Appendix C Risk Dossiers

Appendix C.1 March 2020 Risk Dossiers

ETHYL HEXANOL
[2-ETHYLHEXANOL]

This dossier on ethyl hexanol (designated in this dossier as 2-ethylhexanol) presents the most critical studies pertinent to the risk assessment of ethyl hexanol 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-Ethylhexan-1-ol

CAS RN: [redacted]

Molecular formula: $C_8H_{18}O$

Molecular weight: 130.23

Synonyms: 2-Ethylhexanol, 2-ethylhexan-1-ol, 2-ethyl-*n*-hexyl alcohol

SMILES: CCCCC(CC)CO

II. PHYSICAL AND CHEMICAL PROPERTIES

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

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Clear and colourless liquid	2	ECHA
Melting Point	-89°C	2	ECHA
Boiling Point	184°C; 186°C	2	ECHA
Density	0.833 g/cm^3 @ 20°C	2	ECHA
Vapor Pressure	93 Pa @ 20°C 120 Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})	2.9	2	ECHA
Water Solubility	0.9 g/L	2	ECHA

Property	Value	Klimisch score	Reference
Flash Point	77°C; 75°C @ 1013 hPa	2	ECHA
Auto flammability	280°C	1	ECHA
Viscosity	9.7 mPa s @ 20°C 4.3 mPa s @ 40°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

2-Ethylhexanol is readily biodegradable. It is not expected to bioaccumulate. 2-Ethylhexanol has a low tendency to bind to soil or sediment.

B. Biodegradation

2-Ethylhexanol was considered readily biodegradable in an OECD TG 301C test. After two weeks, degradation was 79 to 99.9% measured by O_2 consumption, 100% degradation measured by TOC removal, and 100% degradation as determined by test material analysis (ECHA) [Kl score = 1]. 2-Ethylhexanol was inherently biodegradable in a Zahn-Wellens test (OECD TG 302B), with >95% degradation within five days (ECHA) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for 2-ethylhexanol. Using KOCWIN in EPISUITE™ (EPA, 2017), the estimated K_{oc} value from log K_{ow} is 105.6 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 35.28 L/kg.

D. Bioaccumulation

No bioconcentration studies have been conducted on 2-ethylhexanol. Per calculations using EPISUITE™ (EPA, 2017), the log BCF via the Arnot-Gobas method for upper trophic level organisms is 1.543 (BCF = 34.88). Thus, 2-Ethylhexanol is not expected to bioaccumulate which is consistent with its experimental log K_{ow} of 2.9 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

2-Ethylhexanol has low acute toxicity by the oral route; virtually no acute toxicity by the dermal route; and has moderate acute toxicity by the inhalation route. It is a skin and eye irritant. No skin sensitisation studies on 2-ethylhexanol were located. Repeated exposure studies in rodents caused liver effects (*i.e.*, peroxisomal proliferation); these effects are not thought to

occur in humans. 2-ethylhexanol is not genotoxic. Lifetime oral studies in rats and mice showed no carcinogenic effects. 2-Ethylhexanol 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 2-ethylhexanol by the oral, dermal, or inhalation routes.

B. Acute Toxicity

The oral LD_{50} values in rats are; 2,047 mg/kg (Smyth et al., 1969); 3,290 mg/kg (Schmidt et al., 1973); and 3,730 mg/kg (Scala and Burtis, 1973). [Kl. scores = 2]

The 4-hour whole body inhalation LC_{50} in rats is >0.89 mg/L as vapor; no deaths were reported (ECHA). [Kl. score 2]

The dermal LD_{50} values in rats and rabbits are >3,000 and >2,600 mg/kg, respectively. There were no deaths in either study (ECHA). [Kl. score = 1 and 2, respectively]

C. Irritation

Application of 0.5 ml 2-ethylhexanol to the skin of rabbits for 4 hours under semi-occlusive conditions was severely irritating (ECHA). [Kl. score = 1]

Instillation of 0.1 ml 2-ethylhexanol into the eyes of rabbits was irritating. The mean of the 24, 48, and 72 hours scores were: 1.44 for corneal opacity; 0.89 for iridial lesions; 2.56 for conjunctival redness; and 0.78 for chemosis. The effects were fully reversible within 21 days (ECHA). [Kl. score = 1]

D. Sensitization

No studies are available.

E. Repeated Dose Toxicity

<u>Oral</u>
Male F344 rats were given in their feed 0 or 2% 2-ethylhexanol for three weeks. The objective of this study was to investigate the liver effects of 2-ethylhexanol on hepatic peroxisome proliferation and peroxisome enzymes. There were no significant treatment-related effects on body weight, but liver weights relative to body weights, catalase activity, liver carnitine acetyltransferase activity, and hepatic peroxisome proliferation (as determined by electron microscopy) were significantly increased. There was also a treatment-related decrease on serum levels of cholesterol and triglycerides. The LOAEL is 2% in the diet; a NOAEL was not established (Moody and Reddy, 1978). [Kl. score = 2]

Male and female F344 rats were dosed with 0, 25, 125, 250, or 500 mg/kg 2-ethylhexanol (in an aqueous suspension with an emulsifier) 5 days/week for 13 weeks. Body weights were decreased in the 500 mg/kg group (both sexes). Relative liver, kidney, and stomach weights were increased in the 250 and 500 mg/kg groups. Gross pathological examination showed forestomach lesions in the 500 mg/kg animals. Palmitoyl CoA oxidase activity was increased in

the livers of the 500 mg/kg animals (both sexes). The NOAEL for systemic toxicity is 125 mg/kg-day (Astill *et al.*, 1996a). [Kl score = 1]

Male and female B6C3F_1 mice were dosed with 0, 25, 125, 250, or 500 mg/kg 2-ethylhexanol (in an aqueous suspension with an emulsifier) 5 days/week for 13 weeks. Treatment-related effects included increased stomach weights (≥250 mg/kg) and increased liver weights (125 and 250 mg/kg). Treatment-related histopathological changes were limited to acanthosis (diffuse hypertrophy or thickening of the prickle cell layer) of the forestomach mucosa in the 500 mg/kg animals (both sexes). No increases in palmitoyl CoA oxidase activity were seen in the livers of male and female mice at any dose level. The NOAEL for systemic toxicity is 500 mg/kg-day (Astill *et al.*, 1996). [Kl. score = 1]

Male and female F344 rats were dosed by oral gavage with 0, 50, 150, or 500 mg/kg 2-ethylhexanol (in 0.0005% Cremophor EL, a polyoxyl-35 castor oil) 5 days/week for two years. A water control was also included in the study. There were no differences of biological importance between the vehicle control and a water control group. Reduced body weight gain occurred in the 150 and 500 mg/kg groups with an increased incidence of lethargy and unkemptness. There were dose-related increases in relative liver, stomach, brain, kidney, and testis weights at study termination. Mortality was significantly increased among the 500 mg/kg females, and there was marked aspiration-induced bronchopneumonia in the high-dose animals. Gross and histopathological non-neoplastic changes were similar between treated and control groups. The NOAEL is 50 mg/kg-day (Astrill *et al.*, 1996b). [Kl. score = 1]

Male and female B6C3F_1 mice were dosed by oral gavage with 0, 50, 200, or 750 mg/kg 2-ethylhexanol (in 0.0005% Cremophor EL, a polyoxyl-35 castor oil) 5 days/week for two years. A water control was also included in the study. There were no differences of biological importance between the vehicle control and a water control group that was also included in the study. All treatment-related effects occurred only in the 750 mg/kg animals (both sexes). Mortality was increased and body weight gain was reduced, and there was a slight increase in nonneoplastic focal hyperplasia in the forestomach. Relative liver and stomach weights occurred in the 750 mg/kg animals (both sexes). The NOAEL is 200 mg/kg-day (Astill *et al.*, 1996b). [Kl. score = 1]

Inhalation

Male and female Wistar rats were exposed by inhalation (whole body exposure) to 0, 15, 40, or 120 ppm 2-ethylhexanol 6 hours/day, 5 days/week for 13 weeks. No adverse effects including cyanide-insensitive palmitoyl CoA oxidation (a parameter for hepatic peroxisome proliferation) were observed. The NOAEC for this study is 120 ppm (ECHA). [Kl. score = 1]

Dermal

No adequately or reliable studies are available.

F. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on 2-ethylhexanol are presented below in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on 2-Ethylhexanol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	1	ECHA
Mammalian cell gene mutation (CHO cells/HGPRT)	-	-	1	ECHA
Mammalian cell gene mutation (L5178Y mouse lymphoma cells)	-	-	1	ECHA
Chromosomal aberration (CHO cells)	-	-	2	ECHA
Sister chromatid exchange (CHO cells)	-	-	2	ECHA

*+, positive; -, negative

In Vivo Studies

Male and female B6C3F$_1$ mice were given 456 mg/kg 2-ethylhexanol either as single intraperitoneal injection or two intraperitoneal injections on two consecutive days. There were no increases in micronuclei in the bone marrow polychromatic erythrocytes under either dosing regimen (ECHA). [Kl. score = 2]

G. Carcinogenicity

Oral

Male and female F344 rats were dosed by oral gavage with 0, 50, 150, or 500 mg/kg 2-ethylhexanol (in 0.0005% Cremophor EL, a polyoxyl-35 castor oil) 5 days/week for two years. A water control was also included in the study. There was no evidence of treatment-related neoplastic lesions in any of the exposed groups (Astill *et al.*, 1996b). [Kl. score = 1]

Male and female F344 rats were dosed by oral gavage with 0, 50, 200, or 750 mg/kg 2-ethylhexanol (in 0.0005% Cremophor EL, a polyoxyl-35 castor oil) 5 days/week for two years. A water control was also included in the study. There was a 12% incidence of hepatic basophilic foci and an 18% incidence of liver carcinomas in the 750 mg/kg male mice, which was not statistically significant compared with either control by Fisher's exact test. There was a 12% incidence of hepatic basophilic foci and a 10% incidence of liver carcinomas in the 750 mg/kg female mice, with was statistically significant compared with the vehicle but not with the water controls by Fisher's exact test. There was a weak trend in hepatocellular carcinoma incidence in the 750 mg/kg dose group, which may have been associated with toxicity. The time-adjusted incidence of hepatocellular carcinomas in male mice (18.8%) was within the historical control range at the testing facility (0–22%), but was outside the normal range of 0–2% for the female mice (13.1%) (Astill *et al.*, 1996b). [Kl. score = 1]

Inhalation
No studies are available.

H. Reproductive Toxicity

There are no reproductive toxicity studies on 2-ethylhexanol. However, a two-generation reproductive toxicity study has been conducted on the surrogate di (2-ethylhexyl) terephthalate at dietary doses of 0, 3,000, 6,000, or 10,000 ppm. Di (2-ethylhexyl) terephthalate is expected to be hydrolyzed in the body by carboxylesterases to 2-ethylhexanol and terephthalic acid. There were no adverse effects on reproductive parameters that included estrous cyclicity, gonadal functions, spermatogenic endpoints (motility, morphology, counts), mating behavior and performance, conception, gestation and parturition, and fertility in general. There were no adverse effects noted in the reproductive organs. Reduced postnatal pup weights (potentially related to maternal toxicity) were observed for both sexes in both generations in the 6,000 and 10,000 ppm dose groups. The NOAELs for reproductive and developmental toxicity are 10,000 ppm (the highest dose tested) and 3,000 ppm, respectively (Faber *et al.*, 2007; ECHA). [Kl. score = 2]

I. Developmental Toxicity

Oral
Pregnant female CD-1 mice were given 2-ethylhexanol in their diet by microencapsulation at 0, 0.009, 0.03, or 0.09% on gestational days 0 to 17. The calculated consumption of 2-ethylhexanol based on food consumption was 0, 17, 59, and 191 mg/kg-day, respectively. No maternal or developmental toxicity was observed. The NOAEL for maternal and developmental toxicity is 191 mg/kg-day (ECHA). [Kl. score = 1]

Inhalation
Pregnant female SD rats were exposed by inhalation to 0 or 850 mg/m^3 (approximately 190 ppm) 2-ethylhexanol 7 hours/day during gestational days 1 to 19. The inhalation exposure was considered to be the highest attainable vapor concentration. The only effect seen in the dams was a slight reduction in feed consumption. No developmental toxicity was observed. The NOAEC for maternal and developmental toxicity is 850 mg/m^3 (Nelson *et al.*, 1989; ECHA).

Dermal
Pregnant female F344 rats were given dermal applications of 0, 252, 840, or 2,520 mg/kg 2-ethylhexanol 6 hours/day during gestational days 6 to 15. The only effects seen in the dams were reduced body weight gain in the high-dose group and local skin irritation in the mid- and high-dose groups. No developmental toxicity was observed. The NOAELs for maternal (systemic) and developmental toxicity were 840 and 2,520 mg/kg-day, respectively (Tyl *et al.*, 1992).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for 2-ethylhexanol 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

Two-year chronic studies have been conducted in rats and mice given oral gavage doses of 2-ethylhexanol. 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 2-ethylhexanol. 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
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 = 0.5 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 = (0.5 x 70 x 0.1)/2 = 1.75 mg/L

B. Cancer

2-Ethylhexanol was not carcinogenic to rats or mice in chronic oral studies. Therefore, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

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

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

2-Ethylhexanol is moderately toxic to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

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

Table 3: Acute Aquatic Toxicity Studies on 2-Ethylhexanol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Fathead minnow	96-h LC_{50}	28.2	1	ECHA
Golden Orfe	96-h LC_{50}	17.1	1	ECHA
Daphnia magna	48-h EC_{50}	39	2	ECHA
Scenedesmus subspicatus	72-h EC_{50} EC_{10}	11.5 (biomass) 16.6 (growth rate) 3.2 (biomass) 5.3 (growth rate)	2	ECHA

Chronic Studies

The 72-hour EC_{10} from an algal study using *Scenedesmus subspicatus* was 3.2 and 5.3 mg/L, based on biomass and growth rate, respectively (ECHA). [Kl. score = 2]

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for 2-ethylhexanol 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 (17.1 mg/L), invertebrates (39 mg/L), and plants (11.5 mg/L). 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 E(L)C_{50} value of 11.5 mg/L for algae. The $PNEC_{aquatic}$ is 0.012 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 0.027 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (2.83/1280) \times 1000 \times 0.012$
$= 0.019$

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]

$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 4.22/1000 \times 2400]$
$= 2.83$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$
$= 105.6 \times 0.04$
$= 4.22$

Where:
K_{oc} = organic carbon normalized distribution coefficient (L/kg). The K_{oc} for 2-ethylhexanol calculated from EPISUITE™ using log K_{ow} is 105.6 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 0.017 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (2.11/1500) \times 1000 \times 0.012$
$= 0.017$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)

BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
= 105.6 x 0.02
= 2.11

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for 2-ethylhexanol calculated from EPISUITE™ using log K_{ow} is 105.6 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).

2-Ethylhexanol is readily biodegradable; thus it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of 2.9, 2-ethylhexanol does not meet the screening criteria for bioaccumulation.

The 72-hour EC_{10} from an algal study on 2-ethylhexanol is >0.1 mg/L. The acute E(L)C_{50} for 2-ethylhexanol in fish, invertebrates and algae are >1 mg/L. Thus, 2-ethylhexanol does not meet the screening criteria for toxicity.

Therefore, 2-ethylhexanol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable Liquid Category 4
Acute Toxicity Category 4 [inhalation]
Skin Irritant Category 2
Eye Irritant Category 2
STOT Single Exposure Category 3 [respiratory irritation]

[Aquatic Acute Category 3]

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. 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, vapors, 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 2-ethylhexanol.

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 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

2-Ethylhexanol 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

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ACETALDEHYDE
[ETHANAL]

This dossier on acetaldehyde presents the most critical studies pertinent to the risk assessment of acetaldehyde 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Ethanal

CAS RN: [redacted]

Molecular formula: C2H4O

Molecular weight: 44.05

Synonyms: Acetic aldehyde, ethyl aldehyde,

SMILES: CC=O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Acetaldehyde

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colorless, pungent liquid	1	ECHA
Melting point	-123.5°C	2	ECHA
Boiling point	20.2°C	2	ECHA
Density	0.785 g/cm^3 @ 18°C	2	ECHA
Vapor pressure	120.2 kPa @ 25°C	2	ECHA
Partition coefficient (log	-0.13 (QSAR)	2	EPA, 2019

Property	Value	Klimisch score	Reference
K_{ow})			
Water solubility	Miscible	2	ECHA
Flash point	-40°C	2	ECHA
Auto flammability	175°C	2	ECHA
Flammability	4% Lower explosion limit, 60% upper explosion limit	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Acetaldehyde is readily biodegradable and not expected to bioaccumulate. Regarding the adsorption coefficient of acetaldehyde, "it is not possible to calculate log of this capacity factor or log Koc." (ECHA).

B. Biodegradation

Acetaldehyde is readily biodegradable. In an OECD 301 C (MITI-I) test, degradation was 80% (BOD demand) and 93% (TOC removal) after 14 days (ECHA) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for acetaldehyde. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value from log K_{ow} is 3.219 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 1 L/kg. Based on the Kow method employed in EPISUITE, Log Koc is 0.508 (EPA, 2019).

