP, 2000). For haematological and bone marrow analyses, additional groups of animals were exposed to 0, 62.5, 125 or 250 ppm for evaluation at 3, 6 and 12 months. Survival of the ≥ 125 ppm males were significantly less than the controls. Body weights of exposed males were generally less than the controls during the last 25 weeks of the study. The 250 ppm females had body weights that were generally lower (20%) than controls from week 30 to the end of the study. The 62.5 and 125 ppm females had lower body weights from about week 60 until the end of the study. There was a persistent and exposure-related normocytic and normochromic, responsive anemia, characterised by haematocrit, hemoglobin concentrations and erythrocyte counts. In general, the anemia lacked changes in mean cell volumes and mean cell haemoglobin concentrations. There were no treatment-related clinical signs. The changes occurred at the 3-, 6- and 12-month time points in the ≥ 125 ppm males and females. Some anemia also occurred at 6 months in the 62.5 ppm females, and there was some indication of a macrocytosis (as seen by a minimal increase in cell volume) in the 250 ppm females at 12 months. Circulating reticulocyte counts were increased in the ≥ 125 ppm males and females at 3 and 6 months and the 250 ppm females at 12 months; these changes are indicative of an erythropoietic response to the anemia. The bone marrow had no change in either cell counts or myeloid/erythroid ratio. A thromobocytosis (increased platelet counts) developed in the ≥ 62.5 ppm animals at 12 months , in the 250 ppm males at 6 months, the 250 ppm females at 3 and 6 months, and in the 125 ppm females at 6 months. At 62.5 ppm, the females showed reduced haemoglobin, hematocrit, erythrocyte count and increased platelets. The 62.5 ppm males showed an increased platelet count. All these changes were statistically significant with a clear dose-response, but the magnitude was small (< 5%), except for the platelet count (15-20%). Splenic hematopoietic cell proliferation was increased in the ≥ 125 ppm males and 250 ppm females, but it was not accompanied by any change in myeloid/erythroid cell ratio. Increased incidence of hemosiderin pigmentation occurred in the ≥ 62.5 ppm males and ≥ 125 ppm females, and increased bone marrow hyperplasia occurred in the ≥ 125 ppm males. The incidence of hyaline degeneration of the nasal olfactory epithelium and respiratory epithelium was increased in the ≥ 62.5 ppm females (but not in males). The severity of the lesion was minimal and did not change with increasing exposure concentration. There was no clear dose-response. There were forestomach lesions which consisted of ulcers (particularly in females), epithelial hyperplasia that was usually focal, and, particularly in females, frequently associated with ulceration. There was also a number of inflammatory changes in the urogenital system in the male mice only; these changes were not considered to be primarily related to treatment. The LOAEC for this study is 62.5 ppm based on haematological changes and increased platelet counts (at 12 months); a NOAEC was not established (NTP, 2000) [KI score = 1].

Dermal

Male and female New Zealand rabbits were given dermal application of 0, 10, 50 or 150 mg/kg EGBE 6 hours/day for 13 weeks. The highest dose was the maximum that could be tolerated without irritation from prolonged exposure. There were no clinical, haematological effects, clinical chemistry or histopathological changes that were considered treatment-related. The NOAEL for this study is 150 mg/kg/day (ECHA) [KI score = 1].

G. Genotoxicity

In Vitro Studies

Table 5 presents the results of the *in vitro* genotoxicity studies on EGBE.

Table 5: *In Vitro* Genotoxicity Studies on EGBE

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	NTP, 1993; NTP, 2000
Mammalian cell gene mutation (CHO cells/HGPRT)	-	-	1	ECHA
Chromosomal aberration (CHO cells)	-	-	1	NTP, 1993; NTP, 2000

*+, positive; -, negative

In Vivo Studies

Male F344 rats were given a single daily intraperitoneal injection of 0, 7.03. 14.06, 28.12, 56.25, 112.5, 225 or 450 mg/kg EGBE for three consecutive days. Two of the five animals in the 450 mg/kg group died. There was no increase in micronuclei in the bone marrow polychromatic erythrocytes at any dose level (NTP, 2000) [KI score = 1].

Male B6C3F_1 mice were given a single daily intraperitoneal injection of 0, 17.19, 34.38, 68.78, 137.5, 275, 550 or 1,100 mg/kg EGBE for three consecutive days. All the animals in the 1,100 mg/kg group died. There was a statistically significant increase in the number of micronucleated polychromatic erythrocytes in the 137.5 mg/kg dose group only in a pairwise comparison with the controls. The analysis for trend was not significant and it was concluded that the test was negative (NTP, 2000) [KI score = 1].

H. Carcinogenicity

Oral Studies

No studies are available.

Inhalation Studies

Rats: Male and female F344/N rats were exposed by inhalation to 0, 31.2, 62.5 or 125 ppm (0, 151, 302 or 604 mg/m^3) EGBE vapour for 6 hours/day, 5 days/week for 104 weeks. Survival was similar across all groups. The incidence of benign or malignant

pheochromocytoma (combined) of the adrenal medulla in females exposed to 125 ppm EGBE was not significantly increased compared to the chamber controls, but it did exceed the historical control range. There was only one malignant pheochromocytoma, which occurred in the 125 ppm group. NTP concluded that there was no evidence for carcinogenicity in male rats and equivocal evidence for carcinogenicity in female rats (NTP, 2000) [KI score = 1].

Mice: Male and female B6C3F$_1$ mice were exposed by inhalation to 0, 62.5, 125 or 250 ppm (0, 302, 604 or 1,208 mg/m^3) EGBE vapour for 6 hours/day, 5 days/week for 104 weeks (NTP, 2000). Survival of the ≥ 125 ppm male mice was significantly less than that of the controls. Increased incidence of tumours was seen in the forestomach of females and liver hemangiosarcomas in males.

Forestomach: There was a positive trend in the incidences of forestomach squamous cell papilloma and squamous cell papilloma or carcinoma combined in female mice. The incidences were significantly increased in the 250 ppm group, in which the only squamous cell carcinoma occurred. These incidences exceeded the historical control range for female mice. There was no significant increase in the incidence of these neoplasms in male mice, but they did exceed the historical control range for male mice. There was one squamous cell carcinoma, but it was in the 125 ppm group.

Liver hemangiosarcomas: There was a positive trend in the incidence of hemangiosarcomas in male mice, which was statistically significant in the 250 ppm group. The incidence at 250 ppm also exceeded the historical control range for this tumour in male mice. There was also a positive trend in the incidence of hepatocellular carcinomas, which was statistically significant in the 250 ppm group. There was, however, no change in the incidence of hepatocellular adenomas and carcinomas combined, because of a reduced incidence of hepatocellular adenomas in the treated groups. The tumour incidence in female mice were not significantly different from the controls.

The NOAEC for tumourigenicity in mice is 125 ppm, based on an increased incidence of liver hemangiosarcomas in males and squamous cell papillomas or carcinomas in females at 250 ppm (NTP, 2000).

I. Mode of Action (MOA) for Mouse Tumours from EGBE Exposure

Liver Hemangiosarcomas

The hypothesised key steps of the MOA are metabolism of EGBE to BAA, hemolysis of RBCs with release of haemoglobin and hepatic hemosiderin accumulation, followed by oxidative stress, modulation of gene expression, cell proliferation, promotion, and neoplasm, leading to the formation of liver tumours (U.S. EPA, 2010). These tumours are unlikely to occur in humans because exposures would have to be much higher than those for rats. *In vitro* data suggest there is a 40- to 150-fold difference in the dose that produces hemolytic changes in the RBCs of humans as compared to rodents. This difference is supported by the Carpenter et al. (1956) study in which no changes in erythrocyte fragility were measured in humans at the highest tested concentration, 195 ppm, but increased erythrocyte fragility was measured in co-exposed rats. In addition, simulations from a PBPK model (Corley et al., 2005) predict that, given the vapour pressure of EGBE, the maximum blood level of BAA that can be obtained from inhalation exposure would be lower than the predicted concentrations from

bolus exposures that have not resulted in hemolytic effects, and lower than concentrations that have been shown to produce an effect on human RBCs *in vitro* (Udden, 2002).

Forestomach Tumours

The incidence of squamous cell papilloma and carcinoma of the forestomach was increased in female mice exposed to 250 ppm EGBE (NTP, 2000). There was also an increase in squamous cell papillomas in male mice, but the incidence was not statistically significant. Forestomach papillomas and carcinomas were not seen in either male or female rats in the 2-year NTP studies. In addition to the tumours, there was also a statistically significant, dose-dependent increase in hyperplasia in mice (both sexes), and for ulceration in female mice. The incidence of ulceration was significantly increased in the 125 ppm male mice.

The hypothesised steps are metabolism to BAA, followed by tissue irritation and subsequent cytotoxicity, compensatory proliferation and the induction of forestomach tumours. Forestomach tumours are unlikely to occur in humans because of the anatomical differences between the human stomach and the mouse forestomach; and because EGBE exposures would have to be higher, if at all possible, in humans than in mice because of the differences between mice and humans in the production and clearance of BAA.

J. Reproductive Toxicity

Male and female Swiss CD-1 mice were given in their drinking water 0 0.5, 1.0 or 2.0% EGBE (equivalent to daily intakes of 0, 720, 1,340 and 2,050 mg/kg/day) during a continuous breeding protocol with a 7-day pre-mating period and a 98-day cohabitation period. There were significant adverse reproductive effects in the females at very high dose levels (≥ 1,340 mg/kg) which also caused severe toxicity, including death. Marginal reductions (3%) in pup weight were noted at 720 mg/kg in the first generation, but not in the second generation. The NOAELs for reproductive and developmental toxicity are 720 mg/kg/day. A NOAEL or LOAEL was not determined for systemic parental toxicity because this protocol is not designed to assess systemic toxicity. However, it was noted that reduced water consumption occurred at all dose levels (Morrissey et al., 1988, 1989; Heindel et al., 1990) [KI score = 1].

Male and female F344/N rats were given in their drinking water 0, 750, 1,500, 3,000, 4,500 or 6,000 ppm EGBE for 13 weeks. Based on water consumption, the average daily intake was 0, 69, 129, 281, 367 or 452 mg/kg/day for males; and 0, 82, 151, 304, 363 or 470 mg/kg/day for females. Testis weights were unaffected by treatment, but the size of the uterus in the ≥ 4,500 ppm groups were reduced. Changes in uterine weight were considered by the authors to be secondary to the reduction in body weight gain rather than a direct effect of EGBE. Sperm concentration was slightly decreased in all treated males (not dose-related); all other sperm measurements were similar to controls. Oestrous cycle length was unaffected by treatment, although the ≥ 4500 ppm females spent more time in diestrous than the other groups. This correlated with the smaller uterine size, which was attributed to a secondary consequence of reduced body weight gain (NTP, 1993; ECHA) [KI score = 1].

K. Developmental Toxicity

Oral Studies

Pregnant female F344 rats were dosed by oral gavage with 0, 30, 100 or 200 mg/kg EGBE on GD 9-11; some animals sacrificed on GD 12 and others sacrificed on GD 20. Another group of pregnant female F344 rats were dosed by oral gavage with 0, 30, 100 or 300 mg/kg EGBE on

GD 11-13; some animals sacrificed on GD 14 and the others sacrificed on GD 20. At ≥ 100 mg/kg on GD 9-11 and GD 11-13, there was marked body weight reduction and/or weight gain, increased kidney and spleen weights, and severe hematotoxicity, in particular marked reduction in circulating red blood cells, haematocrit and hemoglobin, which occurred 24 hours post-treatment. By GD 20, the hematoxic effects were nearly reversed. These changes in organ weights and haematological parameters are indicative of hemolytic anemia and the compensatory haematological changes following cessation of exposure. Increased resorptions, non-live implants and adversely affected implants per litter in the 200 mg/kg treated dams (GD 9 – 11), and decreased foetal platelet count, but no embryolethality, in the 300 mg/kg treated dams (GD 11-13). There were no adverse effects seen on the cardiac system. Increased foetal lethality, but no increase in malformations, occurred in the 200 mg/kg dose (GD 9-11). Increased platelet count was also seen in the foetuses of the 300 mg/kg dose group (GD 11-13). The maternal NOAEL for this study is 30 mg/kg/day. The developmental NOAELs are 100 and 300 mg/kg/day when EGBE was given on GD 9–11 and GD 11-13, respectively (Sleet et al., 1991; ECHA) [Kl score = 1].

In a teratology probe study using the Chernoff-Kavlock assay, pregnant female CD-mice were dosed by oral gavage with 0, 350, 650, 1,000, 1,500 or 2,000 mg/kg EGBE during GD 8 to 14. Maternal toxicity was evident in the dams at dosed of ≥ 650 mg/kg. There were hemolytic effects (≥ 650 mg/kg) and mortality (≥ 1,500 mg/kg). At 1,000 and 1,500 mg/kg, increased resorption rates and numerically reduced number of viable foetuses were observed at 1,000 and 1,500 mg/kg. Cleft palates were seen in 4/43 foetuses (in one litter) at 1,000 mg/kg/day and 1/25 at 1,500 mg/kg. The NOAELs for maternal and developmental toxicity are 350 and 650 mg/kg/day, respectively (Wier et al., 1987; ECHA) [Kl score = 2].

In another Chernoff-Kavlock assay, CD-1 mice were dosed by oral gavage with 1,180 mg/kg/day EGBE (in corn oil) from GD 7 to 14, then allowed to litter and to rear pups to PND 3. Nineteen of the dams died (20%), maternal weight gain was reduced and there were only 24 viable litters (77%) from the surviving dams compared with 97% in the controls. There was no external malformations, pup survival to PND was unaffected and there was no other evidence of developmental toxicity (Schuler et al., 1984; ECHA) [Kl score = 2].

Inhalation Studies

Pregnant female F344 rats were dosed by oral gavage with 0, 25, 50, 100 or 200 mg/kg EGBE on GD 6-15. A dose-related increase in maternal toxicity was observed during the exposure period. There was hematuria (≥ 100 ppm); pale, cold extremities with necrosis of the tail tip (200 ppm); weight loss (≥ 100 ppm), reduction in food consumption (≥ 100 ppm) and water consumption (200 ppm). Absolute and relative organ weight reductions were also noted. Evidence of hemolytic anemia was found in the ≥ 100 ppm dams when blood samples were taken on GD 21. At 200 ppm, there was embryotoxicity (increased resorptions and decreased viable implants per litter) and fetotoxicity (retardations in skeletal ossification). There was no evidence of teratogenicity. The NOAECs for maternal and developmental toxicity are 50 and 100 ppm, respectively (Tyl et al., 1984; ECHA) [Kl score = 2].

Pregnant female New Zealand White rabbits were exposed by inhalation to 0, 25, 50, 100 or 200 ppm EGBE 6 hours/day during GD 6-18. At 200 ppm, four does died or were sacrificed by the third day after the onset of dosing, and four does aborted. All were pregnant. Pregnancy rates were similar across all groups. Body weight loss occurred in all groups including controls during exposure, but the highest difference was in the 200 ppm exposure group; by GD 15, body weights were significantly lower in the 200 ppm group. The high-dose group

had a significant reduction in maternal body weight (8%), gravid uterine weight (22%), and the number of total implants and viable implants. No other developmental effects (including teratogenicity) were noted. The NOAELs for maternal and developmental toxicity are 50 and 100 ppm, respectively (Tyl et al., 1984; ECHA) [Kl score = 2].

Pregnant female SD rats were exposed by inhalation to 0, 150 or 200 ppm EGBE 7 hours/day during GD 7-15. The only maternal effect noted was hematuria in the ≥ 150 ppm dams. There was no developmental toxicity. The NOAEC for developmental toxicity is 200 ppm. A conservative LOAEC for maternal toxicity is 150 ppm, with a NOAEC not established (Nelson et al., 1984) [Kl score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for EGBE follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

An oral RfD was derived by U.S. EPA (2010) based on the findings of the NTP chronic inhalation studies, the rationale being the limited oral database and because the critical endpoint, hemosiderin pigmentation, was more pronounced in the chronic inhalation study (NTP, 2000) versus the available subchronic oral study (NTP, 1993).

U.S. EPA used a route-to-route extrapolation from the NTP (2000) study for the derivation for the RfD. The dose metric used for animal-to-human and route-to-route (inhalation-to-oral) extrapolation for the derivation of the RfD is the area under the curve (AUC) of BAA at 12 months in arterial blood. This dose metric was used for dose-response modelling of chronic inhalation data to derive the point of departure (POD) of 133 µmol-hour/L, expressed as a BMDL based on animal data. The corresponding human BMDL was then back-calculated using the human PBPK model (Corley et al., 1994; Corley et al., 1997) to obtain an equivalent human oral drinking water dose ($BMDL_{HED}$) of 1.4 mg/kg/day. A simplifying assumption was used that the entire dose of drinking water EGBE was consumed over a 12-hour period each day.

Oral Reference Dose (oral RfD)

Oral RfD = $BMDL_{HED}$ / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

- UF_A (interspecies variability) = 1
- UF_H (intraspecies variability) = 10
- UF_L (LOAEL to NOAEL) = 1
- UF_{Sub} (subchronic to chronic) = 1
- UF_D (database uncertainty) = 1
- Oral RfD = 1.4/(1 x 10 x 1 x 1 x 1) = 1.4/10 = 0.14 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (0.14 x 70 x 0.1)/2 = 0.5 mg/L

B. Cancer

Male mice developed hepatocellular carcinomas and hemangiosarcomas that appear to be exposure-related. The incidence of hemangiosarcomas was statistically significant and increased over both concurrent and historical control groups. The hepatocellular carcinomas were within the range of historical controls for male mice but are considered because the dose-response trend is significant and because a similar MOA has been suggested for this tumour. The incidences in the high dose group of these two tumour types were only slightly higher than the upper end of the range for historical controls. These two tumour types were not seen in mice.

The incidence of squamous cell papilloma and carcinoma of the forestomach was increased in female mice exposed to 250 ppm EGBE (NTP, 2000). There was also an increase in squamous cell papillomas in male mice, but the incidence was not statistically significant. Forestomach papillomas and carcinomas were not seen in either male or female rats in the 2-year NTP studies. In addition to the tumours, there was also a statistically significant, dose-dependent increase in hyperplasia in mice (both sexes), and for ulceration in female mice. The incidence of ulceration was significantly increased in the 125 ppm male mice.

The MOAs for these tumours reflect the non-genotoxic nature of EGBE and its metabolites. Both of these MOAs suggests that the MOAs have only limited quantitative significance to humans, principally due to kinetic/dynamic differences from the rodents (U.S. EPA, 2010; ECHA). Because of the MOA, a non-linear approach is used for the dose-response assessment, using the RfD that was derived for the non-cancer assessment. Doses of EGBE below the RfD would not be expected to produce hemolytic effects (i.e., hemosiderin deposition) and therefore is not expected to produce any increase in cancer risk.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

EGBE does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

EGBE is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 6 lists the results of acute aquatic toxicity studies conducted on EGBE.

Table 6: Acute Aquatic Toxicity Studies on EGBE

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-hour LC_{50}	1,464	2	ECHA
Pimephales promelas	96-hour LC_{50}	2,137	2	ECHA
Pimephales promelas	96-hour LC_{50}	1,700	2	ECHA
Pimephales promelas	96-hour LC_{50}	1,580	2	ECHA
Lepomis machrochirus	96-hour LC_{50}	1,490	2	ECHA
Daphnia magna	48-hour EC_{50}	1,800	2	ECHA
Daphnia magna	48-hour EC_{50}	1,815	2	ECHA
Daphnia magna	48-hour EC_{50}	881 (cited) 1,100 (recalculated)	2	ECHA
Daphnia magna	48-hour EC_{50}	2,650	2	ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50} NOEC	911 (biomass) 88	1	ECHA
Selenastrum capricornutum	72-hour EC_{50} NOEC	720 (biomass) 280	2	ECHA

Chronic Studies

A 21-day fish (*Brachydanio rerio*) study was conducted to examine the potential for endocrine disrupting effects; the study design was based on the OECD TG 204. The NOEC was > 100 mg/L (ECHA) [KI score = 2].

The NOEC from a 21-day *Daphnia* reproduction study was 100 mg/L (ECHA) [KI score = 1].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for EGBE follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (1,000 mg/L), *Daphnia* (1,100 mg/L) and algae (911 mg/L). Results from chronic studies are also available for all three trophic levels, with the lowest NOEC being 88 mg/L for algae. On the basis that the data consists of short-term and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC of 88 mg/L for algae. The $PNEC_{water}$ is 8.8 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 6.5 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.94/1280) \times 1000 \times 8.8$
$= 6.46$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3)
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]
$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 0.30/1000 \times 2400]$
$= 0.94\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 7.624 \times 0.04$
$= 0.30$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for EGBE calculated from EPI Suite™ is 7.624 L/kg.
f_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

There are no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.9 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.15/1500) \times 1000 \times 8.8$
$= 0.88$ mg/kg

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
= 7.624 x 0.02
= 0.15 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for EGBE calculated from EPI Suite™ is 7.624 L/kg.
f_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Based on information for read-across substance EGBE, EGMHE is readily biodegradable; thus it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of 0.81 for read-across substance EGBE, EGMHE does not meet the screening criteria for bioaccumulation.

The chronic toxicity data on read-across substance EGBE show NOECs of > 0.1 mg/L. Thus, EGMHE does not meet the screening criteria for toxicity.

The overall conclusion is that EGMHE is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity Category 4 [Oral]

Acute Toxicity Category 4 [Dermal]

Acute Toxicity Category 4 [Inhalation]

Skin Irritant Category 2

Eye Irritant Category 1

B. Labelling

Danger

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

Due to structural analogy and clinical data, this material may have a mechanism of intoxication similar to ethylene glycol.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam (alcohol-resistant is preferred), dry chemical or carbon dioxide.

Specific Exposure Hazards

Container may rupture from gas generation in a fire. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light. Store in the following materials: carbon steel, stainless steel, phenolic lined steel drums. Do not store in: aluminium, copper, galvanised iron, galvanised steel.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace exposure standards have not been established for EGMHE in Australia. The workplace exposure standard for EGBE in Australia is 20 ppm (96.9 mg/m^3) as an 8-hour TWA and a 15-min STEL of 50 ppm (242 mg/m^3) with a skin [absorption] notation.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to this material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

EGMHE is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Carpenter, C.P., Pozzani, U.C., Weil, C.S., Nair, J.H., III, Jeck, G.A., and Smyth, H.F., Jr. (1956). The toxicity of butyl cellusolve solvent. AMA Arch. Ind. Health 14: 114-131.

Corley, R.A., Bormett, G.A., and Ghanayem, B.I. (1994). Physiologically-based pharmacokinetics of 2-butoxyethanol and its major metabolite 2-butoxyacetic acid, in rats and humans. Toxicol. Appl. Pharmacol. 129: 61-79.

Corley, R.A., Markham, D.A., Banks, C., Delorme, P., Masterman, A., and Houle, J.M. (1997). Physiologically based pharmacokinetics and the dermal absorption of 2-butoxyethanol vapor by humans. Fundam. Appl. Toxicol. 39: 120-130.

Corley, R.A., Bartels, M.J., Carney, E.W., Weitz, K.K., Soelberg, J.J., Gies, R.A., and Thrall, K.D. (2005). Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. Toxicol. Sci. 85: 476-490.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Dodd, D.E., Snellings, W.M., Maranpot, R.R., and Ballantyne, B. (1983). Ethylene glycol monobutyl ether. Acute, 9 day and 90 day vapor inhalation studies in Fischer 344 rats. Toxicol. Appl. Pharmacol. 68: 405-414.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances.

EU. (2006). European Union Risk Assessment Report on 2-Butoxyethanol (CAS No. [redacted]). European Chemicals Bureau. Available at: https://echa.europa.eu/documents/10162/e74a38e1-b9e1-4568-92c5-615c4b56f92d.

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Heindel J.J., Gulati D.K., Russel V.S., Reel J.R., Lawton A.D. and Lamb J.C. (1990). Assessment of Ethylene Glycol Monobutyl and monophenol Ether reproductive toxicity using a continuous breeding protocol in Swiss CD-1 mice. Fundam. Appl. Toxicol. 15: 683-696.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Morrissey R.E., Lamb J.C., Schwetz B.A., Teague J.L. and Morris R.W. (1988). Association of sperm, vaginal cytology and reproductive organ weight data with results of continuous breeding reproduction studies in Swiss CD1 Mice. Fundam. Appl. Toxicol. 11: 359-371.

Morrissey R.E., Lamb J.C., Morris R.W., Chapin R.E., Gulati D.K. and Heindel J.J. (1989). Results and evaluations of 48 continuous breeding reproduction studies conducted in mice. Fundam. Appl. Toxicol. 13: 747-777.

National Toxicology Program [NTP]. (1993). Toxicity studies on ethylene glycol ethers administered in drinking water. NIH Publication 93- 3349. NTP Toxicity Report Series No. 26. NTP, Research Triangle Park, NC, USA.

National Toxicology Program [NTP]. (2000). Toxicology and Carcinogenesis Studies of 2-Butoxyethanol (CAS No. [redacted] in F344/N rats and B6C3F1 mice (Inhalation studies). NTP Technical Report Series No.484. NIH Publication No. 00-3974.

Nelson, B.K., Setzer, J.V., Brightwell, W.S., Mathinos, PR., Kuczuk, M.H., Weaver, T.E., and Goad, P.T. (1984). Comparative inhalation teratogenicity of four glycol ether solvents and an amino acid derivative in rats. Environ. Health Perspect. 57: 261-271.

Schuler R.L., Hardin B.D., Niemeier R.W., Booth G., Hazelden K., Piccirillo V. and Smith K. (1984). Results of testing 15 glycol ethers in a short term *in vivo* reprotoxicity assay. Environ. Health Perspect. 57: 141-146.

Sleet R.B., Price C.J., Marr M.C., Morrissey R.M. and Schwetz B.A. (1991). Cardiovascular development (CVD) in F-344 rats following phase-specific exposure to butoxy ethanol. Teratol. 43: 466.

Tyl, R.W., Millicovsky, G., Dodd, D.E., Pritts, I., France, K.A., and Fisher, L.C. (1984). Teratogenic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and new Zealand white rabbits following inhalation exposure. Environ. Health Perspect. 57: 47-68.

Udden, M.M. (2002). Rat erythrocyte morphological changes after gavage dosing with 2-butoxyethanol: a comparison with the in vitro effects of butoxyacetic acid on rat and human erythrocytes. J. Appl. Toxicol. 20: 381-387.

U.S. Environmental Protection Agency [EPA]. (2010). Toxicological Review of Ethylene Glycol Monobutyl Ether (EGBE) (CAS No. [redacted] in Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-08/006F. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0500tr.pdf

U.S. Environmental Protection Agency [EPA]. (2017). EPISuite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

Wier P.J., Lewis S.C., and Traul K.A. (1987). A comparison of developmental toxicity evident at term to postnatal growth and survival using ethylene glycol monoethyl ether, ethylene glycol monobutyl ether and ethanol. Teratog. Carcinog. Mutagen. 7: 55-64.

POTASSIUM CHLORIDE

This dossier on potassium chloride presents the most critical studies pertinent to the risk assessment of potassium chloride in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained primarily from the OECD-SIDS documents on potassium chloride (OECD, 2001a,b) and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Potassium chloride

CAS RN: [redacted]

Molecular formula: KCl

Molecular weight: 74.55 g/mol

Synonyms: Potassium chloride

SMILES: [Cl-] [K+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Potassium Chloride

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid; white crystals	2	ECHA
Melting Point	770°C @ 101.3 kPa	1	ECHA
Boiling Point	1,407°C (pressure not provided)	2	OECD, 2001a,b
Density	1984 kg/m^3	2	ECHA
Vapour Pressure	5.73 hPa @ 906°C	2	OECD, 2001a,b
Partition Coefficient (log Kow)	-	-	-
Water Solubility	255 g/L @ 25°C	2	Lide, 2009; ECHA

III. ENVIRONMENTAL FATE PROPERTIES

Potassium chloride (KCl) dissociates completely in aqueous solutions to potassium (K^+) and chloride (Cl^-) ions. Potassium chloride and its dissociated ions are ubiquitous in the environment.

The transport and/or leaching of potassium (K^+) and chloride (Cl^-) ions is affected by clay minerals (type and content), pH and organic matter. Potassium ions are less mobile and less prone to leaching than anions in soil, such as chloride and nitrate (NO_3^-). Chloride binds only weakly to soil particles, and therefore follows water movement (OECD, 2001b).

Potassium (K^+) and chloride (Cl^-) ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated (OECD, 2001b; Ganong, 1995). Neither potassium chloride nor its dissociated ions are expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Potassium chloride has low acute toxicity by the oral route. It is not a skin or eye irritant. Long-term studies in rats fed potassium chloride showed no systemic toxicity or carcinogenic effects. Potassium chloride has shown some genotoxic effects in *in vitro* assays; these occurred at high concentrations of potassium chloride and is thought to be due to a disruption of the osmotic balance of the cells. No *in vivo* genotoxicity studies have been conducted on potassium chloride. There were no developmental effects in pregnant female rats and mice given potassium chloride in their diet.

B. Toxicokinetics and Metabolism

Potassium chloride dissociates completely in aqueous solutions to potassium (K^+) and chloride (Cl^-) ions. Potassium is an essential nutrient: it has a number of critical roles, one of which is that it is the principal cation involved in maintaining the osmotic balance of bodily fluids (Ganong, 1995). Both potassium and chloride ions are involved in regulating the acid-base balance of the body (Ganong, 1995).

C. Acute Toxicity

The oral LD_{50} in rats was reported to be 3,020 mg/kg (Boyd and Shanas, 1961) [Kl score = 2].

No acute toxicity studies by the dermal or inhalation route were identified.

D. Irritation

Potassium chloride did not produce an irritant response in an *in vitro* skin irritation (OECD TG 439) test (ECHA) [Kl score = 1].

Potassium chloride did not produce an irritant response in an *in vitro* eye irritation test (ECHA) [Kl score = 2].

E. Sensitisation

No studies were identified.

F. Repeated Dose Toxicity

<u>Oral</u>

Male F344/Slc rats were given 0, 0.25, 1, 5 or 5% potassium chloride in their feed for two years. The mean daily intake was calculated to be 0, 110, 450 or 1,820 mg/kg/day, respectively. At the end of the study, survival rates were 48%, 64%, 58% and 84% in the respective dose groups. Nephritis was predominant in all groups, including the controls. The only treatment-related effect was gastritis (inflammation of the stomach lining). The incidence of gastritis and ulcers were 6%, 18%, 18% and 30% in the 0, 110, 450 and 1,820 mg/kg/day groups, respectively. The gastritis was thought to be indicative of a localised effect due to the irritating nature of the test material. The NOAEL for

systemic effects is 1,820 mg/kg/day, the highest dose tested (Imai et al., 1968; OECD 2001a,b) [Kl score = 2].

Male and female Wistar rats were fed diets containing 0 or 3% potassium chloride over a total period of 30 months. Due to the reduction of feed intake, the mean test substance intake and mean body weight decreased in time. The mean daily intake of potassium chloride was not calculated. There was hypertrophy of the zona glomerulosa in the adrenals (24/50 treated rats versus 4/50 in controls); and cystitis in the urinary bladder (males: 3/59; females 3/50) and single epithelial hyperplasia of the bladder (males 3/50; females 2/50) (Lina and Kuijpers, 2004) [Kl score = 2].

Inhalation

No studies were identified.

Dermal

No studies were identified.

G. Genotoxicity

In Vitro Studies

Potassium chloride was not mutagenic to *Salmonella typhimurium* strains TA100, TA 1535, TA 1537 and TA 98 strains in an *in vitro* bacterial mutation assay in the absence or presence of metabolic activation (Mortelmans et al., 1986).

Potassium chloride was weakly mutagenic in two separate L5178Y mouse lymphoma assays (Myhr and Caspary,1988; Mitchell et al., 1988). It was mutagenic at 4,000 and 5,000 μg/mL in the presence of metabolic activation in one study, and mutagenic at 7,000 μg/mL in the absence of metabolic activation. The authors stated that these responses are due to high salt concentrations which affect the ionic balance and osmotic pressure of the medium, inducing mutations in cells surviving the treatment.

Potassium chloride induced a significant increase in chromosomal aberrations in Chinese Hamster lung fibroblasts (V79) cells only at the highest test dose (12,000 μg/mL) in the absence of a metabolic activation system. Measurements of the osmotic pressure of the medium showed a two-fold increase at this test compound concentration when compared to the normal medium (530 mOsmol/kg versus 253 mOsmol/kg) (OECD, 2001b).

There are two other reports on the effect of potassium chloride on the formation of chromosome aberrations in Chinese hamster ovary cells (CHO). In these studies potassium chloride concentrations of 75 and 80 mM (approximately 5,500 and 6,000 μg/mL) resulted in 19% and 28% aberrant cells, respectively. An increased number of chromosome aberrations was observed with potassium chloride concentrations that reduced cell survival of 40% or more. The increases in mutagenicity and chromosome aberrations observed in these studies have been considered to be related to cytotoxicity resulting from the high potassium chloride concentrations used (Brusick, 1988).

The reported mutagenic effect of potassium chloride most probably results from a disruption of the osmotic balance of cells with a subsequent interference with chromosomal stability. This may result in the clastogenic effects (DNA breakage and chromosome structural instability) due to K^+ effects on sequestering of Mg^{++} ions required for normal maintenance of chromatin integrity (OECD, 2001b).

In Vivo Studies

No studies have been identified.

H. Carcinogenicity

Oral

F344/Slc male rats were given 0, 110, 450 or 1,820 mg/kg/day potassium chloride in feed for two years. At the end of the study, survival rates were 48%, 64%, 58% and 84% in the 0, 110, 45 and 1,820 mg/kg/day groups. There was no increased incidence of tumours that were considered to be treatment-related (Imai et al., 1968) [Kl score = 2].

Male and female Wistar rats were fed diets containing 0 or 3% potassium chloride over a total period of 30 months. There were no treatment-related differences in tumour response among the groups (Lina and Kuijpers, 2004) [Kl score = 2].

Inhalation

No studies were identified.

Dermal

No studies were identified.

I. Reproductive Toxicity

No studies were identified.

J. Developmental Toxicity

Pregnant Wistar rats were given doses of 3.1 to 310 mg/kg potassium chloride by oral gavage during gestation days 5 through 15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 310 mg/kg/day, the highest dose tested (FDRL, 1975) [Kl score = 2].

Pregnant CD-1 mice were given doses of 2.35 to 235 mg/kg potassium chloride by oral gavage during gestation Days 5 through 15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 235 mg/kg/day, the highest dose tested (FDRL, 1975) [Kl score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for potassium chloride follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

Two chronic rat feeding studies have been conducted on potassium chloride: only the study by Imai et al. (19686 was conducted with multiple doses and provided mean daily intake values. In this study, the only treatment-related effects were associated with chronic irritation in the gastrointestinal tract (gastritis and ulcers), a localised effect due to the irritating properties of the test material. No systemic toxicity was observed at any of the doses tested. The NOAEL for systemic toxicity in this study is 1,820 mg/kg/day, the highest dose tested. The NOAEL of 1,820 mg/kg/day will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subacute to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 4(10 x 10 x 1 x 1 x 1) = 1,820/100 = 18 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD:

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (18 x 70 x 0.1)/2 = 63 mg/L

Australian Drinking Water Guidelines

The Australian drinking water guideline value for chloride is 250 mg/L based on aesthetics (ADWG, 2011).

B. Cancer

Potassium chloride was not carcinogenic to rats in two chronic feeding studies. Therefore, no cancer reference value was derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Potassium chloride does not exhibit the following physico-chemical properties:

- Flammability
- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Potassium chloride is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

The results of the acute toxicity studies conducted on potassium chloride are presented in Table 2.

Table 2: Acute Aquatic Toxicity Studies on Potassium Chloride

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	880	2	Mount et al., 1997; ECHA
Daphnia magna	48-hour EC_{50}	660	2	Mount et al., 1997; ECHA
Ceriodaphnia dubia	48-hour EC_{50}	630	2	Mount et al., 1997; ECHA
Scenedesmus subspicatus	72-hour EC_{50}	> 100* (growth rate)	1	ECHA

*NOEC = > 100 mg/L

Chronic Studies

In a fish early-life-stage test with the fathead minnow (*Pimephales promelas*), the 7-day NOEC was 500 mg/L (ECHA).

C. Terrestrial Toxicity

No studies were identified.

D. Calculation of PNEC

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (820 mg/L), *Daphnia* (660 mg/L) and algae (> 100 mg/L). Although a chronic study was conducted on fish that fulfils the requirements in the OECD TG 210, it is not considered adequate for deriving a PNEC because of the short duration of the test. On the basis of the short-term results from three trophic levels, an assessment factor of 100 has been applied to the lowest reported effect concentration of 100 mg/L for algae. The $PNEC_{water}$ is 1.0 mg/L.

PNEC sediment

No reliable experimental toxicity data on sediment organisms are available. Potassium chloride dissociates completely in water with its environmental distribution is dominated by its high water solubility. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as potassium chloride. Therefore, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. Based on its properties, no adsorption of potassium chloride to sediment is to be expected, and the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No reliable experimental toxicity data on terrestrial organisms are available. The environmental distribution of potassium chloride is dominated by its water solubility. Sorption of potassium chloride should probably be regarded as a reversible situation, *i.e.*, the substance is not tightly nor permanently bound. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as potassium chloride. Therefore, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, potassium chloride is not expected to significantly adsorb to soil, and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Potassium chloride is an inorganic salt that dissociates completely to potassium and chloride ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both potassium and chloride ions are also ubiquitous and are present in most water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Potassium and chloride ions are essential to all living organisms, and their intracellular, and extracellular concentrations are actively regulated. Therefore, potassium chloride is not expected to bioaccumulate.

There are no adequate chronic aquatic toxicity studies available on potassium chloride. The acute $E(L)C_{50}$ values for potassium chloride are > 1 mg/L in fish, invertebrates and algae. Therefore, potassium chloride does not meet the screening criteria for toxicity.

The overall conclusion is that potassium chloride is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictograms

None.

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

Immediately flush eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. If symptoms persist, seek medical attention.

Skin Contact

Wash with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Do not induce vomiting. Rinse mouth with water and then drink a small amount of water. Get medical attention. Never give anything by mouth to an unconscious person.

B. Firefighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: potassium oxides, hydrogen chloride, chlorine gas.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Avoid creating and breathing dust.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilt

Scoop up and remove.

D. Storage and Handling

General Handling

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls/Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for potassium chloride.

Engineering Controls

Use in a well-ventilated area.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Potassium chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Boyd, E.M., and Shanas, M.N. (1961). The acute oral toxicity of potassium chloride. Arch. Int. Pharmacodyn. Ther. 133: 275-283.

Brusick, D. (1988). Genotoxic effects in cultured mammalian cells produced by low pH treatment conditions and increased ion concentrations. Environ. Mutag. 8: 879-886.

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment (HHRA). (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency (ECHA). (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

FDRL. (1975). Teratological evaluation of FDA 73-78 (KCl) in mice and rats. Final report prepared under DHEW. Contract No. FDA 223-74-2176 by Food and Drug Research Laboratories Inc. Waverly, New York.

Ganong, W.F. (1995). Review of Medical Physiology, 17th Edition, Appleton & Lange, Norwalk, Connecticut, USA.

Imai, S., Morimoto, J., Sekiya, N., Shima, M., Kiyozuka, Y., Nakamori, K., Tsubura, Y. (1986). Chronic toxicity test of KCl and NaCl in F344/Scl rats. J. Nara Med. Ass. 37:115-127 [in Japanese]; cited in OECD 2001a,b.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Lide, D.R. (2009). Physical Constants of Inorganic Compounds. CRC Handbook of Chemistry & Physics, 89th Edition, CRC Press.

Lina, B.A.R., and Kuijpers, M.H.M. (2004). Toxicity and carcinogenicity of acidogenic or alkalogenic diets in rats; effects of feeding NH_4Cl, $KHCO_3$ or KCl. Food Chem. Toxicol. 42: 135-153.

Mitchell, A.D., Rudd, C.J., Caspary, W.J. (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Intralaboratory results for sixty-three coded chemicals tested at SRI international. Env. Molecular Mutagenesis 12(13):37-101.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., Zeiger, E. (1986). Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Env. Mutagenesis 8(7):1-119.

Mount, D.R., Gulley, D.D., Hockett, J.R., Garrison, T.D., and Evans, J.M. (1997). Statistical models to predict the toxicity of major ions to *Ceriodaphnia dubia, Daphnia magna* and *Pimephales promelas* (fathead minnows). Environ. Toxicol. Chem. 16: 2009-2019.

Myhr, B.C., Caspary, W.J. (1988). Evaluation of the L5178Y mouse lymphoma cell mutagenesis assay: Intralaboratory results for sixty-three coded chemicals tested at Litton Bionetics, Inc. Env. Molecular Mutagenesis. 12(13):103-194.

OECD. (2001a). IUCLID Data Set for Potassium chloride (CAS No. [redacted] UNEP Publications. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=68BF142A-D550-432C-8C48-13883944BA1D.

OECD. (2001b). Screening Information Assessment Report (SIAR) for Potassium chloride (CAS No. [redacted] UNEP Publications. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=68BF142A-D550-432C-8C48-13883944BA1D.