D. Bioaccumulation

There are no bioaccumulation studies on acetaldehyde. Acetaldehyde is not expected to bioaccumulate based on a log K_{ow} of -0.17 (EPA, 2019). Consistent with the low Kow, Log BCF using the Arnot-Gobas method for the upper trophic level is -0.033 (BCF = 0.9265) (EPA, 2019).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Acetaldehyde is moderately acutely toxic by the oral route and has low acute toxicity by inhalation and dermal routes. It is a skin, eye and respiratory tract irritant, but is not considered a sensitizer for skin. Based on the available data, the chemical is not considered to cause serious health effects from repeated oral or inhalation exposure; there are no data for dermal exposure. Acetaldehyde is considered genotoxic by National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Several studies for gene mutation, chromosomal damage and sister chromatid exchanges induced by acetaldehyde were reported. Although acetaldehyde is genotoxic in vitro, inducing gene mutations, clastogenic effects, and sister-chromatid exchanges (SCEs) in mammalian cells in the absence of exogenous metabolic activation, negative results were reported in adequate tests on Salmonella. There is indirect evidence from in vitro and in vivo studies to suggest that acetaldehyde can induce protein-DNA and DNA-DNA cross-links. However, ECHA does not classify acetaldehyde as genotoxic. There is limited evidence for carcinogenicity, but it is considered carcinogenic. Increased incidences of tumours have been observed in inhalation studies on rats and hamsters exposed to acetaldehyde. In rats, there were dose-related increases in nasal adenocarcinomas and squamous cell carcinomas (significant at all doses). However, in hamsters, increases in nasal and laryngeal carcinomas were non-significant. All concentrations of acetaldehyde administered in the studies induced chronic tissue damage in the respiratory tract. Acetaldehyde is not considered to cause reproductive or developmental harm.

B. Acute Toxicity

Oral

Based on the available data, acetaldehyde is considered to have moderate acute oral toxicity, warranting hazard classification (see Recommendation section). Median oral lethal dose (LD50) values in rats were between 660 and 1930 mg/kg bw. The oral LD50 value in mice was 1230 mg/kg bw (SCCS, 2012). According to this value acetaldehyde is harmful if swallowed. Nevertheless, the observations from the more relevant inhalation route indicate that the systemic toxicity of acetaldehyde is low and that effects other than systemic might have contributed to the lethality after oral exposure of rats. It is reasonable to follow the current EU legal classification that does not classify acetaldehyde as acutely toxic after oral exposure.

Dermal

The chemical was reported to have low acute toxicity via the dermal route (LD50 in rabbits of 3540 mg/kg bw) (SCCS, 2012) and greater than 5,000 mg/kg bw (RIFM, 1976). Overall, the dermal route is of minor importance due to the volatility of acetaldehyde at room temperature.

Inhalation

The chemical was reported to have low acute toxicity via inhalation (median lethal concentration (LC50) in rats has been calculated as 24,040 mg/m3 (13,300 ppm)) (REACH). A 4-hour inhalation toxicity study was conducted with exposure levels of

10,436 ppm, 12,673 ppm, 15,683 ppm and 16,801 ppm. The experimental study was similar to the method described in OECD Test Guideline (TG) 403. Clinical signs of toxicity reported included restlessness and labored respiration.

C. Irritation

Based on the available data, acetaldehyde is considered to be only slightly irritating to skin. The chemical was reported to cause slight skin irritation when tested in rabbits for 4 hours under occlusive conditions in a guideline (OECD TG 404) study (REACH). In a non-guideline study on rabbits, 500 mg of the chemical produced slight irritation of the skin. Nevertheless, according to literature (RIFM 2003) that was evaluated by the Scientific Committee on Cosmetic Products and non-Food Products Intended for Consumers, concentrations greater than 1% in solution are likely to be irritating to the human skin.

The irritating potential to human eyes at 500 ppm is reported from human exposure to acetaldehyde (Silverman, 1946). Furthermore, an irritating potential for the respiratory tract can be derived from several oral animal studies and human experience.

D. Sensitization

Based on the available data, the chemical is not considered to cause skin sensitisation. The chemical was not found to induce dermal sensitisation when tested according to OECD TG 406 (REACH). Several skin sensitisation studies were also considered by the SCCS who concluded there is limited evidence of skin sensitisation following exposure to the chemical (SCCS, 2012).

E. Repeated Dose Toxicity

<u>Oral</u>
Based on the available data, the chemical is not considered to cause serious health effects from repeated oral exposure.

In a 4-week drinking water study in rats, the no observed adverse effect level (NOAEL) of 125 mg/kg bw/day was reported (SCCS, 2012). At the higher dose (675 mg/kg bw/day), relative kidney weights were slightly increased in males, while urine production was decreased. The effects and variations in serum biochemistry were considered to be attributed to reduced water intake. Effects on liver function or histology were not reported.

<u>Dermal</u>
No data are available.

<u>Inhalation</u>

Based on the available data, the chemical is not considered to cause serious health effects from repeated inhalation exposure.

In a 4-week repeat dose inhalation toxicity study in male Wistar rats, the no observed adverse effect concentration (NOAEC) for the chemical was reported to be 270 mg/m3 (150 ppm) (REACH). At higher concentrations (900 mg/m3 (500 ppm)), degeneration of the olfactory epithelium was reported.

F. Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is considered to be genotoxic, warranting hazard classification for this endpoint.

In Vitro Studies

The chemical did not exhibit mutagenic activity in Salmonella typhimurium with and without metabolic activation (REACH). The chemical was reported to induce chromosomal aberrations and micronuclei in SD rat primary skin fibroblasts (CERI, 2007). The chemical also induced sister chromatid exchanges in Chinese hamster ovary (CHO) cells, aneuploidy in embryonic diploid fibroblasts of Chinese hamster, and nondisjunction in *Aspergillus nidulans*. In human lymphocytes, dose-dependent gene mutation, sister chromatid exchange and chromosomal aberration were induced. The chemical induced DNA strand breaks and DNA cross-links in human lymphocytes, and DNA protein cross links in rat nasal mucosa cells. In addition, in a DNA binding study using calf thymus DNA, positive results were obtained. In a modified OECD TG 471 assay (a single test was performed with one plate per strain and concentration), the chemical induced chromosomal aberrations in human TK6 cells without metabolic activation at levels ³0.25 mM and was cytotoxic at 1 mM.

In Vivo Studies

The chemical induced sister chromatid exchanges in Chinese hamster and mouse bone marrow (CERI, 2007). Chromosomal aberrations were also reported in a study using rat embryo cells administered the chemical through the amnion. In studies using intraperitoneal administration, micronuclei were induced in rat bone marrow cells, rat peripheral lymphocytes and mouse bone marrow cells. Induced micronuclei or morphological abnormalities were not found in mouse spermatids.

Although effects were not seen in the single study examining germ calls, there is sufficient evidence to classify the chemical as possibly causing mutagenic effects.

G. Carcinogenicity

The chemical is classified as hazardous, with the risk phrase 'Limited evidence of carcinogenic effect' (Carc. Cat. 3; R40) in HSIS (Safe Work Australia). The available data support this classification.

The chemical is classified by the International Agency for Research on Cancer (IARC) as Group 2B (possibly carcinogenic to humans) based on sufficient evidence of carcinogenicity in experimental animals (IARC, 1999). The chemical produced tumours of the respiratory tract in rats and hamsters following inhalation exposure at concentrations as low as 750 ppm, particularly adenocarcinomas and squamous cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters.

Tumour formation at the site of exposure suggests a threshold (non-genotoxic) mechanism of carcinogenicity. The US EPA Integrated Risk Information System (IRIS) Chemical Assessment Summary for acetaldehyde calculated a quantitative cancer risk of 1:10 000 at an air concentration of 50 µg/m3 (equivalent to 28 ppb) (US EPA IRIS, 1988). In a subsequent report, IARC also classified the chemical as a Group 1 (Carcinogenic to Humans) when associated with the consumption of alcoholic beverages (IARC, 2012; REACH). However, it must be noted that this IARC Group 1 classification relates to a non-industrial use of the chemical.

H. Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to cause reproductive and developmental toxicity. A NOAEL of greater than 400 mg/kg bw/day was reported for reproductive and developmental toxicity in rats (REACH).

In a reproductive and developmental toxicity screening test the chemical was administered orally to 22 rats at 400 mg/kg bw/day from day 6 through to day 15 of gestation. There were no maternal or developmental effects recorded at that dose level.