SILOXANES AND SILICONES, DIMETHYL, REACTION PRODUCTS WITH SILICA (CAS RN [redacted]
DIMETHYL SILOXANES AND SILICONES (CAS RN [redacted]

This group contains information on dimethyl siloxanes and silicones(CAS RN [redacted] and siloxanes and silicones, dimethyl, reaction products with silica (CAS RN [redacted] They are expected to have similar environmental concerns and have consequently been assessed as a group. Information provided in this dossier is based on dimethyl siloxanes and silicones (CAS RN [redacted]

This dossier presents the most critical studies pertinent to the risk assessment of the siloxanes and their use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): dimethyl-bis(trimethylsilyloxy)silane

CAS RN: [redacted]

Molecular formula: $C_8H_{24}O_2Si_3$

Molecular weight: 236.53 g/mol

Synonyms: polydimethylsiloxanes (PDMS); octamethyltrisiloxane;, trislocane; octamethyl-;dimeticone,

SMILES: C[Si](C)(C)O[Si](C)(C)O[Si](C)(C)C

Chemical Name (IUPAC): Siloxanes dimethyl reaction products with silica

CAS RN: [redacted]

Molecular formula: UVCB substance

Molecular weight: No information is available

Synonyms: hydrophobic silica; PDMS, silicon dioxide reaction product; siliconized silica

SMILES: Not applicable

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of PDMS (CAS RN [redacted])

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	liquid	-	Pubchem
Melting Point	-80.0°C (pressure not provided)	-	Pubchem
Boiling Point	153.0°C (pressure not provided)	-	Pubchem
Density	940 kg/m^3 @ 25°C	-	Pubchem
Vapour Pressure	445.30 Pa (temperature not provided)	-	Pubchem
Partition Coefficient (log K_{ow})	8.21 @ 22°C	-	ECETOC, 20111
Water Solubility	Insoluble	-	EFSA, 2020

No data was available for hydrophobic silica (CAS RN [redacted]) As a result, the information provided in this dossier is based on PDMS. PDMS (CAS RN [redacted]) and hydrophobic silica (CAS RN [redacted]) are linear siloxanes. Siloxanes are the general name for oligomeric or polymeric substances which are characterised by Si-O-Si bonds, methyl groups are usually bound to Si-atoms, but some siloxanes contain vinyl, hydroxyl or other groups in addition (ECETOC, 2011).

NICNAS has assessed PDMS in an IMAP Tier 1 assessment and considers it a polymer of low concern, and concluded that it poses no unreasonable risk to human health and the environment[1] .

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Siloxanes are linear non-volatile substances which are insoluble in water, preferentially strongly adsorb to soil and sediment, and not readily biodegradable. However, they have a low potential for bioaccumulation.

B. Biodegradation

Siloxanes will likely break down slowly via biotic and abiotic processes. Under field conditions, the half-life in soil was 2.4 to 3.9 years. In freshwater sediments, 5 to 10% PDMS was hydrolysed after 1 year (ECETOC, 2011).

If a chemical is found to be not readily or inherently biodegradable, it is categorised as Persistent since its half-life is greater than 60 days (DoEE, 2017).

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

C. Environmental Distribution

No experimental data are available for siloxanes. However, the soil organic partition coefficient (log K_{oc}) value of 5.162 L/kg (MCI method) was estimated using USEPA EPI Suite™ KOCWIN v2.00 module. Based on this estimated value, the substance is expected to sorb substantially to soils or sediments.

D. Bioaccumulation

There is no evidence of PDMS bioaccumulating in aquatic or terrestrial organisms. Bioconcentration studies suggest that due to their molecular size the potential for PDMS fluids to pass biological membranes, neither the gills nor the gastro-intestinal tract, is very unlikely (ECETOC, 2011).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Siloxanes exhibits low acute toxicity by the oral, inhalation and dermal routes. They are non-irritating to the skin and mildly irritating to the eyes. Siloxanes are not a skin sensitiser. In repeated dose toxicity studies, dose-related changes were observed in rats given ammonium sulfate in feed for 52-weeks. Ammonium sulfate is not genotoxic and is not carcinogenic. No reproductive or developmental effects were observed in read-across studies.

Information provided within this section was obtained from *ECETOC JACC Report No. 55: Linear Polydimethylsiloxanes* as read-across for siloxanes (ECETOC, 2011). [Kl. Score = 2].

B. Acute Toxicity

Oral

The acute oral LD_{50} of PDMS was determined to be > 4,800 mg/kg bw/day in Wistar rats.

Dermal

The acute dermal LD_{50} of PDMS was reported to be > 2,000 mg/kg bw/day. It was also determined that siloxanes do not penetrate the skin.

Inhalation

In an OECD Guideline 403 (inhalation) study, Wistar rats were exposed to PDMS via the nose for four hours. The LC_{50} was determined to be 695 mg/m^3.

C. Irritation

Skin

PDMS mainly causes reversible irritation under extreme conditions like occlusion. Siloxanes are generally considered non-irritating to human skin under normal conditions of use.

Eye

PDMS was found to be mildly irritating to the eye due to conjunctival reactions observed in animal studies.

D. Sensitisation

PDMS is not expected to be sensitising to human skin based on the results from a clinical HRIPT.

E. Repeated Dose Toxicity

Oral

In a combined chronic toxicity and oncogenicity study, PDMS was administered to 30 Fischer 344 rats via their diet at dose levels of 0, 100, 300 or 1,000 mg/kg bw/day for 24 months. Ten animals were necropsied following 12 months of treatment. 20 animals were treated for 12 months followed by a 12-month recovery period. Possible substance-related findings were limited to increased incidences of eye opacity in the chronic recovery group. The NOEL for systemic toxicity was determined to be 1,000 mg/kg bw/day, the highest tested dose.

Inhalation

No data were available .

Dermal

In a 4-week study, siloxanes were dermally administered to New Zealand White rabbits. After 6 hours of exposure, the animals were observed daily for 29-30 days. Dermal application of siloxanes was considered non-toxic and the NOAEL for this study was reported to be 1,000 mg/kg bw/day.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on PDMS based are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Siloxanes

Test System[1]	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) S. typhimurium	-	-	2	ECETOC, 2011
OECD Guideline 471 (Bacterial Reverse Mutation Assay) Salmonella typhimurium (TA98, TA100, TA135, TA1537, and TA1538)	-	-	2	ECETOC, 2011

*+, positive; -, negative.

In Vivo Studies

No data were available.

G. Carcinogenicity

Oral

In a combined chronic toxicity and oncogenicity study, PDMS was administered to 60 Fischer 344 rats via their diet at dose levels of 0, 100, 300 or 1,000 mg/kg bw/day for 24 months. No substance-related neoplastic or pre-neoplastic changes were observed. The NOEL for oncogenicity was 1,000 mg/kg bw/day, the highest tested dose. There was no indication of carcinogenicity of PDMS.

Inhalation

No data were available.

Dermal

No data were available.

H. Reproductive Toxicity

Oral

Male Sprague-Dawley rats were exposed to PDMS via their drinking water for four weeks. No clinical signs of toxicity were noted. The NOAEL for this study was reported to be > 1,000 mg/kg bw/day.

Dermal

Albino rabbits were exposed to PDMS via dermal application for four weeks. There were no reproductive effects observed following dermal application of siloxanes. The NOAEL was reported to be > 3,000 mg/kg bw/day.

Charles River CD rats were implanted with a cross-linked silicone gel for up to 61 days. There was no treatment-related mortality reported. No differences in behaviour and general condition, body weight gain or reproductive behaviour and success were recorded in the parental generation. The NOAEL was reported to be 28,500 mg/kg bw/day in dams and offspring.

I. Developmental Toxicity

The teratogenicity of PDMS was evaluated using in pregnant New Zealand White rabbits. Dose levels ere 3, 10, or 30 ml/kg bw/day. Rabbits were implanted 6 weeks prior to insemination. On Day 29 of gestation all surviving animals were necropsied. There were no significant differences between treated and untreated mice. There were also no adverse effects observed in this study. The maternal and developmental NOAEL was 30 ml/kg bw/day (28,500 mg/kg bw/day).

In another study, three groups of 23 pregnant New Zealand White rabbits were administered siloxanes via oral gavage. There were no reproductive changes observed. The NOAEL was determined to be 1,000 mg/kg bw/day.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for siloxanes follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

The NOAEL from a rat 2-year oral feeding study on PDMS was reported to be 1,000 mg/kg bw/day. This NOAEL will be used for determining the oral reference dose (RfD) and the drinking water guidance value for siloxanes.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 1000/(10 x 10 x 1 x 1 x 1 x 1) = 1000/100 = 10 mg/kg/day

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (10 x 70 x 0.1)/2 = 70/2 = 35 mg/L

B. Cancer

Siloxanes are not considered carcinogens. Thus, a cancer reference value will not be calculated for this substance.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Siloxanes does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Siloxanes are of low toxicity concern to aquatic, sediment-dwelling and terrestrial organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity data for PDMS.

Table 3: Acute Aquatic Toxicity Studies on PDMS

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Chanel Catfish (*Ictalurus punctatus*)	72-hour LC_{50}	5.5	2	ECOTOX
Daphnia magna	48-hour LC_{50}	44.5	2	ECOTOX

Chronic Studies

A 7-day fish (*Ictalurus punctatus*) freshwater study was identified in ECOTOX. The reported LC_{50} was 3.16 mg/L [Kl. Score = 2].

C. Sediment Toxicity

Table 4 lists the results of chronic toxicity data for PDMS in sediment-dwelling organisms.

Table 4: Chronic Sediment Toxicity Studies on PDMS

Test Species	Endpoint	Results (mg/kg dw)	Klimisch score	Reference
Chironomus tentans (midge larva)	20-day NOEC	>2,590	2	ECETOC, 2011
Chironomus tentans	14-day NOEC	>560[a]	2	ECETOC, 2011
Hyallela azteca (freshwater amphipod)	28-day NOEC	<2,200	2	ECETOC, 2011
Hyallela azteca	42-day NOEC	>994	2	ECETOC, 2011
Nereis diversicolor (marine polychaeta, ragworm)	28-day NOEC	>1,000	2	ECETOC, 2011

a – maximum concentration tested in the study. No effects observed at any tested concentration.

D. Terrestrial Toxicity

Table 5 lists the results of chronic toxicity data for PDMS in soil-dwelling organisms.

Table 5: Chronic Terrestrial Toxicity Studies on PDMS

Test Species	Endpoint	Results (mg/kg dw)	Klimisch score	Reference
Eisenia foetida (earthworms)	21-day NOEC	>1,100	2	ECETOC, 2011
Folsomia candida (springtail)	28-day NOEC[a]	230	2	ECETOC, 2011
Soil microflora	28-day NOEC	>1,000	2	ECETOC, 2011

a – soil microflora activity evaluated on day 0, 14 and 28 and on day 58 for mineralization only

E. Calculation of PNEC

The PNEC calculations for siloxanes follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for two trophic levels. Acute E(L)C_{50} values are available for fish (5.5 mg/L) and *Daphnia* (45.5 mg/L). Results from chronic studies are also available for fish (3.16 mg/L). On the basis that the data consists of short-term and long-term results from two trophic levels, an assessment factor of 50 has been applied to the lowest reported LC_{50} value of 3.16 mg/L for fish. Therefore, the $PNEC_{water}$ is 0.0632 mg/L.

PNEC sediment

Siloxanes are expected to partition more readily to the sediment phase rather than the aquatic phase. No adverse effects were observed in any of the chronic studies on sediment-dwelling organisms. Results are available for three trophic levels and the lowest NOEC is 560 mg/kg dw. An assessment factor of 50 has been applied to this value. Therefore, the $PNEC_{sediment}$ is 11.2 mg/kg .

PNEC soil

Results are available for three tropic levels (soil mico-organisms, earthworms and arthropods) and the lowest NOEC is 230 mg/kg dw for *Folsomia*. An assessment factor of 10 has been applied to the lowest NOEC value. Therefore, the $PNEC_{soil}$ is 23 mg/kg.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Siloxanes are not readily biodegradable. Thus, they meet the screening criteria for persistence.

There is no evidence of PDMS bioaccumulating in aquatic or terrestrial organisms. Bioconcentration studies suggest that due to their molecular size the potential for PDMS

fluids to pass biological membranes, neither the gills nor the gastro-intestinal tract, is very unlikely (ECETOC, 2011). Thus, siloxanes do not meet the screening criteria for bioaccumulation.

The chronic toxicity data on PDMS show NOECs of > 0.1 mg/L. Acute LC50 values are > 1.0 mg/L. Thus, siloxanes do not meet the screening criteria for toxicity.

The overall conclusion is that siloxanes are not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H226: Flammable liquid and vapour

H319: Causes serious eye irritation

H410: Very toxic to aquatic life with long-lasting effects

B. Signal word

Warning

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Please refer to the product SDS for additional information and for confirmation of the information provided herein.

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of the body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for siloxanes.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure self-contained breathing apparatus. The following should be an effective type of air-purifying respirator: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN number: none

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DoEE. (2017). Chemical Risk Assessment Guidance Manual: for chemicals associated with coal seam gas extraction, Guidance manual prepared by Hydrobiology and ToxConsult Pty Ltd for the Department of the Environment and Energy, Commonwealth of Australia, Canberra.

European Centre for Ecotoxicology and Toxicology of Chemicals [ECETOC]. (2011). ECETOC JACC Report No. 55: Linear Polydimethylsiloxanes CAS No. [redacted] (Second Edition). December 2011.

ECHA. ECHA REACH database: https://echa.europa.eu/information-on-chemicals/registered-substances

ECOTOX. USEPA ECOTOXicology Knowledgebase (ECOTOX). https://cfpub.epa.gov/ecotox/index.cfm

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

PubChem. National Institutes of Health. National Library of Medicine National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/

Stevens. (1998). Environmental fate and effects of dimethicone and cyclotetrasiloxane from personal care applications. International Journal of Cosmetic Science – Wiley Online Library.

U.S. Environmental Protection Agency [EPA]. (2017). EPI Suite™ v. 4.11, United States Environmental Protection Agency, Office of Pollution Prevention and Toxics and Syracuse Research Corporation. Available at: https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

SODIUM CHLORIDE

This dossier on sodium chloride presents the most critical studies pertinent to the risk assessment of sodium chloride in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. CHEMICAL NAME AND IDENTIFICATION

Chemical Name (IUPAC): sodium; chloride

CAS RN: [redacted]

Molecular formula: NaCl

Molecular weight: 58.44 g/mol

Synonyms: Halite, Salt, Table salt, Saline, Rock salt, Common salt, Dendritis, Purex'

SMILES: [Cl-].[Cl-].[Ca+2]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Sodium Chloride

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White crystaline solid	-	ECHA
Melting Point	801 °C @ 101.3 kPa	-	ECHA
Boiling Point	The study does not need to be conducted, because NaCl is a solid which melts above 300°C.	1	ECHA
Density	2163 kg/m^3 @ 20 °C	1	ECHA
Vapour Pressure	The study does not need to be conducted, because NaCl is a solid which melts above 300°C.	1	ECHA
Partition Coefficient (log K_{ow})	The study does not need to be conducted, because NaCl is inorganic.	1	ECHA
Water Solubility	317 g/L @ 20°C	2	ECHA
Dissociation Constant (pKa)	Not applicable, NaCl is an electrovalent substance.	-	ECHA

III. ENVIRONMENTAL FATE SUMMARY

Sodium chloride (NaCl) dissociates completely in aqueous solutions to sodium (Na^+) and chloride (Cl^-) ions. Sodium chloride and its dissociated ions are ubiquitous in the environment.

The transport and/or leaching of sodium (Na^+) and chloride (Cl^-) ions is affected by clay minerals (type and content), pH, and organic matter. Similar to potassium, sodium ions are less mobile and less prone to leaching than anions in soil, such as chloride and nitrate (NO_3^-). Chloride binds only weakly to soil particles, and therefore follows water movement (DoEE, 2017; OECD, 2001).

Chloride (Cl^-) ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated (OECD, 2001). Neither sodium chloride nor its dissociated ions are expected to bioaccumulate.

Release to surface waters under the assessed circumstances is expected to have limited long-term environmental effects as these salts are ubiquitous and are present in most water, soil and sediment, therefore organisms are adapted to a level of exposure. The magnitude of the acute effect for a receiving aquatic environment would depend on the released concentrations as well as the degree of adaptation of species present to these naturally occurring ions and salts (DoEE, 2017).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Historically, sodium chloride (as a major ingredient in edible salt) has been commonly used in cooking as a condiment and food preservative. Sodium is an electrolyte that regulates the amount of water in your body and also plays a part in nerve impulses and muscle contractions. When depleted in the body, sodium must be replaced in order to maintain intracellular osmolarity, nerve condition, muscle contraction and normal renal function. Sodium chloride is used to treat or prevent sodium loss caused by dehydration, excessive sweating or other causes.

The NHMRC has established dietary guidelines for the intake of sodium per day (adult) as less than 2,000 mg sodium per day (NHMRC, 2007 updated 2017). Sodium chloride is categorised under GRAS (Generally Recognised as Safe) by the FDA (U.S. Food and Drug Administration) and the average daily levels of sodium intake for adults range from 2 to 5 grams. A technical report by WHO and the Food and Agriculture Organization (FAO) recommended the consumption of less than 5 grams sodium chloride (or 2 grams sodium) per day as a population nutrient intake goal, while ensuring that the salt is iodised (WHO, 2007).

NICNAS has assessed sodium chloride in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to human health or the environment[1] .

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

Sodium chloride has low acute toxicity by the oral, dermal or inhalation route. It is not a skin irritant or a skin sensitiser. Long-term studies in rats fed sodium chloride showed elevated blood pressure. It is not a carcinogen and nor a developmental toxicant.

B. Acute Toxicity

Oral

The acute oral LD_{50} values of sodium chloride in rats is greater than 3,550 mg/kg with fiducial limits of 3,040 – 4,140 mg/kg (ECHA) [KI scores = 2].

Dermal

A dermal toxicity study was conducted in rabbits and the LD_{50} value was greater than 10,000 mg/kg and hence not classified according to EU Annex VI (ECHA) [KI scores = 2].

Inhalation

An acute inhalation toxicity study was conducted at a dose of 42 mg/L administered as an aerosol of a 20% aqueous solution to male rats and the results of the study indicated that the LC_{50} of sodium chloride was greater than 42 mg/L (42,000 mg/m^3) and hence not classified (ECHA) [KI scores = 2].

C. Irritation

Skin

When in contact with the intact skin, sodium chloride causes no response, either in undiluted form or in solution. Sodium chloride is considered to be slightly to not irritating to the skin (ECHA) [KI score = 2].

Eye

No adequate or reliable studies are available.

D. Sensitisation

Sodium chloride is not considered to be a skin sensitiser (ECHA).

E. Repeated Dose Toxicity

Oral

The estimated fatal dose of sodium chloride is approximately 0.75 to 3.00 g/kg (HSDB - Hazard Substance Data Bank - 750 to 3000 mg/kg). The lowest toxic dose (TDLo) for an adult man with normal blood pressure is 8,200 mg/kg (Patty's Handbook of Toxicology). High oral sodium chloride intake is associated with increased risk of hypertension; however, this is a well studied field in humans and additional animal testing data would not add value. Based on the studies, sodium chloride is not classified for any repeated dose effects.

A two-year feeding study was conducted to investigate the impact of sodium chloride on rats. Animals received a chronic administration at doses of 4% sodium chloride over a period

of 2 years which induces elevated blood pressure in the rats. The LOAEL from this key study identified a dose level of < 4% via the diet and the calculated LOAEL was 2,533 mg/kg/day (ECHA).

Dermal

No adequate or reliable studies are available.

Inhalation

No adequate or reliable studies are available.

F. Genotoxicity

No adequate or reliable studies are available.

G. Carcinogenicity

Sodium chloride is not classified as a carcinogen (ECHA). Sodium chloride is not listed with IARC.

H. Reproductive Toxicity

No adequate or reliable studies are available.

I. Developmental Toxicity

Sodium chloride is not classified as a developmental toxicant (ECHA).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The Australian drinking water guideline value for chloride ions is 250 mg/L based on aesthetics (ADWG, 2011).

The Australian drinking water guideline value for sodium ions is 180 mg/L based on aesthetics (ADWG, 2011).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium chloride does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL EFFECTS SUMMARY

A. Summary

Sodium chloride is of low acute toxicity concern to aquatic organisms, in part because of the effect of pH changes from the dissociated hydrogen ion.

B. Aquatic Toxicity

Acute Studies

The 96-hour LC_{50} value of 5,840 mg/L for sodium chloride was determined in a continuous flow-through exposure system with bluegill sunfish (*Lepomis macrochirus*) (ECHA) [KI score =1].

The EC_{50} 48-hour (immobilisation, *Daphnia magna*) was determined to be 1,900 mg/L (ECHA) [KI score = 2].

The EC_{50} of NaCl at 96 hours to *Lemna* was determined for comparison and found to be 6,870 mg/L (6.87 g/L) (ECHA) [KI score = 1].

Chronic Studies

The 33-day NOEC value of 252 mg/L for sodium chloride was determined in a continuous flow-through exposure system with early life stage fathead minnows (*Pimephales promelas*) (ECHA) [KI score = 2].

A 21-day NOEC (reproduction, *Daphnia pulex*) was determined to be 314 mg/L (ECHA) [KI score = 2].

C. Terrestrial Toxicity

The mean 14-day LC_{50} for three experiments conducted with the earthworm, *E. fetida* was 3,296 mg NaCl/kg soil dw. The 10-week NOEC (based on mortality) was 3,507 mg NaCl/kg soil for the earthworm, *E. fetida* (ECHA) [KI score = 2].

In a 7-day exposure study with red fescue grass, the EC_{50} for germination was 500.8 mg NaCl/kg soil dw. In a 7-day exposure study with Kentucky bluegrass, the NOEC for stem growth was 243 mg NaCl/kg soil dw (ECHA) [KI score = 2].

The 12-hour LD_{50} for wild house sparrows was approximately 3,000 - 3,500 mg/kg NaCl (ECHA) [KI score = 2].

D. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Sodium chloride is an inorganic mineral. Thus, biodegradation is not applicable to this substance. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to sodium chloride.

Bioaccumulation in fish is not expected given the inorganic nature of the substance. Thus, sodium chloride does not meet the screening criteria for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on sodium chloride are greater than 0.1 mg/L. The E(L)C_{50} values from the acute aquatic toxicity studies on sodium chloride are > 1 mg/L. Thus, sodium chloride, does not meet the criteria for toxicity.

The overall conclusion is that sodium chloride is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not Classified

B. Labelling

No signal word.

C. Pictogram

None

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes.

Skin Contact

Wash thoroughly with soap and water.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Keep product and empty container away from heat and sources of ignition. May emit toxic fumes of chloride and sodium oxide (above 1,413°C). Depending on conditions, decomposition products may include hydrogen chloride gas.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Prevent from entering sewers, waterways, or low areas.

Steps to be Taken if Material is Released or Spilled

Soak up with inert absorbent material.

D. Storage And Handling

General Handling

Keep product and empty container away from heat and sources of ignition. Ensure adequate ventilation, especially in confined areas.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for choline chloride.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Wearing of closed work clothing is recommended. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

Sodium chloride is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment and Energy [DoEE]. (2017). Environmental risks associated with surface handling of chemicals used in coal seam gas extraction in Australia, Project report prepared by the Chemicals and Biotechnology Assessments Section (CBAS), in the Chemicals and Waste Branch of the Department of the Environment and Energy as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

HSBD. Hazardous Substances Data Bank. https://pubchem.ncbi.nlm.nih.gov/source/hsdb/6368

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

NHMRC. (2007). Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes, Version 1.2 updated September 2017. National Health and Medical Research Council. Department of Health and Ageing. Australian Government.

OECD. (2001). Screening Information Assessment Report (SIAR) for Potassium chloride (CAS No. [redacted] UNEP Publications. Available at: https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?id=68BF142A-D550-432C-8C48-13883944BA1D.

Patty's Toxicology, 6 Volume Set, 6th Edition. Volume 3: 375. July 2012.

WHO. (2007) Reducing salt intake in populations: report of a WHO forum and technical meeting. https://www.who.int/dietphysicalactivity/Salt_Report_VC_april07.pdf. Accessed 28 Apr 2020

SODIUM HYDROXIDE

This dossier on sodium hydroxide presents the most critical studies pertinent to the risk assessment of sodium hydroxide in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The information presented in this dossier was obtained from the OECD-SIDS documents on sodium hydroxide (OECD, 2002a,b) and the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Sodium hydroxide

CAS RN: [redacted]

Molecular formula: HNaO

Molecular weight: 40 g/mol

Synonyms: Caustic soda, soda lye, NaOH

SMILES: O[Na]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-Chemical Properties of Sodium Hydroxide

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid	2	Lide, 2009; ECHA
Melting Point	318°C (solid, 100%); 52°C (60% solution)	2	ECHA
Boiling Point	1,388°C @ 101.3 kPa	2	Lide, 2009; ECHA
Density	2130 kg/m^3, 20°C (100%) 1430 kg/m^3, 20°C (40%)	2	Lide, 2009; ECHA
Vapour Pressure	1 Pa @ 513°C	2	Lide, 2009; ECHA
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	Very soluble (>10 g/L @ 25°C)	2	Lide, 2009; ECHA
Dissociation Constant (pKa)	14.8 @ 25°C	2	Lide, 2009; ECHA
pH of 5% NaOH solution	14	2	O'Neil, 2006

Sodium hydroxide (NaOH) is a strong alkaline substance that dissociates completely in water to sodium (Na^+) and hydroxyl (OH^-) ions.

III. ENVIRONMENTAL FATE PROPERTIES

Due to its high water solubility and low vapour pressure, sodium hydroxide will be found predominantly in the aquatic environment where it dissociates completely to sodium (Na^+) and hydroxyl (OH^-) ions. Both ions are ubiquitous in the environment (UNEP, 1995).

The addition of sodium hydroxide to an aquatic ecosystem may increase the pH depending on the buffer capacity of the receiving water. In general, the buffer capacity is regulated by the equilibria between CO_2, HCO_3^- and CO_3^{2-}:

$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$ ($pKa_1 = 6.35$)

$HCO_3^- \leftrightarrow CO_3^{2-} + H^+$ ($pKa_2 = 10.33$)

A release of sodium hydroxide into the aquatic environment from the use of NaOH could potentially increase the sodium concentration and the pH in the aquatic environment. Table 2 shows the concentration of sodium hydroxide needed to increase the pH to values of 9.0, 10.0, 11.0 and 12.0.

Table 2: Sodium Hydroxide Concentration (mg/L) Needed to Increase pH (DeGroot et al., 2002; taken from OECD, 2002b)

Buffer capacity*	Final pH			
	9.0	10.0	11.0	12.0
0 mg/L HCO_3 (distilled water)	0.4	4.0	40	400
20 mg/L HCO_3 (10^{th} percentile of 77 rivers)	1.0	8.2	51	413
106 mg/L HCO_3^- (mean value of 77 rivers)	3.5	26	97	468
195 mg/L HCO_3^- (90^{th} percentile of 77 rivers)	6.1	45	145	525

*The initial pH of a bicarbonate solution with a concentration of 20-195 mg/L was 8.25 to 8.35.

Na^+ and OH^- ions will not adsorb on the particulate matter or surfaces and will not accumulate in living tissues (OECD, 2002b).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Limited toxicity data exist for sodium hydroxide (NaOH). Depending on the concentration, solutions of NaOH are corrosive, irritating or non-irritating. These solutions cause direct effects to the skin, eyes, respiratory tract and gastrointestinal tract. Vapours from aqueous solutions of KOH can cause respiratory irritation. NaOH is not a skin sensitiser. There are no repeated dose, reproductive and developmental toxicity studies on sodium hydroxide.

B. Toxicokinetics/Metabolism

Sodium hydroxide dissociates completely in aqueous solutions to sodium (Na^+) and hydroxyl (OH^-) ions. Sodium is an essential nutrient involved in fluid and electrolyte balance and is required for normal cellular function (Ganong, 1995). Sodium is the major extracellular cation in the body; the total body content is tightly regulated (Ganong, 1995).

C. Acute Toxicity

There are no oral toxicity guideline studies on sodium hydroxide. An oral LD_{50} of a 1 to 10% solution of NaOH in rabbits was reported to be 325 mg/kg (expressed as 100% NaOH) (OECD, 2002a,b). Mortality was also observed when a 1% NaOH solution was dosed, but in this case, the applied volume was relatively high (24 mL per kg body weight) (OECD, 2002a,b).

Acute toxicity studies were not identified for the inhalation and dermal route.

D. Irritation

Animal studies have shown that an 8% NaOH solution is corrosive to the skin. In humans, 0.5 to 4% NaOH concentrations produced skin irritation; and, based on the results of two different human patch tests, a NaOH solution that is slightly less than 0.5% would be non-irritating to human skin (OECD, 2002a,b).

Results from animal eye irritation studies indicate that a 0.2-1.0% NaOH solution would be non-irritating, while 1.2 or > 2% NaOH solutions would be corrosive (OECD, 2002a,b).

E. Sensitisation

Male volunteers were exposed on the skin of their back to solutions of 0.063 to 1.0% NaOH in the induction phase of a human patch test. After 7 days the volunteers were challenged to a concentration of 0.125% NaOH. The irritant response correlated well with the concentration of NaOH, but an increased response was not observed when the previously patch tested sites were re-challenged. Based on this study, sodium hydroxide is not a skin sensitiser (OECD, 2002a,b; ECHA) [Kl. score = 2].

F. Repeated Dose Toxicity

No studies were identified for the oral and dermal route. An inhalation study was conducted in rats exposed to aerosols of solutions of NaOH ranging from 5% to 40%. Exposures were twice weekly (hours/day and total exposure days unspecified). All animals in the 40% solution group died within a month mostly from bronchopneumonia. At the lower concentrations, respiratory tract lesions were observed; an NOAEL was not identified (NIOSH, 1975).

G. Genotoxicity

In Vitro Studies

Several *in vitro* studies have been conducted on NaOH (OECD, 2002a,b; ECHA). Although these studies reported negative results, they are considered unreliable (Kl. score = 3) due to methodological or reporting deficiencies.

In Vivo Studies

Several *in vivo* studies have been conducted on NaOH (OECD, 2002a,b; ECHA). Although these studies reported negative results, they are considered unreliable (Kl. score = 3) due to methodological or reporting deficiencies.

H. Carcinogenicity

No studies were identified.

I. Reproductive Toxicity

No valid studies were identified regarding toxicity to reproduction in animals after oral, dermal or inhalation exposure to NaOH.

J. Developmental Toxicity

No valid studies were identified regarding developmental toxicity in animals after oral, dermal or inhalation exposure to NaOH (OECD, 2002a,b; ECHA).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Oral and dermal repeated dose, reproductive, and developmental toxicity studies have not been conducted on NaOH. A repeated dose toxicity study was conducted by the inhalation route, but the methodology and documentation preclude its use for deriving a toxicological reference value. These toxicity studies would have questionable usefulness because of the corrosive/irritating nature of NaOH, which would limit the amount absorbed. NaOH dissociates to sodium and hydroxyl ions in bodily fluids, and a significant amount of these ions are already ingested in foods. Furthermore, both ions are present in the body and are highly regulated by homeostatic mechanisms. Thus, a toxicological reference value was not derived for NaOH.

The Australian drinking water guideline values for sodium (180 ppm, aesthetic) and pH may be applicable (ADWG, 2021).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium hydroxide does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium hydroxide has low acute toxicity to aquatic organisms.

B. Aquatic Toxicity

The OECD-SIDS SIAR on NaOH states that while the toxicity of the NaOH has been assumed to be related to the hydroxyl anion, in general a pH change could influence the speciation of other chemicals and therefore increase and/or decrease toxicity of the substance.

There are no guideline studies on NaOH; the studies summarised below have Klimisch scores of 3 or 4.

Acute Fish

The 24-hour LC_{50} to *Carassius auratus* (goldfish) is 160 mg/L. At 100 mg/L, which was equivalent to a pH of 9.8, no mortality was observed. The 48-hour LC_{50} to *Leuciscus idus melanotus* is 189 mg/L. The 96-hour LC_{50} of *Gambusia affinis* (mosquitofish) is 125 mg/L. At 84 mg/L, no effects on the fish were observed. The pH was 9 at 100 mg/L.

Acute Invertebrate

The 48-hour LC_{50} is 40 mg/L for *Ceriodaphnia cf. dubia*. The toxicity threshold concentration of NaOH for *Daphnia magna* was reported to range from 40 to 240 mg/L.

Acute Algae

No studies were identified.

C. Terrestrial Toxicity

No studies were identified.

D. Calculation of PNEC

The OECD-SIDS SIAR on NaOH states the following regarding the aquatic toxicity studies on NaOH (OECD, 2002b):

> *"In many cases pH, buffer capacity and/or medium composition were not discussed in the publications, although this is essential information for toxicity tests with NaOH. This is the most important reason why most of the studies, mentioned above were considered invalid. Although valid acute ecotoxicity tests and chronic ecotoxicity tests with NaOH are not available, there is no need for additional testing with NaOH. A significant number of acute toxicity tests are available, and the results of the tests are more or less consistent. Altogether they give a sufficient indication of acute toxicity levels of sodium hydroxide."*
>
> *"Furthermore, acute toxicity data cannot be used to derive a PNEC or a PNEC added for sodium hydroxide. Aquatic ecosystems are characterised by an alkalinity/pH, and the organisms of the ecosystem are adapted to these specific natural conditions. Based on the natural alkalinity of waters, organisms will have different optimum pH conditions, ranging from poorly buffered waters with a pH of 6 or less to very hard waters with pH values up to 9. A lot of information is available about the relationship between pH and ecosystem structure and also natural variations in pH of aquatic ecosystems have been quantified and reported extensively in ecological publications and handbooks."*
>
> *"Normally a PNEC or a PNEC added has to be derived from the available ecotoxicity data. A PNEC added is a PNEC which is based on added concentrations of a chemical (added risk approach). Based on the available data it is not considered useful to derive a PNEC or a PNEC added for NaOH because:*
>
> - *The natural pH of aquatic ecosystems can vary significantly between aquatic ecosystems,*

- *Also, the sensitivity of the aquatic ecosystems to a change of the pH can vary significantly between aquatic ecosystems and*
- *The change in pH due to an anthropogenic NaOH addition is influenced significantly by the buffer capacity of the receiving water."*

"Although a PNEC or a PNEC added was not calculated for NaOH, there is a need to assess the environmental effect of a NaOH (alkaline) discharge. Based on the pH and buffer capacity of effluent and receiving water and the dilution factor of the effluent, the pH of the receiving water after the discharge can be calculated. Of course, the pH change can also be measured very easily via a laboratory experiment or by conducting field measurements. The change in pH should be compared with the natural variation in pH of the receiving water and based on this comparison it should be assessed if the pH change is acceptable."

Based on the information above, PNEC values for freshwater, sediment, and soil were not derived for sodium hydroxide.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Sodium hydroxide is an inorganic salt that dissociates completely to sodium and hydroxide ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both sodium and hydroxide ions are also ubiquitous and are present in most water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to this inorganic salt.

Sodium and hydroxide ions are essential to all living organisms, and their intracellular and extracellular concentrations are actively regulated. Thus, sodium hydroxide is not expected to bioaccumulate and does not meet the screening criteria for bioaccumulation.

No chronic toxicity data exist on sodium hydroxide; however, the acute EC_{50} values are > 1 mg/L in fish, invertebrates and algae. Thus, sodium hydroxide does not meet the screening criteria for toxicity.

The overall conclusion is that sodium hydroxide is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Metal Corrosive Category 1

Skin Corrosive, Category 1A

Eye Damage, Category 1

EU Concentration Limits:
≥ 5%: Skin Corrosive 1A
≥ 2 to <5%: Skin Corrosive 1B

≥ 0.5%to <2%: Skin Irritant Category 2
≥ 0.5% to <2%: Eye Irritant Category 2

In addition to the hazard statements corresponding the GHS classification for corrosive, the following non-GHS hazard statement is to be added to the SDS: AUH071: Corrosive to the Respiratory Tract.

B. Labelling

Danger

C. Pictograms

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Flush with plenty of fresh water for 15 minutes holding eyelids open, lifting eyelids occasionally to ensure complete removal of the product. Remove contacts, if present and easy to do. DO NOT allow rubbing of eyes or keeping eyes closed. Seek medical attention.

Skin Contact

Rinse with soap and plenty of water for several minutes. Remove contaminated clothing. Seek medical attention immediately.

Inhalation

Remove person to fresh air. Apply artificial respiration if not breathing. Seek medical attention.

Ingestion

Rinse mouth with water (only if the person is conscious), but do not administer fluids. Do NOT induce vomiting. Seek medical attention immediately.

B. Fire Fighting Information

Extinguishing Media

Carbon dioxide, water spray, foam, dry chemical.

Specific Exposure Hazards

Containers may explode when heated. May form explosive mixtures with strong acids. Hazardous combustion products may include the following materials: halogenated compounds, metal oxides/oxides, sodium monoxide.

Special Protective Equipment for Firefighters

Full protective clothing and approved self-contained breathing apparatus required for firefighting personnel.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment and avoid direct contact. Do not touch damaged containers or spilt material unless wearing appropriate protective clothing. Ventilate the area before entry.

Environmental Precautions

Prevent spills from entering storm drains or sewers and contact with soil.

Steps to be Taken if Material is Released or Spilt

Use an absorbent material to recover as much product as possible, then rinse the affected area with water to dilute the residue. Disposal of leftover product and used containers should be carried out in accordance with all local, state and federal regulations.

D. Storage and Handling

General Handling

Wear appropriate personal protective equipment. Avoid contact with eyes, skin or clothing. Avoid breathing mist, vapours or spray. Use only with adequate ventilation. Wash hands after use. Launder contaminated clothing.

Storage

Store away from acids. Keep container closed when not in use. Store in a cool well-ventilated area.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for sodium hydroxide in Australia is 2 mg/m^3 as a peak limitation, with a sensitisation notation. A peak limitation is defined by Safe Work Australia as a maximum or peak airborne concentration of a substance determined over the shortest analytically practicable period of time which does not exceed 15 minutes.

Engineering Controls

Good general ventilation should be used. If applicable, use process enclosures, local exhaust ventilation or other engineering controls to maintain airborne levels below recommended exposure limits.

Personal Protection Equipment

Respiratory Protection: Use a mask or approved air-purifying respirator with appropriate cartridge or canister in spray applications or in confined spaces.

Hand Protection: Wear impervious gloves to prevent skin contact and absorption of this material. Rubber or Neoprene gloves may afford adequate skin protection.

Skin Protection: Wear appropriate clothes (i.e., coveralls). Use non-slip footwear.

Eye Protection: Wear eye protection in situations where splash or thick mists are possible.

Other Precautions: Avoid contact with skin, eyes and clothing. When using, do not eat or drink. Wash hands thoroughly with soap and water before eating or drinking. Remove contaminated clothing and launder before reuse.

F. Transport Information

For sodium hydroxide solutions of > 5%:
Australian Dangerous Goods
UN1824, Corrosive liquid, (Sodium hydroxide solution)
Class 8
Packing Group: II

Lower concentrations of sodium hydroxide may require a different packing group or may not require any hazard code if the concentration of NaOH is low enough not to be considered a corrosive material.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2011). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

De Groot et al. (2002). The addition of sodium hydroxide to a solution with sodium bicarbonate to a fixed pH. Solvay Pharmaceuticals Int. Doc. No. 8320/47/01; cited in OECD, 2002a,b.

Department of the Environment, Water, Heritage and the Arts (DEWHA). (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

Ganong, W.F. (1995). Review of Medical Physiology, 17th Edition, Appleton & Lange, Norwalk, Connecticut, USA.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology 25:1-5.

Lide, D.R. (2009). Physical Constants of Inorganic Compounds. CRC Handbook of Chemistry & Physics, 89th Edition, CRC Press.

NIOSH. (1975). National Institute of Occupational Safety and Health: Criteria Document: Sodium Hydroxide p.46 (1975) DHEW Pub. NIOSH 76-105; cited in NICNAS IMAP assessment report for sodium hydroxide, https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1406#cas-A [redacted]

O'Neil, M.J. [Ed.]. (2006). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. P. 1485, Whitehouse Station, NJ: Merck and Co., Inc.

OECD. (2002a). IUCLID Data Set for Sodium hydroxide (CAS No. [redacted] UNEP Publications. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=DC48343F-5AEA-4850-9A17-0A89331E4320.

OECD. (2002b). Screening Information Dataset (SIDS) Initial Assessment Report for Sodium hydroxide (CAS No. [redacted] UNEP Publications. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=DC48343F-5AEA-4850-9A17-0A89331E4320.

UNEP. (1995). Water quality of world river basins. UNEP Environment Library No. 14, Nairobi, Kenya; cited in OECD, 2002a,b.

SODIUM SULPHATE

This dossier on sodium sulphate presents the most critical studies pertinent to the risk assessment of sulphate in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained the OECD-SIDS documents on sodium sulphate (OECD, 2005a,b), and from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Disodium sulphate

CAS RN: [redacted]

Molecular formula: Na_2SO_4

Molecular weight: 142.04 g/mol

Synonyms: Sodium sulphate; disodium sulphate; sodium bisulphate; sulphuric acid, disodium salt

SMILES: [O-]S(=O)(=O)[O-].[Na+].[Na+]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Sodium Sulphate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White crystalline solid	2	ECHA
Melting Point	ca. 884°C (pressure not reported)	2	ECHA
Density	2700 kg/m^3 @ 20°C	2	ECHA
Partition Coefficient (Log K_{ow})	-4.38 (temperature not provided)	2	ECHA
Water Solubility	445.5 g/L @ 20°C	1	ECHA
Auto flammability	Not auto flammable	1	ECHA

III. ENVIRONMENTAL FATE SUMMARY

Sodium sulphate dissociates in aqueous media to sodium (Na^+) and sulphate (SO_4^{2-}) ions. Biodegradation is not applicable to inorganic compounds. Sodium sulphate is not expected to bioaccumulate; it will dissociate to ions that are ubiquitous in the environment. Sodium sulphate is not expected to adsorb to soil or sediment because of its dissociation properties and high water solubility.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Sodium sulphate exhibits low acute toxicity by the oral and inhalation routes. It is not irritating to the skin and eyes; and it is not a skin sensitiser. In a reproductive and developmental toxicity screening study, there was no indication of any toxicity in rats given oral doses as high as 1,000 mg/kg/day. Sodium sulphate is not genotoxic.

B. Acute Toxicity

Oral

The oral LD_{50} in rats is > 2,000 mg/kg (ECHA) [KI score = 1].

Human data indicate a very low acute toxicity of sodium sulphate. High oral doses of sodium sulphate, from 300 mg/kg up to 20 grams for an adult, are well tolerated, except from (intentionally) causing severe diarrhea (OECD, 2005a,b).