The chemical was also investigated in several studies for developmental effects following intraperitoneal injection of either a single dose of 0, 50, 75 or 100 mg/kg bw/day on gestation day 10, 11 or 12, or repeated doses of 0, 50, 75 or 100 mg/kg bw/day on gestation days 10 to 12 (CERI, 2007). Foetal resorptions, malformation (oedema, microcephaly, micrognathia, exencephaly and hydrocephaly), retarded development, and decreases in foetal body and placenta weight were observed in the groups given 50 mg/kg and above. However, exposure via the intraperitoneal route is not appropriate for the evaluation of a hazard or risk to humans from industrial use of the chemical. One CERI study examined the developmental effects of the chemical after oral exposure to rats. Pregnant rats were administered a dose of 200 mg/kg/day (3 % water solution) on gestation days 6 to 18. An anomaly of the ribs and vertebrae was observed in the foetuses. In addition, delayed ossification and hypoplasia of the cranial bones and sternum were observed. However, a reliable NOAEL could not be derived from this study due to insufficient data.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for acetaldehyde 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 lowest NOAEL from available studies is 675 mg/kg-day based on a lack of effects in rats from a 28-day drinking water study (Til et al., 1988) (Kl = 2). Effects observed at this dose attributed to acetaldehyde (hyperkeratosis of the forestomach) likely resulted from direct contact irritation rather than the substance, and other effects (increased relative kidney weights in males, decreased urinary production, and variations in serum biochemistry) were attributable to reduced water intake. The NOAEL of 675 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 = 675/(10 x 10 x 1 x 10 x 1) = 675/1000 = 0.7 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 = (0.7 x 70 x 0.1)/2 = 3 mg/L

B. Cancer

A cancer reference value was not developed for acetaldehyde because it is not considered carcinogenic via the oral exposure route. The chemical is classified by the International Agency for Research on Cancer (IARC) as Group 2B (possibly carcinogenic to humans) based on sufficient evidence of carcinogenicity in experimental animals via inhalation (IARC, 1999). The chemical produced tumours of the respiratory tract in rats and hamsters following inhalation exposure at concentrations as low as 750 ppm, particularly adenocarcinomas and squamous cell carcinomas of the nasal mucosa in rats and laryngeal carcinomas in hamsters.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Acetaldehyde is extremely flammable.

Acetaldehyde does not exhibit the following physico-chemical properties:
· Explosivity
· Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

B. Aquatic Toxicity

Acute Studies
Table 2 lists the results of acute aquatic toxicity studies conducted on acetaldehyde.

Table 2: Acute Aquatic Toxicity Studies on Acetaldehyde

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hr LC_{50}	30.8	2	ECHA
Daphnia magna	48-hr EC_{50}	48.3	2	ECHA
Nitzscheria linearis	120-d EC_{50}	>237 and <249	2	ECHA

Chronic Studies

No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for acetaldehyde 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 (30.8 mg/L), invertebrates (48.3 mg/L), and algae (>237 and <249 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 E(L)C_{50} value of 30.8 mg/L for fish. The $PNEC_{water}$ is 0.3 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 $PNEC_{soil}$ is 0.012 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.06/1500) \times 1000 \times 0.3$
$= 0.012$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 3.219 \times 0.02$
$= 0.06$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for acetaldehyde based on the log K_{ow} is 3.219 L/kg (EPA, 2019).
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).

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

Based on an estimated log K_{ow} of -0.34 (EPA, 2019), acetaldehyde does not meet the screening criteria for bioaccumulation.

There are no chronic toxicity studies on acetaldehyde. The acute E(L)C_{50} values are >1 mg/L for fish, invertebrates, and algae. Thus, acetaldehyde does not meet the screening criteria for toxicity.

Thus, acetaldehyde is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Eye Damage/Irritation: Category 2A
Flammable Liquids: Category 1
Specific target organ toxicity - Single Exposure Category 3 (respiratory tract irritation)

B. Labelling

Danger

C. Pictogram

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, lifting upper and lower eyelids occasionally. Remove contact lenses if present and easy to do. Continue rinsing. Seek immediate medical assistance.

Skin Contact
Wash affected area thoroughly with copious amounts of running water. Remove contaminated clothing and wash before reuse. Seek medical attention.

Inhalation
If inhaled, remove from contaminated area to fresh air immediately. Apply artificial respiration if not breathing. If breathing is difficult, give oxygen. Consult a physician.

Ingestion
Rinse mouth thoroughly with water immediately, repeat until all traces of product have been removed. DO NOT INDUCE VOMITING. Seek immediate medical advice

Notes to Physician
Treat symptomatically based on judgement of doctor and individual reactions of the patient. Persons with kidney disease, chronic respiratory disease, liver disease, or skin disease may be at increased risk from exposure to this substance.

Medical Conditions Aggravated by Exposure
Persons with kidney disease, chronic respiratory disease, liver disease, or skin disease may be at increased risk from exposure to this substance.

Emergency Personnel Protection
Avoid skin and eye contact with – and inhalation of – this chemical. Acetaldehyde must be kept away from heat/sparks/open flames/hot surfaces.

B. Fire Fighting Information

Extinguishing Media
Caution: Use of water spray when fighting fire may be inefficient.
Small fire: Use alcohol resistant foam, dry chemical, CO2 or water spray.
Large fire: Use alcohol resistant foam, fog or water spray - Do not use water jets.

If safe to do so, move undamaged containers from fire area. Cool containers with flooding quantities of water until well after fire is out. Avoid getting water inside containers.

Specific Exposure Hazards
Hazards from combustion products may include: methane, other toxic, irritating chemicals, carbon monoxide, carbon dioxide, and peroxides (in air).

HIGHLY FLAMMABLE
Low flashpoint - Will be easily ignited by heat, sparks or flame. Vapours will form explosive mixtures with air. Vapours may travel to source of ignition and flash back. Vapour is heavier than air and will collect in low or confined areas (drains, basements, tanks). Liquids is lighter than water. Containers may explode when heated. Fire will produce irritating, poisonous and/or corrosive gases. Vapours from runoff may create explosion hazard

Special Protective Equipment for Firefighters
Wear SCBA and fully-encapsulating, gas-tight suit when handling these substances. Structural firefighter's uniform is NOT effective for these materials.

C. Accidental Release Measures

Personal Precautions
Evacuate unprotected persons. Avoid inhalation and avoid contact with skin, eyes and clothing.

Environmental Precautions
Prevent entry into waterways, drains or confined areas.

Steps to be Taken if Material is Released or Spilled
ELIMINATE all ignition sources (no smoking, flares, sparks or flame) within at least 50m - All equipment used when handling the product must be earthed. Do not touch or walk through spilled material. Stop leak if safe to do so. Vapour-suppressing foam may be used to control vapours - Water spray may be used to knock down or divert vapour clouds.

Absorb with earth, sand or other non-combustible material. Use clean, non-sparking tools to collect absorbed material and place it into loosely-covered metal or plastic containers for later disposal.

D. Storage And Handling

General Handling

Avoid ingestion and inhalation of dust, vapour, fumes, spray mist, or gas. Avoid contact with eyes, skin, or clothing. Avoid prolonged or repeated exposure. Handle under an inert atmosphere. Store protected from air. This product may be under pressure; cool before opening.

Use only with adequate ventilation. In case of insufficient ventilation, wear suitable respiratory equipment. Wear suitable protective clothing. Ground and bond containers when transferring material. Take precautionary measures against static discharges. Empty containers retain product residue, (liquid and/or vapour), and can be dangerous. Do not pressurize, cut, weld, braze, solder, drill, grind, or expose empty containers to heat, sparks or open flames.

Other Handling Precautions

If peroxide formation is suspected, do not open or move container. Open carefully. Avoid all contamination. Always open containers slowly to allow any excess pressure to vent. Keep container tightly closed when not in use.

Corrosivity to Metals: Dry, pure acetaldehyde is not corrosive to metals. In air, acetaldehyde can be oxidized to acetic acid, which is corrosive to some metals. Acetaldehyde vapour leaking into a building equipped only with flameproof electrical equipment ignited, possibly on contact with rusted steel, corroded aluminium or hot steam lines.
Corrosivity to Non-Metals: Acetaldehyde attacks some plastics.

Storage

Keep away from heat, and all sources of ignition (sparks and flame). Ground all equipment containing material.

Store in a segregated, approved location, in a cool, dry, dark, well-ventilated area away from incompatible materials. This product should be stored away from foodstuffs, strong oxidizing agents, strong acids, reducing agents, combustible materials, organic materials, metals, and alkalis.
Protect against physical damage, air and sunlight (UV light). Air sensitive. Do not expose to air. May develop pressure. Store in explosion-proof refrigerator. Keep from freezing. After opening, purge container with nitrogen before reclosing. Periodically test for peroxide formation on long-term storage. Addition of water or appropriate reducing materials will lessen peroxide formation. Store only if stabilized.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

A time weighted average (TWA) has been established for acetaldehyde (Safe Work Australia) of 36 mg/m^3, (20 ppm). The corresponding STEL level is 91 mg/m^3 (50 ppm).

Engineering Controls
Maintain the concentration values below the TWA. This may be achieved by process modification, use of local exhaust ventilation, capturing substances at the source, or other methods.

Personal Protection Equipment
Respiratory Protection:
Where ventilation is not adequate, respiratory protection may be required. When mists or vapours exceed the exposure standards then the use of the following is recommended: approved respirator with organic vapour and dust/mist filters. Filter capacity and respirator type depends on exposure levels.

Hand Protection:
Protective gloves. Recommendation:
Excellent: Butyl rubber gloves Silver Shield gloves
Fair: NR latex and neoprene.
Poor: Vinyl gloves. PVC or nitrile rubber gloves.

Skin Protection:
Long sleeved clothing

Eye protection:
The use of a face shield, chemical goggles or safety glasses with side shield protection as appropriate.

Other Precautions:
No data available.