Inhalation

The 4-hour inhalation LC_{50} for an aerosol of sodium sulphate is > 2.4 mg/L, which was the highest technically feasible aerosol concentration. The mass median aerodynamic diameters (MMAD) were 2.65 to 2.71 µm (ECHA) [KI score = 1].

Dermal

There is no data on acute dermal toxicity.

C. Irritation

Application of 0.5 g sodium sulphate (in PEG 400) to the skin of rabbits for 4 hours was not irritating (ECHA) [KI score = 1].

Instillation of 90 mg sodium sulphate to the eyes of rabbits was not irritating (ECHA) [KI score = 1].

D. Sensitisation

Sodium sulphate was not considered a skin sensitiser in a mouse local lymph node assay (ECHA) [KI score = 1].

E. Repeated Dose Toxicity

Oral

In a reproductive and developmental toxicity screening (OECD 421) study, male and female Wistar rats were dosed by oral gavage with 0, 100, 300 or 1,000 mg/kg sodium sulphate for a total of 4 weeks for males and 7 weeks for females. There was no evidence of toxicity at any dose level. The NOAEL for systemic toxicity is 1,000 mg/kg/day, the highest dose tested.

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on sodium sulphate are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Sodium Sulphate

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (S. typhimurium and E. coli strains)	-	-	1	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	-	1	ECHA
Chromosomal aberration (Chinese hamster lung fibroblasts)	-	-	1	ECHA

*+, positive; -, negative

In Vivo Studies

No studies are available.

G. Carcinogenicity

No valid studies are available.

H. Reproductive/Developmental Toxicity

A reproductive and developmental toxicity screening (OECD 421) study has been conducted on sodium sulphate. Male and female Wistar rats were dosed by oral gavage with 0, 100, 300 or 1,000 mg/kg sodium sulphate. There were no deaths during the study and no clinical signs of reproductive or developmental toxicity at any dose level. Body weights, body weight gain and feed consumption were similar across all groups. The NOAEL for systemic, reproductive and developmental toxicity is 1,000 mg/kg/day, the highest dose tested (ECHA) [KI score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Toxicological reference values were not derived. Sodium sulphate dissociates in water to sodium and sulphate ions.

The Australian drinking water guideline value for sodium is 180 mg/L based on aesthetics (ADWG, 2021).

The Australian drinking water guideline value for sulphate is 500 mg/L based on health. Concentrations of > 500 mg/L can have purgative effects. There is also an Australian drinking water guideline value for sulphate of 250 mg/L based on aesthetics; it is the taste threshold (ADWG, 2021).

I. Cancer

There are no valid carcinogenicity studies on sodium sulphate. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium sulphate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

J. A. Summary

Sodium sulphate is of low acute concern to aquatic life.

K. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on sodium sulphate.

Table 3: Acute Aquatic Toxicity Studies on Sodium Sulphate

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hour LC_{50}	7,960	2	Mount et al. (1997)
Daphnia magna	48-hour EC_{50}	4,736*	2	Davies and Hall (2007)

* Standard test conditions: 100 mg $CaCO_3$/L and Ca:Mg ratio of 0.7.

Chronic Studies

The 7-day LOEC from a *Ceriodapnia dubia* reproduction study, in which the test media contained varying degrees of water hardness, was 1,329 mg/L. The NOEC was extrapolated to be approximately 1,109 mg/L (Soucek, 2007).

L. Sediment Toxicity

The lowest 96-hour LC_{50} value to *Hyalella azteca* in a series of studies involving different hardnesses of water was 757 mg/L (Soucek and Kennedy, 2005). In another study with *Hyalella azteca*, the lowest 96-hour LC_{50} value (in water with the lowest hardness) was 841

mg/L (Davies and Hall, 2007). The lowest 96-hour LC_{50} value to *Chironomus tentans* in a series of studies involving different hardnesses of water was 20,899 mg/L (Soucek and Kennedy, 2005).

M. Terrestrial Toxicity

No adequate studies were located.

N. Calculation of PNEC

The PNEC calculations for sodium sulphate follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for two trophic levels. Acute E(L)C50 values are available for fish (7,960 mg/L) and *Daphnia* (4,736 mg/L). The NOEC from a chronic study on invertebrates was 1,109 mg/L. On the basis that the data consists of results from short-term studies from two trophic levels and a single long-term study, an assessment factor of 100 has been applied to the chronic NOEC value of 1,109 mg/L for invertebrates. The $PNEC_{water}$ is 11 mg/L.

PNEC sediment

No reliable experimental toxicity data on sediment organisms are available. Sodium sulphate dissociates completely in water with its environmental distribution is dominated by its high water solubility. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as sodium sulphate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sediment}$. Based on its properties, no adsorption of sodium sulphate to sediment is to be expected, and the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

No reliable experimental toxicity data on terrestrial organisms are available. The environmental distribution of sodium sulphate is dominated by its water solubility. Sorption of sodium sulphate should probably be regarded as a reversible situation, i.e., the substance is not tightly nor permanently bound. K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as sodium sulphate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, sodium sulphate is not expected to significantly adsorb to soil, and the assessment of this compartment will be covered by the aquatic assessment.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Sodium sulphate is an inorganic salt that dissociates completely to sodium and sulphate ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both sodium and sulphate ions are also ubiquitous and are present in most water, soil and sediment. For

the purposes of this PBT assessment, the persistent criteria are not considered applicable to sodium sulphate or its dissociated ions.

Sodium and sulphate ions are essential to all living organisms and their intracellular and extracellular concentrations are actively regulated. Thus, sodium sulphate is not expected to bioaccumulate.

The NOEC from a chronic toxicity study with *Ceriodaphnoa rerio* is > 0.1 mg/L. The acute E(L)C_{50} values for fish and *Daphnia* are > 1 mg/L. Thus, sodium sulphate does not meet the criteria for toxicity.

Therefore, sodium sulphate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal words.

C. Pictogram

None

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

Immediately flush eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. If symptoms persist, seek medical attention.

Skin Contact

Wash with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Do not induce vomiting. Rinse mouth with water and then drink a small amount of water. Get medical attention. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

May emit toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: sodium and sulfur oxides.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Avoid creating and breathing dust.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop and remove.

D. Storage And Handling

General Handling

Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational standard for sodium sulphate.

Engineering Controls

Use in a well-ventilated area.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Sodium sulphate is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods Code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Davies, T.D. and Hall, K.J. (2007). Importance of calcium in modifying the acute toxicity of sodium sulphate to hyalella Azteca and Daphnia magna. Environ. Toxicol. Chem. 26: 1243-1247.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Mount, D.R., Gulley, D.D., Hockett, J.R., Garrison, T.D., and Evans, J.M. (1997). Statistical models to predict the toxicity of major ions to Ceriodaphnia dubia, Daphnia magna and Pimephales promelas (Fathead minnows). Environ. Toxicol. Chem. 16: 2009-2019.

OECD. (2005a). Screening Information Dataset (SIDS) Initial Assessment Report for Sodium sulphate (CAS No. [redacted] UNEP Publications.

OECD. (2005b). IUCLID Data Set for Sodium sulphate (CAS No. [redacted] UNEP Publications.

Soucek, D.J. (2007). Comparison of hardness and chloride regulated acute effects of sodium sulphate on two freshwater crustaceans. Environ. Toxicol. Chem. 26: 773-779.

Soucek, D.J., and Kennedy, A.J. (2005). Effects of hardness, chloride, and acclimation on the acute toxicity of sulphate to freshwater invertebrates. Environ. Toxicol. Chem. 24: 1204-1210.

BORIC ACID (CAS NO. [redacted]
SODIUM TETRABORATE DECAHYDRATE (BORAX) (CAS NO. [redacted]

This dossier presents the most critical studies pertinent to the risk assessment of two boron compounds (boric acid and borax) in their use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): boric acid

CAS RN: [redacted]

Molecular formula: BH_3O_3

Molecular weight: 61.84 g/mol

Synonyms: orthoboric acid; boracic acid; borofax; boron hydroxide; boron trihydroxide

SMILES: B(O)(O)O

Chemical Name (IUPAC): disodium bicyclo[3.3.1]tetraboroxane-3,7-bis(olate)

CAS RN: [redacted]

Molecular formula: $B_4Na_2O_7$

Molecular weight: 381.4 g/mol

Synonyms: sodium tetraborate decahydrate; borax; monosodium metaborate; sodium borate; sodium borate (NaBO2); sodium diborate; sodium meta borate; sodium metaborate; sodium tetraborate

SMILES: B1(OB2OB(OB(O1)O2)[O-])[O-].O.O.O.O.O.O.O.O.O.O.[Na+].[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Limited measured data are available for borax. In the environment, borax is expected to dissociate and/or hydrolyse to release boric acid at neutral pH. Therefore, measured data available for boric acid have been presented as analogue data for this substance.

Key physical and chemical properties for boric acid are shown in Table 1.

Table 1: Overview of the Physico-chemical Properties of Boric Acid

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, odourless, crystalline solid	2	ECHA
Melting Point	> 100°C (decomposes)	1	ECHA
Boiling Point	Not Applicable	-	ECHA
Density	1,489 kg/m^3 @ 20°C	1	ECHA
Vapour Pressure	0 Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})	Not Applicable, substance is inorganic	-	ECHA
Water Solubility	48.8 g/L @ 20°C	1	ECHA
Dissociation Constant (pKa)	8.94 @ 20°C	1	ECHA

Boron is almost exclusively found in the environment in the form of boron-oxygen (B-O) compounds, which are often referred to as borates. The high strength of the B-O bond relative to those between boron and other elements makes boron oxide compounds stable compared to nearly all non-oxide boron materials. Indeed, the B-O bond is among the strongest found in the chemistry of naturally occurring inorganic substances (ECHA).

In the environment, borates and compounds of boric acid will dissociate and/or hydrolyse to form the same boron species. For example, when borax dissolves in dilute solutions, it dissociates into Na^+ ions and the tetraborate anion ($B_4O_5(OH)_4^{2-}$). Boric acid ($B(OH)_3$) is formed following acid catalysed hydrolysis of the tetraborate anion. Under alkaline conditions, dilute solutions of the tetraborate anion depolymerise rapidly to the mononuclear borate anion ($B(OH)_4^-$) (NICNAS, 2019).

Boric acid is a Lewis acid that acts as a weak monoprotic acid by accepting OH^- and not as a proton donor (pKa 9.14). Therefore, at the near neutral pH of most environmental systems and at low concentrations (< 0.025 mol B/L), the neutral mononuclear species ($B(OH)_3$) will dominate and only a small proportion of boron will exist as the borate monoanion, $B(OH)_4^-$. Therefore, in the environment boric acid is in equilibrium with borate anions. Both species are very stable as they do not undergo biotransformation or redox reactions under normal environmental conditions (NICNAS, 2019).

Exposure to borates are often expressed in terms of boron (B) equivalents based on the fraction of boron in the source substance on a molecular weight basis. The B equivalents used are a generic designation rather than a designation of the element boron. The factor for converting boric acid to B-equivalents is 0.1748. The factor for converting borax to B-equivalents is 0.2149.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Borax will transform into boric acid in the aquatic environment. In the environment boric acid is in equilibrium with borate anions. Degradation is not applicable to inorganic borates.

Boric acid is highly soluble in water. Some partitioning to soil and sediment does occur, but this adsorption is pH dependent. It has a low potential for bioaccumulation.

B. Partitioning

Borax will transform into boric acid in the aquatic environment. In the environment boric acid is in equilibrium with borate anions. Both species are very stable as they do not undergo biotransformation or redox reactions under normal environmental conditions. Boric acid is highly water soluble and it tends to remain in surface waters. Although some partitioning from water to soil and sediment does occur, the adsorption is pH dependent with the greatest adsorption occurring under alkaline conditions (pH 7.5 to 9.0) (NICNAS, 2019).

C. Biodegradation

Degradation is not applicable to inorganic borates. It is not subject to hydrolysis, photodegradation or biodegradation (ECHA). Inorganic borates are subject to chemical transformation processes (adsorption, complexation, precipitation, fixation) once released into the environment (ECHA).

D. Environmental Distribution

The Kp value for boron compounds was calculated as the median of all measured Kp values from the GEMAS project (Geochemical Mapping of Agricultural and Grazing Land Soil project): 2.19 L/kg dry weight (ECHA) [KI score = 2]. The chemistry of boron in soils and aquatic systems is simplified by the absence of oxidation-reduction reactions or volatilisation. Redox processes can mobilise Fe oxides and Mn oxides, which may lead to a release of boron in aquatic systems. Generally, sediments are characterised with higher pH values than the soil matrix, which increases the boron sorption capacity (ECHA).

If released to soil, based on this low Kp value, low vapour pressure and high water solubility, boric acid and borax are considered relatively mobile in the environment, under certain conditions (ECHA).

E. Bioaccumulation

The WHO review of boron (WHO, 1998) noted that “highly water soluble materials are unlikely to bioaccumulate to any significant degree and that borate species are all present essentially as un-dissociated and highly soluble boric acid at neutral pH”. BCFs of < 0.1 to 10.5 L/kg have been reported from laboratory tests of fish and oysters (Hamilton and Wiedmeyer, 1990; Thompson et al., 1976).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Borax exhibits low acute toxicity by the oral and dermal routes. Boric acid exhibits low acute toxicity by the oral, dermal and inhalation routes. Neither substance is a skin or eye irritant, nor a skin sensitiser. In aqueous media at physiological pH, borax will predominantly exist as un-dissociated boric acid. The developing foetus and the testes are the two most sensitive targets of boron toxicity in multiple species. The testicular effects include reduced organ weight and organ to body weight ratio, atrophy, degeneration of the spermatogenic

epithelium, impaired spermatogenesis, reduced fertility and sterility. The developmental effects from boron exposure include high prenatal mortality, reduced foetal body weight, malformations and variations. Repeated inhalation exposure to read-across substance boron oxide resulted in slight irritation to the respiratory tract, but no systemic toxicity. Boric acid was not genotoxic, and boric acid and borax was not carcinogenic to rodents.

B. Toxicokinetics

Boric acid is not metabolised in either animals or humans, owing to the high energy level required (523 kJ/mol) to break the B-O bond. Other inorganic borates convert to boric acid at physiological pH in the aqueous layer overlying the mucosal surfaces prior to absorption. Most of the simple inorganic borates exist predominantly as undissociated boric acid in dilute aqueous solution at physiological and environmental pH, leading to the conclusion that the main species in the plasma of mammals is un-dissociated boric acid. Since other borates dissociate to form boric acid in aqueous solutions, they too can be considered to exist as un-dissociated boric acid under the same conditions. Additional support for this derives from studies in which more than 90% of administered doses of inorganic borates are excreted in the urine as boric acid. Absorption of borates via the oral route is nearly 100%. For the inhalation route also, 100% absorption is assumed as worst-case scenario. Dermal absorption through intact skin is very low with a percent dose absorbed of 0.226 ± 0.125 in humans. Using the % dose absorbed plus standard deviation (SD) for boric acid, a dermal absorption for borates of 0.5% (rounded from 0.45%) can be assumed as a worse-case estimate (ECHA).

In the blood boric acid is the main species present and is not further metabolised. Boric acid is distributed rapidly and evenly through the body, with concentrations in bone 2 to 3 times higher than in other tissues. Boric acid is excreted rapidly, with elimination half-lives of 1 hour in the mouse, 3 hours in the rat and < 27.8 hours in humans, and has low potential for accumulation. Boric acid is mainly excreted in the urine (ECHA).

C. Acute Toxicity

The oral LD_{50} of borax in rats is > 2,500 mg/kg (ECHA) [KI score = 1]. The oral LD_{50} of boric acid in rats is 3,450 mg/kg (ECHA) [KI score = 1].

There are no acute inhalation studies on borax. In a read-across study for borax, the 4-hour inhalation LC_{50} value for disodium tetraborate pentahydrate in rats is > 2.04 mg/L (ECHA) [KI score = 1]. The 4-hour inhalation LC_{50} value for boric acid in rats is > 2.01 mg/L. The mass median aerodynamic diameter (MMAD) was 2.8 µm (ECHA) [KI score = 1]. In another study, the 4-hour inhalation LC_{50} value for boric acid in rats was > 2.03 mg/L (ECHA) [KI score = 1].

The dermal LD_{50} of borax in rabbits is > 2,000 mg/kg (ECHA) [KI score = 2]. The dermal LD_{50} of boric acid in rabbits is > 2,000 mg/kg (ECHA) [KI score = 1].

D. Irritation

Application of 0.5 g of borax to the skin of rabbits for 4 hours under occlusive conditions was not irritating. The mean erythema and oedema scores were 0.00 (ECHA) [KI scores = 2]. Application of 0.5 g. of boric acid to the skin of rabbits for 24 hours under occlusive conditions was not irritating. The mean of the 24 and 72-hour scores were 0.13 for erythema and 0.00 for oedema (ECHA) [KI scores = 1].

Disodium tetraborates are eye irritants. Instillation of 0.08 mL of read-across substance disodium tetraborate pentahydrate into the eyes of rabbits was slightly irritating. The mean of 24, 48, and 72 hours scores were 0.22 for corneal opacity; 0.22 for iridial lesions; 2.8 for conjunctival redness; and 1.89 for chemosis. The effects were fully reversible (ECHA) [KI score = 1].

Boric acid induced mild conjunctivae redness and chemosis and minor effects on the iris. The effects were reversible within 7 days (ECHA). Instillation of 100 mg of boric acid into the eyes of rabbits was slightly irritating. The mean of 24, 48, and 72-hour scores were 0.00 for corneal opacity; 0.11 for iridial lesions; 0.94 for conjunctival redness; and 0.56 for chemosis (ECHA) [KI score = 1].

E. Sensitisation

There are no skin sensitisation studies on Borax. Read-across substances disodium tetraborate pentahydrate was not a skin sensitiser to guinea pigs in a Buehler test (ECHA) [KI score = 1].

Boric acid was not a skin sensitiser to guinea pigs in a Buehler test (ECHA) [KI score = 1]. Sodium tetraborate pentahydrate was not a skin sensitiser to guinea pigs in a Buehler test (ECHA) [KI score = 1]. Sodium tetraborate decahydrate was not a skin sensitiser to guinea pigs in a Buehler test (ECHA) [KI score = 1].

F. Repeated Dose Toxicity

<u>Oral</u>

Male and female SD rats were given in their feed boric acid at doses of 0, 52.5, 175, 525, 1,750 or 5,250 ppm B equivalents for 90 days. The average intake has been estimated to be approximately 0, 2.6, 8.8, 26, 87.5 or 262.5 mg B/kg/day, respectively (USEPA, 2004). By week 6, all animals in the highest dose died. Clinical signs in the top two dose levels were rapid respiration, inflamed eyes, swollen paws and desquamated skin on the paws and tails. There was also reduced food consumption and body weight gain. The 1,750 ppm females showed reduced liver, spleen ovary and adrenal weights; the 1,750 ppm males showed reduced liver, spleen, kidney, testes and adrenal weights. The adrenals of 4 of the 1,750 ppm males showed minor increases in lipid content and size of the cells in the zona reticularis. Atrophied testis (complete atrophy of the spermatogenic epithelium and decreased in the size of the seminiferous tubules) was seen in all of the 1,750 ppm males. One 525 ppm male had partial testicular atrophy. The NOAEL for this study is 175 ppm boron or 8.8 mg B/kg/day (Weir and Fisher, 1972) [KI score = 2].

Male and female SD rats were given in their diet borax at doses of 0, 52.5, 175, 525, 1,750 or 5,250 ppm B equivalents for 90 days. The average intake has been estimated to be approximately 0, 2.6, 8.8, 26, 87.5 or 262.5 mg B/kg/day, respectively (USEPA, 2004). By week 6, all the animals in the highest dose died. Clinical signs in the top two dose levels were rapid respiration, inflamed eyes, swollen paws and desquamated skin on the paws and tails. There was also reduced food consumption and body weight gain. The 1,750 ppm females showed reduced liver, spleen and ovary weights; the 1,750 ppm males showed reduced liver, spleen, kidney, testes and brain weights. The adrenals of the majority of the 1,750 ppm males and females showed slight to moderate increases in lipid content and size of the cells in the zona reticularis. Atrophied testis (complete atrophy of the spermatogenic epithelium

and decreased in the size of the seminiferous tubules) was seen in all the 1,750 ppm males. Four 525 ppm males had partial testicular atrophy. Spermatogenic arrest was found in one 525 ppm male. The NOAEL for this study is 175 ppm boron or 8.8 mg B/kg/day (Weir and Fisher, 1972) [KI score = 2].

Male and female B6CF1_1 mice were given in the diet 0, 1,200, 2,500, 5,000, 10,000 or 20,000 ppm boric acid for 13 weeks (control and highest dose group) or 16 weeks (remaining dose groups). These dietary levels correspond to approximately 0, 34, 70, 141, 281 and 563 mg B/kg/day for males, respectively: and 0, 47, 97, 194, 388 and 776 mg B/kg/day for females, respectively (USEPA, 2004). There was mortality (8/10 males; 6/10 females) in the 20,000 ppm group, as well as hyperkeratosis and acanthosis. One male also died in 10,000 ppm group. Degeneration or atrophy of the seminiferous tubules occurred in the ≥ 5,000 ppm males. Minimal to mild extramedullary haematopoiesis of the spleen was observed in all dose groups. The LOAEL for this study is 1,200 ppm, corresponding to 34 and 47 mg B/kg/day for males and females, respectively (NTP, 1987) [KI score = 2].

Male and female SD rats were given in their diet 0, 117, 350 or 1,170 ppm boric acid for two years. The average intake has been estimated to be approximately 0, 5.9, 17.5 or 58.5 mg B/kg/day, respectively (USEPA, 2004). The 1,170 ppm rats had decreased food consumption during the first 13 weeks of the study and suppressed growth throughout the study. Signs of toxicity in the 1,170 ppm animals included swelling and desquamation of the paws, scaly tails, inflammation of the eyelids and bloody discharge from the eyes. All the 1,170 ppm males had testicular atrophy at the 6, 12 and 24-month time points. The seminiferous epithelium was atrophied, and the tubular size in the testes was decreased. There were significant decreases in the absolute and relative testes weights. Brain and relative thyroid weights were increased. The NOAEL for this study is 350 ppm B equivalents or 17.5 mg B/kg/day (Weir and Fisher, 1972) [KI score = 2].

Male and female B6C3F_1 mice were given up to 20,000 ppm boric acid in their feed for 13 weeks (NTP, 1987). Eight out of the 10 males and 6 out of the 10 females from the 20,000 ppm group died and 1 of the 10 males from the 10,000 ppm group died before the end of the study. Symptoms included nervousness, haunched appearance, dehydration, foot lesions and scaly tails. Incidences of extra medullary haematopoiesis of the spleen were observed of varying severity in all dose groups for both males and females and hyperkeratosis and/or acanthosis of the stomach observed at the highest dose only in both males and females. At doses > 5,000 ppm (142 mg B/kg bw for the male), degeneration or atrophy of the seminiferous tubules was observed. The NOAEL for this study is 34 mg B/kg/day (NTP, 1987) [KI score = 2].

Inhalation

Male and female rats were exposed by inhalation to 0, 77, 175 or 470 mg/m^3 boron oxide. The exposures were 6 hours/day, 5 days/week for 24, 12, and 10 weeks for the 77, 175, and 470 mg/m^3 concentrations groups, respectively. The MMAD were 2.5, 1.9 and 2.4 µm for the 77, 175 and 479 mg/m^3 concentrations groups, respectively. There was no evidence of systemic toxicity. Some of the 470 mg/m^3 had reddish exudate from the nose. As these animals were covered with dust, this effect may have been local irritation of the nose and from the animals scratching the nose. The NOAEL for systemic toxicity is 470 mg/m^3, the highest exposure concentration tested. The NOAEL for localised effects (irritation) is 175 mg/m^3 (ECHA) [KI score = 2].

Dermal

No studies are available.

G. Genotoxicity

In Vitro Studies

There are no *in vitro* genotoxicity studies on borax. Table 2 presents the results of the *in vitro* genotoxicity studies on boric acid.

Table 2: *In vitro* Genotoxicity Studies on Boric Acid

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	ECHA
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	-	1	ECHA
Chromosomal aberrations (Chinese Hamster Ovary cells)	-	-	1	ECHA
Chromosomal aberrations (Chinese Hamster Ovary cells)	-	-	1	ECHA
Chromosomal aberrations (Human peripheral lymphocytes)	NS	+	2	ECHA
Unscheduled DNA synthesis (rat liver cells)	NA	-	1	ECHA

*+, positive; -, negative; NA, not applicable; NS, not specified.

In Vivo Studies

No studies are available on borax.

Male and female Swiss Webster mice were given two daily doses of 0, 225, 450, 900, 1,800 or 3,500 mg/kg boric acid. The frequency of micronucleated polychromatic erythrocytes were not increased at any dose level (ECHA) [KI score = 1].

H. Carcinogenicity

Oral

Male and female SD rats were given in their diet disodium tetraborate decahydrate (Borax) or boric acid at doses of 0, 117, 350 or 1,170 ppm as B equivalents (approximately 0, 5.9, 17.5 or 58.5 mg B/kg/day) for two years. There was no mention of tumours in the report. Nevertheless, NTP (1987) concluded that this study provided adequate data on the lack of carcinogenic effects of boric acid in rats (Weir and Fisher, 1972; USEPA, 2004).

Male and female B6C3F_1 mice were given in their diet 0, 2,500 or 5,000 ppm boric acid for 103 weeks. The dietary levels are equivalent to 0, 446 or 1,150 mg/kg/day boric acid or 0,

78.1 or 201.3 mg B/kg/day. There was no evidence of carcinogenicity (NTP, 1987) [Kl score = 2].

I. Reproductive Toxicity

A three-generation reproductive toxicity study was conducted in Sprague-Dawley rats with boric acid. Male and female rats were fed a diet containing 0, 117, 350 or 1,170 ppm boron (approximately 0, 5.9, 17.5 or 58.5 mg B/kg/day, respectively). In the lower two dose groups, there were no treatment-related effects on reproduction. Litter size, progeny weights, fertility, live birth indices, lactation and appearance were similar to the controls. No gross abnormalities were noted in these two dose groups. The 1,170-ppm dose group were found to be sterile, and there were no litters from mating the treated females with control males. Lack of viable sperm was found in the atrophied testes of all 1,170 ppm males. Decreased ovulation was also seen in the majority of the ovaries of the 1,170 ppm females. The NOAEL for this study is 350 ppm boron or approximately 17.5 mg B/kg/day (Weir and Fisher, 1972) [Kl score = 2].

A three-generation reproductive toxicity study was conducted in Sprague-Dawley rats with borax. Male and female rats were fed a diet containing 0, 117, 350 or 1,170 ppm boron (approximately 0, 5.9, 17.5 or 58.5 mg B/kg/day, respectively). In the lower two dose groups, there were no treatment-related effects on reproduction. Litter size, progeny weights, fertility, live birth indices, lactation, appearance were similar to the controls. No gross abnormalities were noted in these two dose groups. The 1,170-ppm dose group were found to be sterile, and there were no litters from mating the treated females with control males. Lack of viable sperm was found in the atrophied testes of all 1,170 ppm males. Decreased ovulation was also seen in the majority of the ovaries of the 1,170 ppm females. The NOAEL for this study is 350 ppm boron or approximately 17.5 mg B/kg/day (Weir and Fisher, 1972) [Kl score = 2].

In a continuous breeding protocol, male and female CD-1 mice were given in their diet 0, 1,000, 4,500 or 9,000 ppm boric acid in their feed. The authors estimated that the average daily intakes were 0, 26.6, 111 and 220 mg B/kg/day to males; and 0, 31.8, 152 and 257 mg B/kg/day to females. Boric acid consumption did not differ among the groups. There were no litters in the 9,000 ppm breeding pairs. At 4,500 ppm, there was a successful first litter, after which there was a progressive decrease in fertility; only one pair produced a fourth and fifth litter. All fertility indices were affected in the 4,500 ppm group. A complete crossover mating trial was conducted using control mice and the 4,500 ppm mice. The results showed that the probable cause of the reduced fertility was a decrement in male fertility. A dose-related decrease in body, testicular and epididymal weights was observed in the 4,500 and 9,000 ppm F_0 males. Sperm count was significantly decreased in these two dose groups, and percent motile sperm was decreased in all dose groups. Testicular histopathology showed seminiferous tubular atrophy in the 9,000 ppm males and partial atrophy of the seminiferous tubules in the 4,500 ppm males. There were no histopathologic changes in the 4,500 ppm females. No statistically significant decreases in mating index, fertility index or live pups/litter in the 4,500 ppm females, but the number of days to litter in this dose group was increased. Oestrous cyclicity was unaffected. Reproductive organ weights were unaffected, but relative maternal liver and kidney/adrenal weights were reduced. An F_1 fertility trial was performed using offspring from the 1,000 ppm groups. There were no decreases in mating, fertility or reproductive performance. The F_2 adjusted live pup weight was slightly, but significantly, reduced from controls. A clear NOAEL for reproductive toxicity in males was not seen in this study. The 1,000 ppm males had decreased sperm motility in

the F_0 generation and decreased sperm concentration in the F_1 generation. Decreased F_2 pup relative body weight was statistically significant from controls. The NOAEL in this study for females is 1,000 ppm boric acid or 32 mg B/kg/day). The LOAEL in this study for males is 1,000 ppm or 27 mg B/kg/day; a NOAEL was not established (Fail et al*.,* 1991) [Kl score = 2].

J. Developmental Toxicity

No studies are available on borax.

Pregnant female SD rats were given 0, 0.1, 0.2 or 0.4% boric acid in their feed on gestational days (GD) 0 to 20 or 0.8% boric acid on GD 6 to 15. The average amounts of boric acid ingested were estimated to be 0, 78, 163, 330 or 539 mg/kg/day (0, 13.6, 28.5 or 57.7 mg B/kg/day), respectively. Effects on the pregnant rats were altered food and/or water intake at ≥ 0.2% boric acid, increased liver and kidney weights relative to body weights at ≥ 0.2%, reduced weight gain at ≥ 0.4%, and increased corrected weight gain at 0.4% boric acid. There was a reduction in foetal body weights in all treated groups (94, 87, 63 and 47% of control weight, respectively). Increased malformations occurred at ≥ 0.2%, and prenatal mortality was increased at 0.8%. There was a dose-response for altered skeletal morphology in rats (≥ 0.1%), and specific findings were significantly elevated above controls at ≥ 0.2%. Specifically, there was an increased incidence of short rib XIII (a malformation) and a decreased incidence or rudimentary or full rib(s) at lumbar I (an anatomical variation) (Heindel et al., 1992) [Kl score = 2].

Pregnant female SD rats were given in their feed 0, 0.025, 0.005, 0.075, 0.1 or 0.2% boric acid on GD 0 to 20. Approximately half of the dams were terminated on GD 20, and the remaining dams delivered their litters. Pup growth and viability were monitored until postnatal day (PND) 21. The average amounts of boron ingested on GD 20 were: 0, 3.3, 6.3, 9.6, 13.3 and 25 mg B/kg/day, respectively. The average amounts of boron ingested on PND 21 were 0, 3.2, 6.5, 9.7, 12.9 and 25.3 mg B/kg/day, respectively. There were no maternal deaths and no treatment-related clinical signs. Maternal body weights were similar across all groups during gestation. However, decreased maternal body weights (GD 19 and 20 at sacrifice) and decreased maternal body weight gain (GD 15-18 and GD 0-20) were statistically significant in trend tests. There was a 10% reduction in gravid uterine weight (statistically significant) in the 0.2% group. Corrected maternal weight (maternal gestational weight minus reduced gravid uterine weight) was unaffected by treatment. Feed intake in the 1,000 ppm dams was minimally affected and only during the first three days of dosing. Water consumption was higher in the treated groups after GD 15. The number of corpora lutea and uterine implantation sites, and the percentage of preimplantation loss were similar across all groups. Increased relative kidney weights were increased in the 0.2% group. There were no differences in the viability of the offspring between treated and controls. On GD 20, foetal body weight was 94% and 88% of controls in the 0.1% and 0.2% groups, respectively; recovery was complete at birth (~GD 22). The incidence of short rib XIII was increased on GD 20 in the ≥ 0.1% groups, but only in the 0.2% group at PND 21. The incidence of wavy rib was increased on GD 20 in the ≥ 0.1% group; the reversibility of this effect was confirmed on PND 21. There was a slight decrease in extra lumbar ribs in the 0.2% group on GD 20, and extra lumbar ribs were seen in the 0.2% group on PND 21. The developmental NOAEL was considered to be 0.075% boric acid or 9.6 mg B/kg/day on GD 20; and 0.1% boric acid or 12.9 mg B/kg/day on PND 21 (Price et al., 1996a) [Kl score = 1].

Pregnant Swiss mice were given in their diet 0, 0.1, 0.2 or 0.4% boric acid on gestational days (GD) 0 to 17. The average amounts of boric acid ingested were estimated to be 248, 452 or

1,003 mg/kg/day (0, 43.4, 79.0 or 175.3 mg/B/kg/day), respectively. Maternal toxicity consisted of mild kidney lesions (≥ 0.1%), increased water intake and relative kidney weights (0.4%), and decreased water intake during treatment. Foetal body weights were reduced in the ≥ 0.2% groups, and there were increased incidences of resorptions and malformed foetuses per litter in the 0.4% group. The LOAEL for maternal toxicity is 248 mg/kg/day boric acid or 43.4 mg B/kg/day; a NOAEL was not established. The NOAEL for developmental toxicity is 248 mg/kg/day boric acid or 43.4 mg B/kg/day (Heindel et al., 1992) [KI score = 2].

Pregnant female New Zealand rabbits were dosed by oral gavage with 0, 62.5, 125 or 250 mg/kg boric acid (0, 10.9, 21.9 or 43.7 mg B/kg) during GD 6-19. Feed intake was in the 250 mg/kg maternal animals during the exposure period, but it was increased in the ≥ 125 mg/kg dose groups. In the 250 mg/kg group, maternal body weights during GD 9-30, weight gain during GD 6-19, gravid uterine weight and number of corpora lutea per dam were significantly reduced. In the ≥ 125 mg/kg groups, maternal corrected gestational weight gain was increased compared to controls. Maternal liver weights were unaffected by treatment. In the 250 mg/kg group, relative, but not absolute, kidney weights were increased, although no effects in the kidney were noted in the histopathological examination. Prenatal mortality was increased in the 250 mg/kg group (90% resorptions/litter versus 6% for controls); the proportion of pregnant females with no live foetuses was increased (73% versus 0%), and live litter size was reduced (2.3 foetuses versus 8.8). Thus, there were only 14 live foetuses (6 live litters) available for evaluation in the 250 mg/kg group. The percentage malformed foetuses/litter was increased in the 250 mg/kg group, primarily due to cardiovascular defects (72% versus 3% of controls). There was no definitive maternal or developmental toxicity in the 62.5 or 125 mg/kg dose groups. The NOAEL for maternal and developmental toxicity is 125 mg/kg/day boric acid or 21.9 mg B/kg/day (Price et al., 1996b) [KI score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for boric acid follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021)).

A. Non-Cancer

An oral reference dose was not derived for boric acid or borax.

The Australian drinking water guideline value for boron (4 mg/L) may be applicable (ADWG 2011 updated 2021). The health-based ADWG value was based on a tolerable daily intake (TDI) of 0.16 mg/kg bw. This TDI is based on the NOAEL of 9.6 mg/kg/bw/day for foetal bodyweight effects in a rat developmental study (Price et al., 1996a) with an uncertainty factor of 60 (10 for interspecies and 6 for human intraspecies).

B. Cancer

There was no evidence of carcinogenicity in rat and mouse chronic studies conducted on borax and/or boric acid. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Borax and boric acid do not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Borax and boric acid have low acute and chronic toxicity to aquatic organisms.

B. Aquatic Toxicity

In ecotoxicological tests for boron, the exposure concentrations are expressed as boron equivalents, i.e., mg B/L. This is because boric acid and borate salts will have the same boron speciation when dissolved in environmental matrices. Therefore, in the following sections toxicological values are given as mg B/L regardless of the form of boron that was tested.

Acute Studies

Borax will transform into boric acid in the aquatic environment. Table 3 lists the results of acute aquatic toxicity studies conducted on boric acid.

Table 3: Acute Aquatic Toxicity Studies on Boric Acid

Test Species	Endpoint	Results (mg B/L)	Klimisch score	Reference
Fathead minnow	96-hour LC_{50}	79.7	2	ECHA
Legumia recta (Black sandshell mussel)	96-hour LC_{50}	147	2	ECHA
Hyalella azteca	96-hour LC_{50}	64	2	ECHA
Pseudokirchneriella subcapitata	72-hour EC_{50}	52.4 mg B/L	1	ECHA

Chronic Studies

Long-term effects (LC_{10}) on freshwater fish ranged from 3.5 to 47 mg B/L. Adequate long-term LC_{10} of 21.6 mg B/L was found for the freshwater fish *P. promelas* in a study according to USEPA OPPTS 850.1400 (ECHA) [KI score = 2].

Long-term effects (LC_{10}/NOEC) on reproduction on freshwater vertebrates ranged from 6.6 to 32 mg B/L based on several well-accepted guideline studies (ECHA) [KI scores =1 or 2].

Boric acid has been evaluated for its toxicity towards the freshwater alga *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) in an Alga growth inhibition test according to OECD 201 under GLP requirements. The exposure duration was 72 hours under static conditions. The NOEC growth rate determined from the study was 17.5 mg B/L (ECHA) [KI score = 1].

The ANZG water quality guideline (2021) derived a very high reliability default guideline value (DGVs) for (dissolved) boron in freshwater from 22 chronic (long-term) toxicity data, comprising eight fish, two amphibians, three crustaceans, one bivalve, three macrophytes, one green microalga, three diatoms and one blue–green alga. The summary of representative data used by ANZG to develop a water quality guideline for boron is presented in Table 4. These values are noted to be consistent with those reported in ECHA. Additional chronic aquatic toxicity data is found in the ANZG Technical Brief (ANZG, 2021).

Table 4: Chronic Aquatic Toxicity Studies on Boron[1]

Test Species	Endpoint	Results (mg B/L)
Danio rerio	34-day NOEC (Biomass)	1.8
Pimephales promelas	32-day NOEC (Mortality)	11
Daphnia magna	14-day NOEC (Reproduction)	2.4
Pseudokirchneriella subcapitata	4-day NOEC (Growth)	2.8

1 - The DGVs are based on toxicity data for boron as either boric acid, H_3BO_3 (CAS [redacted] or borax, $Na_2B_4O_710H_2O$ (CAS [redacted] in freshwater.

In the chronic toxicity data set, fish sensitivity to boron ranged from the least sensitive species in the dataset (*Melanotaenia splendida*, LC_{10} 102 mg/L) to the third most sensitive species in the dataset (*Danio rerio*, NOEC 1.8 mg/L). Of the crustaceans, *D. magna* was best represented in the literature, with 18 published NOEC values (ranging from 2.4 mg/L to 29 mg/L) for six different endpoints from six different publications. The final NOEC of 2.4 mg/L used in the DGV derivation was lower than that for *C. dubia* (NOEC 5.6 mg/L) and for the amphipod *H. azteca* (NOEC 6.6 mg/L). For *P. subcapitata*, there were three separate studies available with toxicity data for boron. The toxicity values from these studies ranged from a NOEC of 2.8 mg/L to a NEC of 27 mg/L, varying with endpoint, duration and test medium used. Boron was least toxic to *P. subcapitata* when tested in algal growth medium with added $NaHCO_3$, suggesting that carbonate addition may have influenced boron toxicity. Therefore, although NECs are preferred to NOECs or EC10s, in this instance, a reliable NOEC of 2.8 mg/L was the most sensitive toxicity value for *P. subcapitata* (ANZG, 2021).

C. Sediment Toxicity

Limited sediment toxicity data are available for boric acid and boron containing compounds in general (NICNAS, 2019).

Chronic toxicity values for the effects of boric acid on sediment-dwelling invertebrates have been obtained for a freshwater midge (*Chironomus riparius*, harlequin fly), a freshwater bivalve (*Lampsilis siliquoidea*, fatmucket clam) and the aquatic worm (*Lumbriculus variegatus,* California blackworm). The respective toxicity values for these species are as follows: 28-day NOEC = 37.8 mg B/kg; 21-day LC_{25} (survival) = 363.1 mg B/kg; and 28-day NOEC = 100.8 mg B/kg (NICNAS, 2019).

Due to the high water solubility of boron and its low partitioning to sediment, sediment toxicity testing for boron is particularly challenging as it is difficult to ensure that exposure is through the solid phase (i.e., sediment) and not from the aqueous boric acid in the overlying water (NICNAS, 2019).

D. Terrestrial Toxicity

Ecotoxicological tests with plants and soil invertebrates have recorded modest chronic toxicity values (NOECs/ECs) in the range of 15.3 to 84.0 and 5.2 to 315 mg total B/kg, respectively (ECHA, 2008). However, to predict the potential toxicity of boron to plants and soil organisms, measuring the total boron concentration may be unsuitable. Instead, potential toxicity is better predicted using boron concentrations in the soil solution (extractable boron) (Mertens et al., 2011). In Australia, it is generally accepted that boron toxicity will pose a risk to terrestrial plants when soil concentrations exceed 15 mg/kg of extractable boron (NICNAS, 2019).

E. Calculation of PNEC

PNEC water

The ANZG water quality guideline (2021) derived a very high reliability DGV for (dissolved) boron in freshwater. The DGVs for 99, 95, 90 and 80% species protection are 340 µg/L, 940 µg/L, 1,500 µg/L and 2,500 µg/L, respectively. The 95% species protection level for boron in freshwater (940 µg/L) is recommended for adoption in the assessment of slightly-to-moderately disturbed ecosystems (ANZG, 2021).

PNEC sediment

Limited sediment toxicity data are available for boric acid and boron containing compounds in general (NICNAS, 2019). Due to the high water solubility of boron and its low partitioning to sediment, sediment toxicity testing for boron is particularly challenging as it is difficult to ensure that exposure is through the solid phase (i.e., sediment) and not from the aqueous boric acid in the overlying water (NICNAS, 2019). K_{ow} and K_{oc} parameters do not readily apply to inorganics, such as boric acid and borax. Therefore, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. As a result, the assessment of this compartment will be covered by the aquatic assessment.