F. Transport Information

UN Number 1089
Transport hazard class 3

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

AICS: Listed

XIII. REFERENCES

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ACETIC ACID

This dossier on acetic acid presents the most critical studies pertinent to the risk assessment of acetic acid in its use in coal seam or shale 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).

NICNAS has assessed acetic acid in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to the environment.

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Acetic acid

CAS RN: [redacted]

Molecular formula: $C_2H_4O_2$

Molecular weight: 60.1 g/mol

Synonyms: Acetic acid, ethanoic acid, ethylic acid, methane carboxylic acid, vinegar acid

SMILES: CC(=O)O

II. PHYSICO-CHEMICAL PROPERTIES

Key physical and chemical properties for the substance are shown in Table 1.

Table 1: Overview of the Physico-Chemical Properties of Acetic Acid

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Colourless liquid with a pungent odour.	2	ECHA
Melting Point	16.64°C @ 101.3 kPa	2	ECHA
Boiling Point	117.9°C @ 101.3 kPa	2	ECHA
Density	1040 kg/m^3 @ 25°C	2	ECHA
Vapour Pressure	2079 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	-0.17 @ 20°C	2	ECHA
Water Solubility	602.9 g/L @ 25°C	2	ECHA
Viscosity	1.056 mPa s @ 25°C	2	ECHA
Dissociation constant (pKa)	4.756 @ 25°C	2	ECHA

Acetic acid readily dissociates in aqueous media to the acetate ($H_3C2O_2^-$) and hydrogen (H^+) ions.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

The acetate ion of acetic acid is readily biodegradable, is not expected to bioaccumulate, and has a low potential to adsorb to soil.

B. Partitioning

The pKa of acetic acid is 4.76, 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).

Volatilization of acetic acid from water and moist soil surfaces is not expected to be an important fate process given a Henry's Law constant of 0.21 pascal cubic metre per mole (Pa-m^3/mol) (ECHA). Acetic acid is expected to volatilise from dry soil surfaces based upon its vapour pressure.

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

Acetic acid was readily biodegradable in a non-acclimated freshwater study. Degradation was 96% after 20 days (Price et al., 1974; ECHA) [Kl. score = 2]. Acetic acid is also readily biodegradable under anaerobic conditions (Kameya et al., 1995) [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, 2017a).

D. Environmental Distribution

No experimental data are available for acetic acid. Using KOCWIN in EPISuite™ (USEPA, 2017), the estimated K_{oc} values from log K_{ow} and the molecular connectivity index (MCI) are 1.153 and 1.0 L/kg, respectively. Based on these values, acetic acid has a low potential for adsorption to soil and sediment and is expected to have very high mobility in soil.

Acetic acid is highly soluble in water and dissociates completely in aqueous solution to acetate and its hydrogen ion. However, the chemistry of the receiving water compartment, such as its pH and the presence of metal ions, may affect the speciation and partitioning of this substance and its buffering capacity (DoEE, 2017b).

E. Bioaccumulation

There are no bioaccumulation studies on acetic acid. Bioaccumulation of acetic acid is not expected to occur because acetic acid dissociates completely in aqueous solution to acetate and its hydrogen ion.

Both ions are ubiquitous in the environment. Acetate is naturally found in eukaryotic and prokaryotic cells and is involved in their biochemical pathways.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Acetic acid is a corrosive liquid. Depending on the concentration, aqueous solutions of acetic acid are either corrosive, irritating, or non-irritating to the skin, eyes, and gastrointestinal tract. Vapours from aqueous solutions of acetic acid can cause respiratory irritation. There are no adequate repeated dose toxicity studies on acetic acid. Acetic acid is not genotoxic. Positive findings have been reported in some in vitro genotoxicity studies and are considered to be the result of the pH change in the test system. There are no carcinogenicity studies by the oral or inhalation route. It is not carcinogenic by the dermal route. Animal studies have shown no developmental toxicity from ingestion of acetic acid.

B. Acute Toxicity

Oral

The oral LD_{50} of the sodium salt of acetic acid in rats is 3,310 milligrams per kilogram (mg/kg) (Woodard et al., 1941; ECHA) [Kl. score =2]. The oral LD_{50} of the acetic acid in unfasted rats is 3,530 mg/kg (ECHA) [Kl. score =4]. The oral LD_{50} of the sodium salt of acetic acid in mice is 4,960 mg/kg (Smyth et al., 1951; ECHA) [Kl. score =2].

Inhalation

The 4-hour inhalation LC_{50} in rats for acetic acid vapor is 11.4 milligrams per litre (mg/L). There were clinical signs that were indicative of corrosion (ECHA) [Kl. score = 2].

C. Irritation

Application of a 3.3% or a 10% aqueous solution of acetic acid to the skin of rabbits for 4 hours was slightly irritating. The Primary Dermal Irritation Index scores were 0.5 and 1.1, respectively (Nixon et al., 1990; ECHA) [Kl. score = 2]. Application of a 10% solution of acetic acid to the skin of rabbits for 4 hours under semi-occlusive conditions was slightly irritating (ECHA) [Kl. score = 2].

Instillation of 0.1 mL of a 10% solution of acetic acid to the eyes of rabbits was considered irritating. The mean of the 24-, 48-, and 72-hours scores were: 2.67 for erythema; 1.67 for chemosis; 1.72 for corneal opacity; and a mean of 87% corneal swelling (Jacobs and Martens, 1989; ECHA) [Kl. score = 2]

D. Sensitisation

No studies are available.

E. Repeated Dose Toxicity

Oral

No adequate studies for human health risk assessment are available.

Inhalation

No studies are available.

Dermal

No adequate studies are available.

F. Genotoxicity

In Vitro Studies

The *In Vitro* genotoxicity studies on acetic acid are presented below in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Acetic Acid

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	NC	-	2	Ishidate et al. (1984); ECHA
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	Zeiger et al. (1992); ECHA
Chromosomal aberrations (CHO cells)	-**	-**	2	Morita et al. (1990); ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-***	-***	2	Seifried et al. (2006); ECHA

*+, positive; -, negative; NC, not conducted.
**A dose-dependent increase in chromosomal aberrations was observed with 10 mM acetic acid (-S9) and 8 mM acetic acid (+S9). These concentrations were close to the cytotoxic limit at which the cells could no longer be evaluated. These effects were abolished by neutralizing the test medium or increasing the buffer capacity. These results suggest that the positive findings are due to the acidic pH of the incubation medium rather than a consequence of an intrinsic clastogenic potential of acetic acid.
***Acetic anhydride (hydrolyses to acetic acid in aqueous media).

In Vivo Studies

No studies are available on acetic acid.

A bone marrow micronucleus study has been conducted on acetic anhydride, which hydrolyses to acetic acid. Male and female SD rats were exposed by inhalation to 0, 1, 5, or 20 parts per million (ppm) acetic anhydride, 6 hours/day, 5 days/week for 13 weeks. The incidence of micronucleated immature erythrocytes was not increased at any exposure concentration (ECHA). [Kl. score = 1]

G. Carcinogenicity

No oral or inhalation studies are available.

No deaths nor skin tumours were seen when acetic acid was applied dermally once a week to CD-1 mice for 32 weeks (Slaga et al., 1975; ECHA) [Kl. score = 4].

H. Reproductive Toxicity

No studies are available.

I. Developmental Toxicity

Pregnant female Wistar rats were dosed with 0 or various concentrations up to 1,600 mg/kg apple cider vinegar (5% acetic acid) by oral gavage on gestational days 6 to 15. There were no maternal or developmental toxicity effects noted at any dose level. The no observed adverse effect level (NOAEL) for maternal and developmental toxicity is 1,600 mg/kg-day (ECHA). [Kl. score = 2]

Pregnant female CD-1 mice were dosed with 0, 16, 74.3, 345, or 1,600 mg/kg apple cider vinegar (5% acetic acid) by oral gavage on gestational days 6 to 15. There were no treatment-related effects on maternal or foetal survival, or on soft or skeletal tissues. There was no effect on the foetal development in the presence of slight maternal toxicity (reduced body weight gain) at 345 mg/kg. At 1,600 mg/kg, there was an increase in the number of litters containing a dead foetus and some reductions in ossification. The NOAELs for maternal and developmental toxicity are 74.3 and 345 mg/kg-day, respectively (ECHA). [Kl. score = 2]

Pregnant female Dutch-belted rabbits were dosed with 0, 16, 74.3, 345, or 1,600 mg/kg apple cider vinegar (5% acetic acid) by oral gavage on gestational days 6 to 18. There were no treatment-related effects on maternal or foetal survival, or on soft or skeletal tissues. There was a reduction in the pregnancy rate in the high-dose group; and a dose-dependent decrease in maternal body weights at >74.3 mg/kg. Some deaths or abortions occurred in all treated groups and some litter losses were reported at >345 mg/kg. Maternal effects were much more noticeable than the effects on foetal development. These findings have been considered a consequence of the bactericidal properties of orally administered acetic acid within the gastrointestinal tract of female rabbits, and not a direct effect on embryonic implantation and development of acetic acid (EU, 2008). It is likely that this accounts for the apparent increased sensitivity of this species to oral administration of acetic acid. The NOAEL for developmental toxicity is 1,600 mg/kg-day; a NOAEL for maternal toxicity was not identified (ECHA). [Kl. score = 2]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for acetic 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).

A. Non-Cancer

Oral

There are no repeated dose toxicity studies that were considered adequate for human health risk assessment.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has maintained a group acceptable daily intake (ADI) of "not limited" for acetic acid and its potassium and sodium salts (JECFA).

While concentration of acetic acid will affect pH, and extreme pH values (<4 and >11) may adversely affect health, there are insufficient data to set a health guideline value (ADWG, 2011)

B. Cancer

There are no carcinogenicity studies by the oral or inhalation route. A dermal carcinogenicity study in mice showed no carcinogenic activity when acetic acid was applied to the skin for 32 weeks. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Acetic acid is a flammable liquid.

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

- Explosivity
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Acetic acid is of moderate acute toxicity concern to aquatic organisms, in part because of the effect of pH changes from the dissociated hydrogen ion. The acetate ion 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 acetic acid and potassium acetate.

Table 3: Acute Aquatic Toxicity Studies on Acetic Acid and Potassium Acetate

Test Substance	Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Potassium acetate	*Oncorhynchus mykiss*	96-hour LC_{50}	>300.82*	2	ECHA
Potassium acetate	*Danio rerio*	96-hour LC_{50}	>300.82*	2	ECHA

Test Substance	Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Acetic acid	*Oncorhynchus mykiss*	96-hour LC_{50}	64.8 (measured)	4	ECHA
Acetic acid	*Oncorhynchus mykiss*	96-hour LC_{50}	31.3 – 67.6	4	ECHA
Potassium acetate	*Daphnia magna*	48-hour EC_{50}	>300.82*	2	ECHA
Acetic acid	*Daphnia magna*	48-hour EC_{50}	79.5 (measured)	4	ECHA
Acetic acid	*Daphnia magna*	48-hour EC_{50}	18.9 (measured)	4	ECHA
Acetic acid	*Desmodesmus subspicatus*	72-hour EC_{50}	486.5	4	ECHA

*As the acetate ion.

Chronic Studies

In a 21-day fish (*Oncorhynchus mykiss*) chronic study, the measured no observed effect concentration (NOEC) values for 60% and 100% acetic acid were 57.2 and 34.3 mg/L, respectively (ECHA). [Kl. score = 4]

In a 21-day *Daphnia* reproduction study, the measured NOEC for 60% and 100% acetic acid were 80 and 31.4 mg/L, respectively (ECHA). [Kl. score = 4]

In a 21-day *Daphnia* reproduction study, the measured NOEC for 100% acetic acid was 22.7 mg/L (ECHA). [Kl. score = 4]

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

Despite the low Klimisch scores for aquatic toxicity testing (K=4), the PNEC calculations for acetic acid follow the methodology discussed in DEWHA (2009).

PNEC Water

Experimental results are available for three trophic levels. For the acute toxicity studies, data are available on both acetic acid and potassium acetate; both substances dissociate completely in aqueous media to the acetate anion and the corresponding cations (H+ and K+). The toxicity of these substances is expected to be driven by the acetate ion, with the cations having a minor role. The toxicity data on potassium acetate are preferred because of the absence of a potential pH change from the dissociated H+ ion of acetic acid. For the chronic toxicity studies, only acetic acid has been tested for two trophic levels: fish and invertebrates. These studies will not be used to derive the PNEC value; however, an assessment factor of 100 will be applied to the lowest acute $E(L)C_{50}$ values for the acetate ion.

From the potassium acetate studies, acute $E(L)C_{50}$ values (adjusted for acetic acid) are available for fish (300.82 mg/L) and Daphnia (300.82 mg/L). By applying an assessment factor of 100 to the $E(L)C_{50}$ value of 300.82 mg/L from either fish or Daphnia, the $PNEC_{water}$ for acetic acid is 3.0 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 1.9 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1{,}000 \times PNEC_{water}$

$= (0.82/1{,}280) \times 1{,}000 \times 3.0$

$= 1.9$ mg/kg

Where:

$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (cubic metre per cubic metre [m^3/m^3])

BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]

$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1{,}000 \times BD_{solid}]$

$= 0.8 + [(0.2 \times 0.04/1{,}000 \times 2{,}400]$

$= 0.82$ kg/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]

$Kp_{sed} = K_{oc} \times f_{oc}$

$= 1.0 \times 0.04$

$= 0.04$ L/kg

Where:

K_{oc} = organic carbon normalized distribution coefficient (L/kg). The K_{oc} for acetic acid calculated from EPISUITE™ using the MCI is 1.0 L/kg .

F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC Soil

There is no toxicity data for terrestrial or soil organisms. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.04 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$

$= (0.02/1500) \times 1000 \times 3.0$

$= 0.04$ 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]

$Kp_{soil} = K_{oc} \times f_{oc}$

$= 1.0 \times 0.02$

= 0.02 m^3/m^3

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for acetic acid calculated from EPISUITE™ using the MCI is 1.0 L/kg .
F_{oc} = fraction of organic carbon in soil = 0.02 [default].

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY 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, 2017).

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

Bioaccumulation of acetic acid is not expected to occur because acetic acid dissociates completely in aqueous media to acetate and its hydrogen ion. Both ions are ubiquitous in the environment. Acetate is naturally found in eukaryotic and prokaryotic cells and is involved in their biochemical pathways. The log K_{ow} for acetic acid is -0.17. Thus, acetic acid does not meet the screening criteria for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on acetic acid are >0.1 mg/L. The EC_{50} values for potassium acetate are > 1 mg/L. Thus, acetic acid does not meet the criteria for toxicity.

The overall conclusion is that acetic acid is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable Liquid Category 3

Skin Corrosion Category 1A

EU:

≥90%: Skin Corrosion 1A

≥25% to <90%: Skin Corrosion 1B

≥10% to <25%: Skin irritant Category 2; Eye irritant Category 2

In addition to the hazard statements corresponding the GHS classifications (if Skin Corrosion 1A or 1B is included), the following non-GHS hazard statement is to be added to the SDS: AUH071: Corrosive to the Respiratory Tract.

B. Labelling

Danger

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 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 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

Rinse mouth and lips with plenty of water if person is conscious. Do not induce vomiting. Do not use mouth-to-mouth method if victim had ingested the substance. Obtain medical attention immediately if ingested.

Notes to Physician

Treat as a corrosive due to pH of the material. 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. Do not use straight streams of water.

Specific Exposure Hazards

Flammable liquid and vapor. 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

Structural firefighter's 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 fire area if you can do it without risk.

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. All equipment used when handling the material must be grounded. A vapor 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 vapor. 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 vapor 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.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for acetic acid in Australia is 10 ppm (25 mg/m^3) as a 8-hr time-weighted average (TWA) and 15 ppm (37 mg/m^3) as a 15-min short-term exposure limit (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.

Hand Protection:

Use gloves chemically resistant to this material. Consult the safety data sheet (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

For glacial acetic acid or >80% acetic acid solutions:
UN 2789 (ACETIC ACID, GLACIAL or ACETIC ACID SOLUTION)
Class: 8
Packing Group: II

For ≥50% to 80% acetic acid solutions:
UN 2790 (ACETIC ACID SOLUTION)
Class: 8
Packing Group: II

For >10% to <50% acetic acid solutions:
UN 2790 (ACETIC ACID SOLUTION)
Class: 8
Packing Group: 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

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ACRYLONITRILE

This dossier presents the most critical studies pertinent to the risk assessment of acrylonitrile 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-Propenenitrile

CAS RN: [redacted]

Molecular formula: C3H3N

Molecular weight: 53.064

Synonyms: Acrylonitrile monomer, Cyanoethene, Cyanoethylene, Propenenitrile, Vinyl cyanide, Vinylcyanide

SMILES: C1=CC=C(C=C1)C=CC#N

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Acrylonitrile

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Clear, colorless liquid with a faintly pungent odor.	2	ECHA
Melting point	-83.5°C	2	ECHA
Boiling point	77.3°C	2	ECHA
Density	0.8004 g/cm^3 @ 25°C 0.81 g/cm^3 @ 20°C	2	ECHA

Property	Value	Klimisch score	Reference
Vapor pressure	11.5 kPa @ 20°C 133.3 hPa @ 23.6°C	2	ECHA
Partition coefficient (log K_{ow})	1.04 @ 21°C	2	ECHA
Water solubility	73 g/L @ 20°C	2	ECHA
Flash point	0°C	2	ECHA
Auto flammability	481°C	2	ECHA
Viscosity	0.34 mPa s @ 25°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Acrylonitrile is inherently biodegradable. Several studies indicate that acrylonitrile does not meet the criteria for ready biodegradability. However, other studies suggestive of environmental non-persistence show significant decreases in concentration in environmental media. Acrylonitrile does undergo biodegradation in a variety of circumstances; it does not meet criteria for bioaccumulation.