PNEC soil

In the ECHA REACH database (ECHA), a $PNEC_{soil}$ was derived for boron using the species sensitivity distribution method and an assessment factor of 2. The $PNEC_{soil}$ was determined to be 5.7 mg/kg soil dry weight.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Borax is an inorganic compound that dissociates completely to boric acid and the borate anion in aqueous media. Biodegradation is not applicable to these inorganic compounds; both boric acid and borate are also ubiquitous and are present in most water, soil and sediment. For the purposes of this PBT assessment, the persistent criteria are not considered applicable.

A BCF of < 0.1-10.5 L/kg has been reported for borates in fish and oysters. This data suggests that boric acid does not bioaccumulate in the aquatic environment. Thus, boric acid and borax do not meet the criteria for bioaccumulation.

The chronic toxicity data on boric acid has a NOEC > 0.1 mg/L. Acute E(L)C_{50} values are > 1 mg/L. Thus, borax and boric acid do not meet the criteria for toxicity.

The overall conclusion is that borax and boric acid are not PBT substances.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity Category 4 [Inhalation]

Eye Damage Category 1

Reproductive Toxicant Category 1B

STOT SE Category 3 [Respiratory irritation]

In addition to the hazard statements corresponding the GHS classifications, the following non-GHS hazard statement is to be added to the SDS: AUH071: Corrosive to the Respiratory Tract.

B. Labelling

Danger

According to the classification provided by companies to ECHA in CLP notifications this substance may damage fertility or the unborn child, causes serious eye damage, is harmful if swallowed, is harmful if inhaled, is suspected of damaging fertility or the unborn child, may cause respiratory irritation and causes skin irritation.

C. Pictogram

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS)

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water. Do not induce vomiting. Get medical attention. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

None identified.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Use personal protective clothing. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust. Wear respiratory protection if ventilation is inadequate. Avoid contact with skin, eyes and clothing.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove.

D. Storage and Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place. Do not store with alkalis, acids or reducing agents.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for sodium perborate tetrahydrate.

Engineering Controls

Ensure adequate ventilation. Localised ventilation should be used to control dust levels below permissible exposure limits.

Personal Protection Equipment

Respiratory Protection: Use respiratory protection when airborne concentrations are expected to be high.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye Protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Sodium tetraborate decahydrate is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

ANZG. (2021). Toxicant default guideline values for aquatic ecosystem protection: Boron in freshwater. Australian and New Zealand Guidelines for Fresh and Marine Water Quality. CC BY 4.0. Australian and New Zealand Governments and Australian state and territory governments, Canberra, ACT, Australia.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Fail, P.A., George, J.D., Seely, J.C., Grizzle, T.B., and Heindel, J.J. (1991). Reproductive toxicity of boric acid in Swiss (CD-1) mice: assessment using the continuous breeding protocol. Fundam. Appl. Toxicol. 17: 225-239.

Hamilton, S.J., and Wiedmeyer, R.H. (1990). Concentrations of boron, molybdenum and selenium in chinook salmon. Trans. Amer. Fisheries Soc. 119: 500-510.

Heindel, J.J., Price, C.J., Field, E.A., Marr, M.C., Myers, C.B., Morrissey, R.E., and Schwetz, B.A. (1992). Developmental toxicity of boric acid in mice and rats. Fundam. Appl. Toxicol. 18: 266-272.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Mertens, J., Van Laer, L. and Salaets, P. (2011). Phytotoxic doses of boron in contrasting soils depend on soil water content. Plant Soil. 342:73-82.

National Toxicology Program [NTP]. (1987). Toxicology and Carcinogenesis Studies of Boric Acid (CAS No. [redacted] in $B6C3F_1$ Mice. NTP TR 324, NIH Publication No. 88-2580. National Toxicology Program, U.S. Department of Health and Human Services, National Institute of Health.

NICNAS. (2019). Boric acid and precursors to boric acid: Environment tier II assessment. Available on-line: https://www.industrialchemicals.gov.au/sites/default/files/Boric%20acid%20and%20precursors%20to%20boric%20acid_%20Environment%20tier%20II%20assessment.pdf

Price, C.J., Strong, P.L., Marr, M.C., Myers, C.B., and Murray, F.J. (1996a). Developmental toxicity NOAEL and postnatal recovery in rats fed boric acid during gestation. Fundam. Appl. Toxicol. 32: 179-193.

Price, C.J., Marr, M.C., Myers, C.B., Seely, J.C., Heindel, J.J., and Schwetz, B.A. (1996b). The developmental toxicity of boric acid in rabbits. Fundam. Appl. Toxicol. 34: 176-187.

Thompson, J.A., David, J.C. and Drew, R.E.(1976). Toxicity, uptake and survey studies of boron in the marine environment. Water Research. 10(10): 869-875.

USEPA. (2004). U.S. EPA (United States Environmental Protection Agency). Integrated Risk Information System (IRIS) – Boron and Compounds; CASRN [redacted] Available at: http://www.epa.gov/iris.

Warner et al. (2018). Revised Method for Deriving Australian and New Zealand Water Quality Guideline Values for Toxicants – update of 2015 version. Prepared for the revision of the Australian and New Zealand Guidelines for Fresh and Marine Water Quality. Australian and New Zealand Governments and Australian state and territory governments, Canberra, 48 pp.

Weir, R.J., Jr., and Fisher, R.S. (1972). Toxicologic studies on borax and boric acid. Toxicol. Appl. Pharmacol. 23: 351-364.

WHO. (1998). Environmental Health Criteria 204, Boron, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

ULEXITE

This dossier on ulexite presents the most critical studies pertinent to the risk assessment of ulexite in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Sodium-calcium pentaborate octahydrate

CAS RN: [redacted]

Molecular formula: $(NaCaB_5O_6(OH)_6 \bullet 5H_2O)$

Molecular weight: 405 g/mol

Synonyms: Ulexite; sodium-calcium pentaborate octahydrate

Smiles: B1(OB2OB(O1)OB(O2)OB([O-])[O-])[O-].O.O.O.O.O.O.O.O.[Na+].[Ca+2]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Commercially Available Ulexite

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, granular, ground or powder form	4	Etimine USA, Inc. (2016)
Melting Point	870°C	4	Etimine USA, Inc. (2016)
Boiling Point	Not Applicable	-	-
Bulk Density	1,410 to 1,500 kg/m^3	4	Etimine USA, Inc. (2016)
Water solubility	26.67% as dissolved Ulexite @ 25°C by weight of solution	4	American Borate Company (2016)

Ulexite is a naturally-occurring mineral that is slightly soluble in water. Limited measured data are available for ulexite. In a study investigating the relative rates of boron from soluble and controlled-release boron fertilizers, ulexite showed releases of boron of 20% in just under 10 weeks; 40% in approximately 25 weeks; 60% by 40 weeks; and 80% by 60 weeks (Broschat, 2008). In the environment, borates will dissociate and/or hydrolyse to release boron as boric acid [$B(OH)_3$ (also formulated as H_3BO_3)] and/or borate anions. Therefore, the information presented within this dossier is for boron (CAS No. [redacted]

III. ENVIRONMENTAL FATE PROPERTIES

Boron is found almost exclusively in the environment in the form of boron-oxygen compounds, which are often referred to as borates. In the environment, borates and compounds of boric acid will dissociate and/or hydrolyse to form the same boron species. For example, when borax dissolves in dilute solutions, it dissociates into Na+ ions and the tetraborate anion ($B_4O_5(OH)_4^{2-}$). Boric acid ($B(OH)_3$) is formed following acid catalysed hydrolysis of the tetraborate anion. Under alkaline conditions, dilute solutions of the tetraborate anion depolymerise rapidly to the mononuclear borate anion ($B(OH)_4^-$) (DoEE, 2017).

Boron is an inorganic, elemental compound and can therefore not be biodegraded by micro-organisms or other biotic-related processes (ECHA).

The WHO (1998) review of boron noted that highly water-soluble materials are unlikely to bioaccumulate to any significant degree and that borate species are all present essentially as undissociated and highly soluble boric acid at neutral pH. The available data indicate that both experimental data and field observations support the interpretation that borates are not significantly bioaccumulated (ECHA).

Bioconcentration factors of < 0.1 to 10.5 L/kg have been reported from laboratory tests of fish and oysters (Thompson et al. 1976). Saiki et al. (1993) measured boron levels in aquatic food chains and observed the highest concentrations of boron in detritus and filamentous algae. Invertebrates and fish had lower concentrations, indicating that bioaccumulation was not occurring. Based on these data, boron does not bioaccumulate in the aquatic environment (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

No information is available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

No values were derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Ulexite does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

There are no mammalian or aquatic toxicity studies on ulexite. Toxicity for boron is provided within this section.

Boron is of a low toxicity concern to aquatic organisms. Although boron is required by plants at low concentrations, at high concentrations it is toxic. In Australia, it is generally accepted that boron toxicity will pose a risk to terrestrial plants when soil concentrations exceed 15 mg/kg of extractable boron. The phytotoxicity of boron is dependent on the plant species and soil type (DoEE, 2017).

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies on boron.

Table 2: Acute Aquatic Toxicity Studies on Boron[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
P. promelas	4-day LC_{50}	79.7 mg/B/L	2	ECHA
Freshwater invertebrates	48-hr LC_{50}	64 to >544 mg/B/L	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	52.4 mg/B/L	2	ECHA

1 – CAS No. [redacted]

Chronic Studies

Table 3 lists the results of chronic aquatic toxicity studies on boron.

Table 3: Chronic Aquatic Toxicity Studies on Boron[1]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Micropterus salmoides	4d-EC_{10}	36.8 mg/B/L	2	ECHA
Oncorhynchus mykiss	long term NOEC-LOEC	19.2. mg/B/L	2	ECHA
Brachydanio rerio	long term NOEC-LOEC	36.mg/B/L	2	ECHA
Pimephales promelas	long term NOEC-LOEC	21.3 mg/B/L	2	ECHA
Daphnia magna	NOEC	13.9 mg/B/L	2	ECHA
Hyalella Azteca	NOEC	6.3 mg/B/L	2	ECHA
Chironomus riparius	NOEC	20.1 mg/B/L	2	ECHA
Brachionus calyciflorus	NOEC	24.6 mg/B/L	2	ECHA
Lampsilis siliquoidea	NOEC	30 mg/B/L	2	ECHA

1 – CAS No. [redacted] for boron

ANZG has developed a water quality guideline for boron (ANZG, 2021). Very high reliability default guideline values (DGVs) for (dissolved) boron in freshwater were derived from 22 chronic (long-term) toxicity data, comprising eight fish, two amphibians, three crustaceans,

one bivalve, three macrophytes, one green microalga, three diatoms and one blue–green alga. The DGVs for 99, 95, 90 and 80% species protection are 340 µg/L, 940 µg/L, 1,500 µg/L and 2,500 µg/L, respectively. The 95% species protection level for boron in freshwater (940 µg/L) is recommended for adoption in the assessment of slightly-to-moderately disturbed ecosystems.

C. Terrestrial Toxicity

Relevant and reliable chronic no-effects values were identified for 39 terrestrial species or microbial processes. No-effect levels for dissolved boron ranged between 7.2 mg B/kg soil dw and 86.7 mg B/kg soil dw. The plant *Zea mays* was the most sensitive trophic level. The least sensitive species was the nematode *C.elegans*. A Species Sensitivity Distribution (SSD) has been developed for the assessment of boron in the terrestrial compartment, using the reliable species-specific chronic toxicity effect levels that have been generated in various research studies (ECHA) [KI Score = 2].

D. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Ulexite is a naturally-occurring mineral. For the purposes of this PBT assessment, the persistence criteria is not considered applicable to this inorganic substance.

Bioaccumulation is not applicable to naturally-occurring minerals, such as ulexite. Although boron is slowly released from ulexite, limited data indicate that bioaccumulation is not significant in aquatic and terrestrial food chains. Thus, it does not meet the criteria for bioaccumulation.

There are no aquatic toxicity studies on ulexite. The lowest chronic toxicity value for boron is > 0.1 mg/L. The acute E(L)C_{50} values for boron is > 1 mg/L. Thus, based on boron, ulexite does not meet the criteria for toxicity.

Therefore, ulexite is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

GHS07, GHS08

B. Labelling

Warning!

Danger!

According to the classification provided by companies to ECHA in CLP notifications this substance may damage fertility or the unborn child and causes serious eye irritation.

C. Pictogram

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. If symptoms persist, seek medical advice.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

B. Fire Fighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Ulexite is non-flammable, combustible, or explosive. It is a flame retardant.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment.

Environmental Precautions

Ulexite is slightly water-soluble; at high concentrations it may cause damage to trees or vegetation by root absorption. Do not flush to drains.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove.

D. Storage And Handling

General Handling

No special measures necessary provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact. Avoid creating or inhaling dust.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for ulexite.

Engineering Controls

None

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required.

Hand Protection: Chemical resistant protective gloves.

Skin Protection: Body protection must be chosen depending on activity and possible exposure.

Eye protection: Safety glasses with side-shields.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Ulexite is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

American Borate Company. (2016). Technical specifications on Ulexite 45 micron ground. Available at: http://www.americanborate.com/media/19191/ulexite-[redacted]2016-technical-specification.pdf.

ANZG. (2021). Toxicant default guideline values for aquatic ecosystem protection: Boron in freshwater. Australian and New Zealand Guidelines for Fresh and Marine Water Quality. CC BY 4.0. Australian and New Zealand Governments and Australian state and territory governments, Canberra, ACT, Australia.

Broschat, T.K. (2008). Release rates of soluble and controlled-release boron fertilizers. HorTechnology 18(3): 471-474.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

DoEE. (2017). Environmental risks associated with surface handling of chemicals used in coal seam gas extraction in Australia, Project report Appendices A, B, C, D, F, and G prepared by the Chemicals and Biotechnology Assessments Section (CBAS) in the Department of the Environment and Energy as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

Etimine USA, Inc. (2016). Safety Data Sheet on Ulexite. Available at: http://www.etimineusa.com/sites/etimineusa.com/files/SDS%20-%20Ulexite%202016%20-%202018_0.pdf

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

Saiki, M.J., Jennings, M.R., and Brumbaugh, W.B. (1993). Boron, Molybdenum, and Selenium in aquatic food chains from the Lower San Joaquin River and its tributaries, California. Archives of Environmental Contamination and Toxiciology. 24, 307-319.

Thompson et al. (1976). Toxicity, uptake and survey studies of boron in the marine environment. Water Research Vol. 10. pp 869 to 875, 1976.

WHO. (1998). World Health Organisation, Environmental health criteria 204 – boron, viewed 26 August 2015. http://www.inchem.org/documents/ehc/ehc/ehc204.htm.

UREA

This dossier on urea (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of the substance in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. The majority of information presented in this dossier was obtained from the ECHA database that provides information on chemicals that have been registered under the EU REACH (ECHA). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Urea

CAS RN: [redacted]

Molecular formula: CH_4N_2O

Molecular weight: 60.056 g/mol

Synonyms: carbamide; carbonyldiamide; isourea

SMILES: C(=O)(N)N

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Urea

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid	2	ECHA
Melting Point	133.3°C	1	ECHA
Boiling Point	Urea decomposes before the boiling point is reached	2	ECHA
Density	1330 kg/m^3 @ 20°C	1	ECHA
Vapour Pressure	0.00016 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-1.73 at 22°C	1	ECHA
Water Solubility	624 g/L at 20°C	1	ECHA
Flash Point	Not applicable as substance is solid	1	ECHA
Auto flammability	There was no self-ignition observed up to the melting point	2	ECHA
Viscosity	Not applicable as substance is solid	1	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Urea is hydrophilic and readily biodegradable due to enzymatic mineralisation. This substance is not expected to sorb to soils or sediments based on its low log K_{ow} value. In addition to this, urea is not expected to bioaccumulate.

B. Biodegradation

Urea is considered to be readily biodegradable. In an OECD Guideline 302B (Inherent biodegradability) study, degradation levels of 3% (3 hours), 52% (7 hours), 60% (10 days), 85% (14 days) and 96% (16 days) was seen. Urea is ultimately biodegradable according to this study. (ECHA) [KI Score = 2].

In an OECD Guideline 301 A (Ready Biodegradability DOC Die Away Test) study using read-across substance 1,3 dimethylurea, the biodegradation of urea was found to be 90-100% after 21 days (ECHA) [KI score = 1].

In a non-guideline study in soil, the main mode of degradation of urea was found to be enzymatic mineralisation to ammonia and bicarbonate (ECHA) [KI Score = 2].

In an OECD Guideline 304 A (Inherent Biodegradability in Soil) study, 64% degradation was observed in soil after 30 hours of incubation. (ECHA) [KI score = 2].

C. Environmental Distribution

A 30-day study found that the K_{oc} value for urea is 0.037 to 0.064 L/kg which indicates that it is unlikely to partition to organic matter in in soil (ECHA) [KI Score = 2]. If released to water, based on this K_{oc} value and high water solubility, urea is not expected to adsorb to suspended solids or sediments. Similarly, if released to soil, urea is expected to have very high mobility.

D. Bioaccumulation

Urea is not expected to bioaccumulate based on its low K_{ow} value. Additionally, urea is utilised by fish species as a nutrient and is excreted by some species as a product of protein catabolism (ECHA).

In a 6 to 72 hr bioaccumulation study using carp (*Cyprinus carpio*), the concentration of urea was found to be equally distributed between tissue and water during all time periods; thus, the bioconcentration factor (BCF) would be 1 for this species. In 3-day static-system tests using golden ide fish (*Leuciscus idus melanotus*), the BCF of urea was <10. According to a classification scheme, these BCF values suggest the potential for bioconcentration in aquatic organisms is low (PubChem).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Urea is of very low acute oral toxicity in the rat and mouse. Urea is a mild eye irritant. It is not a skin irritant and is very unlikely to be a skin sensitiser. No systemic toxicity was seen in

rats and mice exposed to urea in the diet. Urea is not genotoxic and is not carcinogenic. Developmental toxicity testing in rats dosed orally up to 1000 mg/kg bw/day did not result in adverse effects. There are no studies in animals showing clear evidence of reproductive effects.

B. Acute Toxicity

Oral

In an OECD Guideline 401 (Acute Oral Toxicity) study, urea was found to be of low acute oral toxicity. The LD_{50} of urea in Wistar rats was determined to be 14,300 and 1,500 mg/kg bw/day in male and females, respectively (ECHA) [KI score = 2].

In another study, mice were exposed to urea via oral gavage. The LD_{50} was determined to be 11,500 mg/kg bw/day and 13,000 mg/kg bw/day in male and female mice respectively (ECHA) [KI score = 2].

Inhalation

No data are available from acute inhalation toxicity. The substance is a non-volatile solid and is produced as crystals with a particle size of >100 um. There is therefore no potential for inhalation exposure. In addition, the substance has been demonstrated to be of very low toxicity by other routes of exposure (ECHA).

Dermal

No data were available.

C. Irritation

Skin

An OECD Guideline 404 (Acute Dermal Irritation / Corrosion) was conducted to determine the skin irritation potential of urea to New Zealand White rabbits. The rabbits were exposed to urea for 4 hours and were observed 72 hours after dressing removal. Urea was found to be non-irritating to the skin of rabbits (ECHA) [KI score = 1].

Eye

An OECD Guideline 405 (Acute Eye Irritation / Corrosion) primary eye irritation study was performed using Vienna White rabbits exposed to urea. Urea was determined to be mildly irritating to the eyes of Vienna White rabbits (ECHA) [KI Score = 2].

D. Sensitisation

No data were available. Urea is naturally present at relatively high concentrations in human skin (up to 1% by weight) and it is widely used in skin creams to treat dry and irritant skin conditions (ECHA). This substance is not considered to be a skin sensitiser.

E. Repeated Dose Toxicity

Oral

In an NCI screening study, C57BL mice and Fischer 344 rats were exposed to urea via their feed for 12 months followed by a 4-month recovery period. No evidence of toxicity was seen in this study at dose levels of up to 45000 ppm. Survival and bodyweights were unaffected by treatment. Gross and microscopic pathology did not reveal any treatment-related effects. It was concluded that urea is of very low chronic toxicity. Using default conversion factors, the dose level of 45000 ppm is calculated to be equivalent to approximately 2250 mg/kg bw/day in the rat and 6750 mg/kg bw/day in the mouse (ECHA) [KI score = 2].

Inhalation

No data were available.

Dermal

In a subacute (28-day) toxicity study Wistar rats were exposed to urea on their back skin (20 cm^2 in size). There was no dose dependent toxicity observed in this study. Bodyweights, food and water consumption were unaffected by treatment. Clinical chemistry, haematology and urinalysis parameters were comparable in all groups. There was no effect of treatment on organ weights or pathology (ECHA) [KI score = 2].