B. Biodegradation

Acrylonitrile is inherently biodegradable.

In an inherent biodegradability:modified MITI II (OECD 302C) test, degradation was 61% after 14 days (determined by BOD (NO_2)); 96% after 14 days (determined by BOD (NH_3)); 100% after 14 days (determined by TOC removal); and 100% after 28 days (determined by GC) (ECHA) [Kl. score = 1].

In an inherent biodegradability:modified MITI I (OECD 301C) test, degradation was 15% after 28 days (determined by BOD (NO_2)); 23% after 28 days (determined by BOD (NH_3)); 38% after 28 days (determined by TOC removal); and 44% after 28 days (determined by GC) (ECHA) [Kl. score = 1].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for acrylonitrile. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value from log K_{ow} method is 28.55 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 8.51/kg.

D. Bioaccumulation

There are no bioaccumulation studies on acrylonitrile. Acrylonitrile is not expected to bioaccumulate based on a log K_{ow} of 0.017 (ECHA) nor does study need to be conducted because the substance has a low potential for bioaccumulation based on log Kow <=3 (ECHA 2019)

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Acrylonitrile is listed in Annex VI of the CLP Regulation (1272/2008/EC) with classification in Acute Toxicity Category 3, H301: Toxic if swallowed, H311: Toxic in contact with skin and H331: Toxic if inhaled. The available data are consistent with this harmonised classification and no change is proposed.

The acute toxicity data for acrylonitrile were reviewed in detail in the EU Risk Assessment Report (2004). The following summary is based largely on the EU RAR, supplemented by literature reviews conducted in 2014 and, more recently, in March 2017.

B. Acute Toxicity

Oral

The EU RAR (2004) reviews the available data on the acute oral toxicity of acrylonitrile. Oral LD50 values for various species are reported to be in the range 25 -186 mg/kg bw with a species sensitivity of mouse>guinea pig>rabbit and rat. Following oral dosing, the mouse appears to be the most sensitive species, with oral LD50 values ranging from 28-48 mg/kg bw. The reported range in the guinea pig is 50-85 mg/kg bw, an oral LD50 of 93 mg/kg bw is reported in the rabbit, while in the rat the range of reported LD50 values is 72 -186 mg/kg bw (EU RAR, 2004).

Vernon et al., in a study carried out in 1969 but reported in the Journal of the American College of Toxicology in 1990, orally dosed four groups of 5 young adult male CF Nelson rats with 50, 100, 200 and 400 mg/kg bw acrylonitrile and observed them for 14 days.

All deaths occurred during the first 24 hours with no significant clinical signs being observed; the acute oral LD50 was calculated to be 81 (62 -107) mg/kg bw.

Rao et al. (2013) report an acute 24-hour LD50 of 95.1 mg/kg bw in female Wistar rats. The acute oral LD50 of acrylonitrile is lower in mice than in rats, as would be expected based on the comparative metabolism. The oral LD50 in mice was reported by Tullar (1947) to lie between 25-48 mg/kg bw, as summarised in WHO (1983). Tanii & Hashimoto (1984) reported similar values of 27 and 38 mg/kg bw. These values, however, appear artificially low relative to other studies. For instance, Ghanayem et al. (2002) dosed mice with 20 mg/kg bw/d on five days per week for 2 years without any observable cyanosis. Leonard (1981) also dosed mice with 30 mg/kg bw and found no lethality. Tanii (1989) administered mice 60 mg/kg bw and observed 80% mortality, but subsequently administered 79 mg/kg bw without lethality. Data indicate that mice excrete a higher percentage of administered acrylonitrile as thiocyanate (and hence appear to metabolise more acrylonitrile to cyanide) than rats or humans (EU RAR, 2004). Reported oral LD50 values for acrylonitrile in various species lie in the range 25 -186 mg/kg bw (GDCh/BUA, 1995). No human data are identified.

Dermal

Dermal LD50 values for various species are in the range 148 -693 mg/kg bw, with the rat being the most sensitive species (BUA, 1995). In a study by Vernon et al. (1969) a single dose of 200 mg/kg bw was applied to the intact skin of 15 young adult male rabbits and occluded for an exposure period of 24 hours. This study resulted in death of all animals within the first 24 hours, with no clinical signs being noted. The acute dermal LD50 of acrylonitrile in this study was therefore <200 mg/kg bw. Roudabush et al. (1965) reported an LD50 for the rabbit of 226 mg/kg bw. In a more recent rat study (SNF, 2005), acrylonitrile administered topically with occlusion at a dose level of 200 mg/kg bw for 4 hours resulted in 10% mortality (1 of 10 rats). While some human data also indicate a potential for systemic toxicity following dermal exposure to acrylonitrile, conclusive data suitable for determination of a human dermal LD50 or other such metric are not available.

Inhalation

The LC50 values reported for a range of species following a 4-hour inhalation exposure lie in the concentration range of 0.3 -1.21 mg/L. Dudley & Neal (1942) investigated the susceptibility of rats, guinea pigs, rabbits, cats, dogs and monkeys to a single 4-hour exposure to varying concentrations of acrylonitrile. The results indicated that rabbits were moderately susceptible; exposure to 260 ppm (0.56 mg/L) for 4 hours caused 100% mortality in 4 -5 hours, while a level of 135 ppm produced marked but transitory effects. Rats and cats were of about equal susceptibility, 100% mortality being observed in rats within 2–6 hours of exposure to 635 ppm (1.38 mg/L) and in cats within 1.5 hours of exposure to 600 ppm (1.30 mg/L). Exposure of two monkeys to 90 ppm (0.196 mg/L) produced only slight transitory effects. Delayed mortality (25%) was observed in guinea pigs exposed to a level of 575 ppm (1.25 mg/L) as a result of lung oedema 3 -5 days

following exposure. In general guinea pigs appeared to be less sensitive than rats following inhalation exposure, but the lethality in both species after administration by other routes is comparable. Dudley & Neal (1942) report that the dog was the most sensitive species. Exposure to 110 ppm (0.24 mg/L) acrylonitrile was fatal in 2 out of 3 dogs exposed, while a 4-hour exposure to a level of 100 ppm resulted in convulsions followed by coma in 2 out of 3 dogs. One of these dogs recovered completely within 48 hours while the other showed partial paralysis of the hind legs for 3 days. The third dog exposed to 100 ppm acrylonitrile showed severe salivation during the test but recovered fully within 24 hours. At an exposure level of 29 ppm (0.063 mg/L) for 4 hours, signs of toxicity in dogs were confined to slight salivation.

With regard to the acute lethality of aceylonitrile in animals, dogs appeared to be the most sensitive species following exposure via inhalation but the dataset for dogs is limited. At least some of the species variability in the toxic response to acrylonitrile may be a function of the cyanide metabolite and activity levels of rhodanese. It is reported that dogs have relatively low concentrations of rhodanese and rats have relatively high concentrations; overall species variability was about 3-fold. Data from studies of rats provide the most extensive evaluation of exposure durations and the best definition of dose response. A total of seven rat studies were identified that contain information useful for calculating the 4 -hour or 1 -hour LC50 of acrylonitrile.

C. Irritation

A number of skin irritation and eye irritation studies are available. Studies are of variable design but indicate that acrylonitrile is a skin irritant (but not corrosive) and a severe eye irritant. The animal data are also consistent with experiences of accidentally exposed workers. Findings from animal studies and human experience also indicate that the substance is a respiratory irritant.

In a guideline-comparable study (Vernon et al., 1990), 0.5 mL acrylonitrile was applied for 24 hours under occlusive conditions to the shorn (intact and abraded) dorsal skin of six New Zealand White rabbits. Dermal reactions were assessed at 24 and 72 hours following application and mean scores (24 and 72 hour) scores (on a scale of 0 to 4) for both erythema and oedema are reported. The mean score both erythema and oedema was 3.6, with slightly higher scores reported for abraded skin. This study that acrylonitrile is a skin irritant and should be classified as such. The EU RAR also reviews the available animal data on the skin irritation of acrylonitrile. The dataset consists of two studies, the most reliable of which is that of Vernon et al (1990). Both studies are consistent in indicating that acrylonitrile is a skin irritant. The animal data are consistent with experience of skin irritation in workers following accidental exposure. No further testing is proposed.

In a guideline-comparable study (DuPont, 1975), 0.1 mL acrylonitrile was instilled into in the conjunctival sac of the right eye of two rabbits. After 20 seconds the treated eye of

one of the rabbits was washed with tap water for 1 minute, the other rabbit remained unwashed. Corneal opacity/conjunctive irritation occurred up to 3 days in the washed eye and up to 21 days in the unwashed treated eye. Acrylonitrile was therefore found to be an eye irritant under the conditions of this study; the lack of complete reversibility of corneal effects within the 21-day study period supports the harmonised classification of the substance for serious eye damage (Cat 1). Several additional rabbit studies are reported in the EU RAR document; the individual study designs and quality vary, however the results are consistent in demonstrating that acrylonitrile is an eye irritant. The EU RAR concludes that classification of acrylonitrile for serious eye damage is appropriate. This classification is also consistent with human experience.