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on urea based are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Urea

Test System[1]	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (Bacterial Reverse Mutation Assay) S. typhimurium, other: TA98, TA100, TA1537	-	-	2	ECHA
OECD Guideline 471 (Bacterial Reverse Mutation Assay) S. typhimurium TA 1538 and S9 - liver of male Sprague-Dawley rats	-	-	2	ECHA
Alkaline elution/rat hepatocyte assay	-	-	2	ECHA
Rapid genotoxicity test measuring proportion of single to double stranded DNA breaks by alkaline unwinding and hydroxyapatite elution in mouse lymphoma cells	-	-	2	ECHA

*+, positive; -, negative.

In Vivo Studies

A positive result is reported in a mouse bone marrow assay of unconventional design, however this study is not considered to be reliable (ECHA).

G. Carcinogenicity

Oral

A 12-month carcinogenesis screening study was performed using Fischer 344 rats and C57BL mice were exposed to urea in the diet at concentrations of 4500, 9000 or 45000 ppm for 12 months. Five animals/sex/group were sacrificed at the end of the 365-day exposure period and a comprehensive list of tissues were investigated histopathologically; interim deaths were similarly investigated. All remaining animals were sacrified after the 4-month recovery period and investigated histopathologically. There were no signs of toxicity. A significant linear trend in the incidence of interstitial cell tumours was noted in male rats. The incidence was 21/50 in controls 27/48, 25/48 and 35/50 in the low, intermediate and high dose groups respectively. The authors did not consider this finding to be of biological significance as the background incidence of this tumour type is noted to be up to 100% in F344 rats. A significantly increased incidence of haematopoietic tumours (malignant lymphoma) was seen in female mice in the mid-dose group. The incidence of this finding was 10 -92 in controls; 7/43, 10/38 and 9/50 in low, mid and high dose group animals, respectively. There was no relationship to treatment in the absence of a dose-response relationship. The NOAEL was determined to be 45,000 ppm (4.5% in the diet). Using default conversion factors, the dose level of 45000 ppm is calculated to be equivalent to approximately 2250 mg/kg bw/day in the rat and 6750 mg/kg bw/day in the mouse (ECHA) [KI score = 2].

Inhalation

No studies are available.

Dermal

No studies are available.

H. Reproductive Toxicity

No studies are available. Large quantities of urea are formed naturally in the human body as a consequence of normal protein catabolism. Urea is shown to be essentially without toxicity in the available studies and no effects (organ weight, gross pathology, histopathology) were observed on the reproductive organs of rats and mice exposed to urea at very high dietary levels for 12 months (ECHA). The level of any primary, occupational or secondary exposure to urea is likely to be insignificant compared to the quantities (20-50 g/day) produced by normal metabolism and present at high concentrations in the blood. It is therefore considered that urea is very unlikely to be a reproductive toxin (ECHA).

I. Developmental Toxicity

An OECD Guideline 414 study (Prenatal Developmental Toxicity Study) was performed on CD rats exposed to urea via oral gavage for 22 days. The rats were dosed daily via oral gavage at dose levels of 100, 300, or 1,000 mg/kg-bw/day from the 6th to the 20th day of pregnancy. In the dams, there were no item-related effects on the maternal and reproductive parameters.

In the fetuses, there was also no test item-related influence on the prenatal fetal development and no malformations nor variations were noted during the macroscopic, skeletal and soft tissue examinations. In conclusion, the NOAEL was above 1000 mg Urea/kg bw/day for maternal developmental and foetal toxicity as well as for teratogenicity. It is considered extremely unlikely that occupational, primary or secondary exposure to urea will result in developmental toxicity as the levels of exposure will be insignificant compared to those present in the maternal and foetal circulation as a result of protein catabolism (ECHA) [Kl Score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for urea follow the methodology discussed in enHealth (2012). The approach used to develop drinking water guidance values is described in the Australian Drinking Water Guidelines (ADWG, 2021).

A. Non-Cancer

Oral

Developmental toxicity testing in rats dosed orally up to 1000 mg/kg bw/day did not result in adverse effects. This NOAEL will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / (UF_A x UF_H x UF_L x UF_{Sub} x UF_D)

Where:

UF_A (interspecies variability) = 10
UF_H (intraspecies variability) = 10
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 10
UF_D (database uncertainty) = 1
Oral RfD = 1000/(10 x 10 x 1 x 1 x 10 x 1) = 1000/1000 = 1 mg/kg/day.

Drinking water guidance value

Drinking water guidance value = (animal dose) x (human weight) x (proportion of intake from water) / (volume of water consumed) x (safety factor)

Using the oral RfD,

Drinking water guidance value = (oral RfD) x (human weight) x (proportion of water consumed) / (volume of water consumed)

Where:

Human weight = 70 kg (ADWG, 2021)
Proportion of water consumed = 10% (ADWG, 2021)
Volume of water consumed = 2L (ADWG, 2021)
Drinking water guidance value = (1 x 70 x 0.1)/2 = 3.5 mg/L

B. Cancer

Urea is not considered a carcinogen. Thus, a cancer reference value will not be calculated for this substance.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Urea does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Urea is of very low acute toxicity to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on urea.

Table 3: Acute Aquatic Toxicity Studies on Urea

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Golden orfe fish	48-hour LC_{50}	10,000	2	ECHA
Tilapia mossambica	96-hour EC_{50}	>20,000	2	ECHA
Barilius barna	96-hour EC_{50}	>9100	2	ECHA
Daphnia magna	24-hour EC_{50}	>10 000	2	ECHA
Helisoma trivolvis	48-hour LC_{50}	13,477	2	ECHA
Biomphalaria havanensis	48-hour LC_{50}	21,412	2	ECHA

Chronic Studies

No chronic aquatic toxicity studies are available for fish or invertebrates. Urea is of low toxicity to fish since it is a normal product of protein catabolism and fish have evolved effective excretion mechanisms. In addition to this, microorganisms incorporate urea in the nitrogen cycle (ECHA).

The 192-hour and 7-day study of the toxicity threshold for *Scenedesmus quadricauda* (green algae) is > 10,000 mg/L (ECHA) [KI score = 2]. The 192-hour toxicity threshold for *Microcystis aeruginosa* (blue-green algae) is 47 mg/L (ECHA) [KI score = 2].

C. Terrestrial Toxicity

No toxicity data are available.

D. Calculation of PNEC

The PNEC calculations for urea follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. Acute E(L)C_{50} values are available for fish (9,100 mg/L) and invertebrates (>10,000 mg/L). Toxicity threshold values from long-term studies are available for algae (47 mg/L). On the basis that the data consists of short-term results from two trophic levels and long-term results from one trophic levels, an assessment factor of 50 has been applied to the chronic threshold value of 47 mg/L for algae (most sensitive species). Therefore, the $PNEC_{water}$ is 0.94 mg/L.

PNEC sediment

Urea is expected to degrade rapidly in the environment. Moreover, based on the low K_{ow} and log K_{oc} values, the substance is not expected to bind substantially to sediment. Therefore, a PNEC for sediment has not been calculated.

PNEC soil

Urea is expected to degrade rapidly in the environment. Moreover, based on the low K_{ow} and K_{oc} values, the substance is not expected to bind substantially to soil. Therefore, a PNEC for soil has not been calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Urea is readily biodegradable in the environment based on its low log K_{ow} and K_{oc} values. Thus, it does not meet the screening criteria for persistence.

The estimated log K_{ow} is equal to -1.73. Measured bioconcentration factors are less than 10. Based on these values, urea has a low potential for bioaccumulation. Therefore, urea does not meet the screening criterion for bioaccumulation.

The toxicity threshold values from chronic aquatic toxicity studies are > 0.1 mg/L. The acute E(L)C_{50} values for fish and invertebrates are > 1 mg/L. Thus, urea does not meet the criteria for toxicity.

The overall conclusion is that urea is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Signal word

None

C. Pictogram

None

X. SAFETY AND HANDLING

Please refer to the product SDS for additional information and confirmation of the information provided herein.

A. First Aid

Eye Contact

Immediately flush open eyes with plenty of water for at least 15 minutes. Remove contacts, if present and easy to do. Get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact

For minor skin contact, avoid spreading material on unaffected skin. Remove and isolate contaminated clothing. Wash the contaminated area of body with soap and fresh water. Get medical attention. Launder contaminated clothing before reuse.

Inhalation

Move person to fresh air. Administer oxygen if breathing is difficult. Do not use mouth-to-mouth method if victim inhaled the substance; give artificial respiration with the air of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Give artificial respiration if victim is not breathing. Get medical attention immediately.

Ingestion

Do not induce vomiting. Get medical attention immediately.

Notes to Physician

All treatments should be based on observed signs and symptoms of distress in the patient.

B. Fire Fighting Information

Extinguishing Media

Use water spray or fog, foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: ammonia, carbon dioxide, carbon monoxide.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions

Isolate area. Keep unnecessary and unprotected personnel from entering the area. Use personal protective clothing. Ensure adequate ventilation. Wear respiratory protection if ventilation is inadequate. Do not breath mist, vapours or spray. Avoid contact with skin, eyes and clothing. Eliminate all sources of ignition.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Eliminate all sources of ignition. Pick up with suitable absorbent material and transfer to a container for chemical waste. For large amounts: dike spillage and pump off product into container for chemical waste. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling

Keep away from heat, sparks and flame. Avoid contact with eyes, skin and clothing. Avoid breathing vapour. Wash thoroughly after handling. Keep container closed. Use with adequate ventilation.

Storage

Keep container tightly closed. Store away from heat and light.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for urea.

Engineering Controls

Good general ventilation should be used. Ventilation rates should be matched to conditions. If applicable, use process enclosures, local exhaust ventilation, or other engineering controls to maintain airborne levels below recommended exposure limits. If exposure limits have not been established, maintain airborne levels to an acceptable level.

Personal Protection Equipment

Respiratory Protection: If workers are exposed to concentrations above the exposure limit, they must use appropriate, certified respirators. If there are no applicable exposure limit requirements or guidelines, use an approved respirator. Selection of air-purifying or positive pressure supplied-air will depend on the specific operation and the potential airborne concentration of the product. For emergency conditions, use an approved positive-pressure

self-contained breathing apparatus. The following should be effective types of air-purifying respirators: organic vapour cartridge with a particulate pre-filter.

Hand Protection: Use gloves chemically resistant to this material. Consult the SDS for appropriate glove barrier materials.

Skin Protection: Use protective clothing chemically resistant to the material. Selection of specific items such as face shield, boots, apron or full body suit will depend on the task.

Eye Protection: Use chemical goggles.

Other Precautions: Wash hands, forearms and face thoroughly after handling chemical products; before eating, smoking, and using the lavatory; and at the end of the working period. Appropriate techniques should be used to remove potentially contaminated clothing. Wash contaminated clothing before reusing. Ensure that eyewash stations and safety showers are close to the workstation location.

F. Transport Information

UN number: none

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations.

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

ADWG. (2021). National Water Quality Management Strategy. Australian Drinking Water Guidelines, Section 6, Australian Government, National Health and Medical Research Council, Natural Resource Management Ministerial Council.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

ECETOC. (2000). European Centre for Ecotoxicology and Toxicology of Chemicals The Role of Bioaccumulation in Environmental Risk Assessment: The Aquatic Environment and the Related Food Web. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Technical Report No. 68, Brussels.

ECHA. ECHA REACH database: http://echa.europa.eu/information-on-chemicals/registered-substances

enHealth Human Risk Assessment [HHRA]. (2012). Environmental Health Risk Assessment, Guidelines for Assessing Human Health Risks from Environmental Hazards. Office of Health Protection of the Australian Government Department of Health.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

PubChem. National Institutes of Health. National Library of Medicine National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/

VINYLIDENE CHLORIDE/METHYLACRYLATE COPOLYMER

This dossier on vinylidene chloride/methylacrylate copolymer presents the most critical studies pertinent to the risk assessment of vinylidene chloride/methylacrylate copolymer in its use in coal seam gas extraction activities. It does not represent an exhaustive or critical review of all available data. Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. CHEMICAL NAME AND IDENTIFICATION

Chemical Name (IUPAC): 1,1-dichloroethene; methyl prop-2-enoate

CAS RN: [redacted]

Molecular formula: $(C_2H_2Cl_2)_x(C_4H_6O_2)_y$ [This substance is a polymer.]

Molecular weight: 183.03 g/mol (monomer); polymer assumed to be > 1,000 g/mol (NICNAS, 2017)

Synonyms: vinylidene chloride/methylacrylate copolymer; methyl acrylate-vinylidene chloride copolymer; 2-propenoic acid, methyl ester, polymer with 1,1-dichloroethene

SMILES: COC(=O)C=C.C=C(Cl)Cl

II. PHYSICO AND CHEMICAL PROPERTIES

No chemical-specific information is available. Vinylidene chloride/methylacrylate copolymer is a non-ionic synthetic polymer. It is formed by addition polymerisation, which typically affords high molecular weight polymers with stable saturated carbon-chain backbones. Water solubility is expected to be low based on the predominantly hydrophobic structure of the substance.

As noted, no information is available regarding the molecular weight and the percentage of low molecular weight (LMW) species in this polymer. However, synthetic addition polymers of this type are generally high to very high molecular weight species. It is assumed for this polymer that the number average molecular weight (NAMW) is greater than 1,000 daltons (Da) with an insignificant percentage of LMW species (DoEE, 2017).

III. ENVIRONMENTAL FATE PROPERTIES

No experimental data are available for vinylidene chloride/methylacrylate copolymer.

Polymers with a molecular weight greater than 1,000 g/mol generally have a negligible vapour pressure, which indicates that the chemical is likely to exist solely as particulate matter in the atmosphere. As particulate matter, atmospheric oxidation is not expected to be a significant route of environmental removal. Likewise, volatilisation from water or moist soil is not expected to occur at an appreciable rate (USEPA, 2013).

Non-ionic polymers such as vinylidene chloride/methylacrylate copolymer are not expected to be highly soluble in water based on its predominantly hydrophobic structure. If

discharged to the aquatic environment, this polymer is expected to partition to soil or sediment. It is not expected to be highly mobile if released to the soil compartment (Boethling and Nabholz, 1997).

Synthetic non-ionic polymers are not expected to undergo rapid degradation (NICNAS, 2017). However, the high molecular weight of the polymer is expected to preclude or minimise bioaccumulation. Polymers with a number average molecular weight (NAMW) greater than 1,000 g/mol cannot cross biological membranes (Boethling and Nabholz, 1997).

IV. HUMAN HEALTH HAZARD ASSESSMENT

These polymers are considered chemically and biologically inert. As such, no toxicity studies have been conducted on this material.

NICNAS has assessed vinylidene chloride/methylacrylate copolymer in an IMAP Tier 1 assessment and considers it a polymer of low concern[1]. In addition, based on an assessment of human health and environmental hazards, NICNAS also identified vinylidene chloride/methylacrylate copolymer as a chemical of low concern to the environment (NICNAS, 2017 and DoEE, 2017). Chemicals of low concern are unlikely to have adverse environmental effects or be a concern to human health if they are released to the environment from coal seam gas operations.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

No toxicological reference values or drinking water guidance values were developed.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Vinylidene chloride/methylacrylate copolymer does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Aquatic Toxicity

No ecotoxicity data was identified for vinylidene chloride/methylacrylate copolymer. Information on Non-Ionic Polymers Group (DoEE, 2017) is provided below.

> *"Non-ionic polymers with low water solubility, such as the methyl acrylate-vinylidene chloride copolymer, generally have low toxicity to aquatic life (Beothling and Nabholz 1997). Insoluble non-ionic polymers have low bioavailability and their adverse effects result from physical. effects such as*

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

occlusion of respiratory organs (e.g. the gills of fish). These adverse effects occur only at very high loading levels in water (Beothling and Nabholz 1997).

Water soluble or dispersible non-ionic polymers, such as polyacrylamide, are also typically of low concern for ecotoxicity. Non-ionic polymers with NAMW greater than 1 000 cannot be absorbed across biological membranes in aquatic organisms, and therefore toxicity only occurs through indirect effects such as chelation of essential nutrients (Beothling and Nabholz 1997). However, the structure of polyacrylamide suggests that it will have low potential to act by this mode of action. This is further supported by median effective concentration (EC50) and median lethal concentration (LC50) values available for other water soluble or dispersible non-ionic polymers, which are greater than 100 mg/L (Beothling and Nabholz 1997).

Water soluble or dispersible polymers with NAMW less than 1 000 Da, or significant levels of LMW substances and trapped monomers, are of potential concern because of their increased bioavailability. However, this assessment was conducted assuming that the polymers in this group have NAMW greater than 1 000 Da and the percentage of LMW species is low."

B. Terrestrial Toxicity

No data are available.

C. Calculation of PNEC

No PNEC values were calculated.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

The methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment is based on the Australian and EU REACH Criteria methodology (DEWHA, 2009; ECHA, 2008).

Vinylidene chloride/methylacrylate copolymer is not expected to be biodegradable. Thus, it meets the criteria for persistence.

Vinylidene chloride/methylacrylate copolymer is not expected to bioaccumulate. Polymers with a NAMW greater than 1,000 g/mol cannot cross biological membranes (Boethling and Nabholz, 1997). Thus, it does not meet the screening criteria for bioaccumulation.

No aquatic toxicity studies are available for vinylidene chloride/methylacrylate copolymer. It is expected to be a low concern of toxicity to aquatic organisms because of its low potential for bioavailability. Thus, it does not meet the screening criteria for toxicity.

The overall conclusion is that vinylidene chloride/methylacrylate copolymer is not a PBT substance.

IX. CLASSIFICATION AND LABELING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictograms

None

X. SAFETY AND HANDLING

A. First Aid

Eye Contact

In case of contact, immediately flush eyes with plenty of water for at least 5 minutes. If symptoms persist, seek medical advice.

Skin Contact

Wash thoroughly with soap and water.

Inhalation

If inhaled, remove from area to fresh air. Get medical attention if respiratory irritation develops or if breathing becomes difficult.

Ingestion

Rinse mouth with water and then drink plenty of water. Never give anything by mouth to an unconscious person. If symptoms develop, seek medical advice.

B. Fire Fighting Information

Extinguishing Media

Water fog, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Burning produces harmful and toxic fumes. Heat from fire may melt, decompose polymer and generate flammable vapours. Combustion products may include: carbon oxides, hydrogen chlorine gas.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Potential combustible dust hazard. Avoid generating dust. Creates dangerous slipping hazard on any hard smooth surface.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Scoop up and remove.

D. Storage and Handling

General Handling

Avoid dust accumulation in enclosed space. Avoid generating dust; fine dust dispersed in air in sufficient concentrations, and in the presence of an ignition source is a potential dust explosion hazard. Electrostatic charge may build up during handling. Equipment, container and metal containers should be grounded and bonded.

Storage

Keep container tightly closed and in a dry and well-ventilated place. Keep in a cool place. Use adequate ventilation to avoid excessive dust accumulation. Store away from excessive heat and away from strong oxidising agents. Take measures to prevent the build-up of electrostatic charge.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure limit for vinylidene chloride/methylacrylate copolymer.

Engineering Controls

Use in a well-ventilated area. Avoid creating dust. Take precautionary measures against static charge.

Personal Protection Equipment

Respiratory Protection: Not normally needed; however, if significant exposures are possible, then the following respirator is recommended: Dust/mist respirator.

Hand Protection: Normal work gloves.

Skin Protection: Normal work coveralls.

Eye Protection: Wear safety glasses or goggles to protect against exposure.

Other Precautions: Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Vinylidene chloride/methylacrylate copolymer is not considered hazardous for purposes of transportation by road or rail. An Australian Dangerous Goods code is not required.

XI. DISPOSAL MANAGEMENT

Disposal should be in accordance with all local, state and federal regulations

XII. REGULATORY INFORMATION

Australian AICS Inventory: Listed.

XIII. REFERENCES

Boethling, R.S. and Nabholz, J.V. (1997). 'Environmental assessment of polymers under the US Toxic Substances Control Act', in Hamilton J and Sutcliffe R (eds), Ecological assessment of polymers: strategies for product stewardship and regulatory programs, Van Nostrand Reinhold, New York, USA, pp 187-234.

Department of the Environment, Water, Heritage and the Arts [DEWHA]. (2009). Environmental risk assessment guidance manual for industrial chemicals, Department of the Environment, Water, Heritage and the Arts, Commonwealth of Australia.

Department of the Environment and Energy [DoEE]. (2017). Environmental risks associated with surface handling of chemicals used in coal seam gas extraction in Australia, Project report Appendices A, B, C, D, F, and G prepared by the Chemicals and Biotechnology Assessments Section (CBAS) in the Department of the Environment and Energy as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

European Chemicals Agency [ECHA]. (2008). Guidance on Information Requirements and Chemical Safety Assessment, Chapter R11: PBT Assessment, European Chemicals Agency, Helsinki, Finland.

Klimisch, H.J., Andreae, M., and Tillmann, U. (1997). A systematic approach for evaluating the quality of experimental and toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 25:1-5.

NICNAS (2017), Chemicals of low concern for human health based on an initial assessment of hazards, Project report prepared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as part of the National Assessment of Chemicals Associated with Coal Seam Gas Extraction in Australia, Commonwealth of Australia, Canberra.

United States Environmental Protection Agency (USEPA). (2013). Interpretive Assistance Document for Assessment of Polymers: Sustainable Futures Summary Assessment. June 2013.