No specific animal studies of respiratory irritancy such as the Alarie test have been carried out. The EU RAR states that both long-term and short-term toxicity studies in a range of species indicate that acrylonitrile has irritant effects on the upper respiratory tract. Occupational exposure has also been reported to result in respiratory irritation.

D. Sensitization

Acrylonitrile is listed on Annex VI of the CLP Regulation with classification for skin sensitisation (H317: may cause an allergic skin reaction'. In addition, there are also reports of sensitisation in exposed workers.

A guideline-compliant maximisation assay using female SPF Dunkin-Hartley guinea pigs is also reported (Koopmans & Daamen, 1989). In this study, sensitisation was induced by intradermal injection of 2.5% acrylonitrile and an epidermal application of 2% acrylonitrile. Animals challenged with acrylonitrile concentrations of 0.5% and 1.0% acrylonitrile showed a 95% positive sensitisation rate. Exposure to 0.2% on challenge caused an 80% sensitisation rate while control animals exhibited a 5% sensitization rate.

No animal data are available for assessing respiratory sensitisation; there is no recognised validated test guideline for the investigation of this endpoint. There are no reports, from exposed workers of occupational asthma, which indicates that acrylonitrile does not have the potential to cause respiratory sensitisation.

E. Repeated Dose Toxicity

Repeated exposure to acrylonitrile results in damage to the kidney, gastrointestinal tract, central nervous system and adrenal gland. The respiratory tract is also affected following repeated exposure by inhalation. Dogs appear to be the most sensitive species to exposure to acrylonitrile by inhalation, with mortalities being seen at exposure levels causing no deaths in other species, however no reliable long-term oral study has been carried out in the dog. In relation to target organ toxicity, the central nervous system appears to be a primary target organ, with neurofunctional changes being observed, although the evidence for frank neurotoxicity is limited. Nephrotoxicity is observed at

high dose levels. Gastrointestinal lesions seen following oral dosing may in part be due to a local irritant effect. The neurotoxicity of acrylonitrile can partly be explained by cyanide released during metabolism. Other effects may occur through the alkylation of molecules in the central nervous system by the reactive epoxide metabolite CEO. Additionally, acrylonitrile itself is capable of non-enzymatically cyanoethylating essential functional groups in the body. All of these factors may contribute to the overall toxicity of acrylonitrile.

For repeated dose toxicity by the oral route, the key study is the F344 rat drinking water study of Johannsen & Levinskas (1980), from which a NOAEL of 3 ppm (equivalent to average daily dose levels of 0.25 mg/kg bw/d in males and 0.36 mg/kg bw/d in females) was derived. Groups of F344 rats were exposed to acrylonitrile in the drinking water for approximately 2 years as part of a combined chronic toxicity/carcinogenicity study, at doses of 0, 1, 3, 10, 30 and 100 ppm. The study was terminated at 23 months in females because of low survival rates. The males were exposed for 26 months. A consistent decrease in survival, reduced bodyweight and reduced water intake, and small reductions in haematology parameters were observed in both sexes of the 100 ppm group. Mortality was significantly increased compared to controls in the 100 ppm group, while mortality in the males receiving 10 ppm and the females receiving 3 and 30 ppm was also significantly greater than controls. Organ to body weight ratios at various study intervals were consistently elevated in the high dose groups, and were thought to be related to the lower body weights seen in this group. Due to the lack of a dose response relationship in the female mortality data, the NOAEL was considered to be 3 ppm for both males and females; equivalent to average daily dose levels of 0.25 mg/kg bw/d in males and 0.36 mg/kg bw/d in females.

A number of additional repeated dose oral toxicity studies are summarised in the EU RAR. Refer to this document for further documentation.

Dermal

No data are available for the repeated dose toxicity of acrylonitrile by the dermal route. However studies are not required as comprehensive data are available for repeated dose toxicity by the oral and inhalation routes. Testing by the inhalation route is considered to be most relevant (with regard to the likely route of occupational exposure) for volatile substances. Based on kinetic considerations, the systemic dermal toxicity of acrylonitrile is not predicted to be fundamentally different to that seen following oral and/or inhalation exposure, therefore specific data for this route are not required (ECHA) . Due to the irritant and sensitising properties of the substance, it is likely that the effects of repeated dose dermal exposure will be dominated by local (site of contact) effects which will severely limit systemic exposure to the substance and consequently limit the relevance of the study. The use of engineering controls and PPE will also minimise dermal exposure to the substance under normal occupational conditions. Testing is therefore not scientifically justified and additionally cannot be supported on grounds of animal welfare.

Inhalation

For repeated dose inhalation toxicity, the key study is the 2 -generation rat study of Nemec et al. (2008), a two-generation reproductive toxicity study in Sprague-Dawley rats; the data presented here relate to the repeated dose inhalation toxicity to parental animals. Twenty-five rats/sex/group were exposed to vapour atmospheres of acrylonitrile via whole-body inhalation at concentrations of 0, 5, 15, 45 and 90 ppm, 6 hours daily, on 7 days a week for 10 weeks. Males were exposed for 10 weeks prior to mating and throughout mating until one day prior to termination. Females were exposed for 10 weeks prior to mating and throughout mating, gestation, and lactation until 1 day prior to termination. Exposure of the dams was suspended for 5 days following parturition (lactation days 0 -4) to avoid confounding nesting and nursing behaviour and neonatal survival. Exposure of the dams resumed on Day 5; rats were removed from the litters for 6 hours exposure at about the same time each day. There were no exposure-related mortalities. Bodyweight gain was significantly reduced at 45 and 90 ppm. Food consumption was also reduced at these dose levels, but the difference was only significant at 90 ppm. Clinical signs indicative of the irritant properties of acrylonitrile were observed in rats exposed to 90 ppm throughout the exposure period and within 1 hour of cessation of exposure; the irritant effects of the test material did not generally persist to the following day. Acrylonitrile-related microscopic alterations were limited to morphologically similar nasal lesions in the F0 males and females at 45 ppm, F1 males at 5, 15, and 45 ppm, and the F1 females at 15 and 45 ppm. Four levels of the nasal cavity were examined microscopically for the 5, 15, and 45 ppm groups. Lesions showed a clear exposure-response relationship in incidence and included respiratory/transitional epithelial hyperplasia, sub-acute inflammation, squamous metaplasia, and/or degeneration of the olfactory epithelium. The majority of the lesions were present in the most rostral section (level I) of the nasal tissues examined and are consistent with site-of-contact irritation resulting from exposure to irritant chemicals as reported in the literature by a number of authors. All of the nasal lesions noted in this study are common findings in the nasal epithelium of the rat following sub-chronic to chronic inhalation exposure with an irritating compound and represent the effects of local irritation, rather than a systemic effect. No other treatment-related histopathological findings were noted at any exposure level. Based on the incidence of local irritant effects in the nasal cavity at all exposure levels, a NOAEC cannot be determined for this study. A LOAEC of 5 ppm was determined.

The EU RAR summarises a number of additional studies investigating the repeated exposure inhalation toxicity of acrylonitrile. The studies were not of standard design or are considered to be of questionable quality, and therefore are not considered to be of critical relevance for this dossier.

F. Genotoxicity

The genotoxicity of acrylonitrile has been extensively investigated in a large number of standard and non-standard studies in vivo. A number of expert reviews are also available.

In vitro and ex vivo Studies

The mutagenicity of acrylonitrile has been investigated in a large number of bacterial mutation assays. The results of studies in Salmonella strains sensitive to frameshift mutation (TA97, TA98, TA1537, TA1538) are almost entirely negative, whereas mostly positive results are reported in Salmonella strains (TA100, TA1530, TA1535, TA1950) carrying the hisG46 allele and sensitive to GC to AT base pair substitution. It is notable that studies in TA102, which is considered to be sensitive to oxidative damage, have proved to be largely negative. Studies of bacterial mutation in E. coli strains have given mixed results, although more recent studies in strains WP2, WP2uvrA, and WP2(PKM101) have more consistently reported positive results in the presence of metabolic activation. WP2 tester strains include an AT base pair as the critical site. Fungal studies in *S. cerevisiae* and *Schizosaccharomyces pombe* have given mixed results for gene mutation endpoints but more consistently positive results for chromosomal level mutation, both with and without metabolic activation. A positive result has also been reported for aneuploidy/non-disjunction in *Aspergillus nidulans*.

In mammalian cell studies, a number of positive results are reported for acrylonitrile in L5178Y mouse lymphoma cells (Tk locus) both with and without metabolic activation; negative results are reported for this cell line at the Oua locus. L5178Y cells are particularly sensitive to mutations, in part because they have a mutation in the P53 tumour suppressor gene, but also because they may be especially sensitive to oxidative damage. The results of studies in other cell lines are variable, with both negative and positive results reported. There is no consistent association with metabolic activation; some studies report positive results with activation only, others both with and without activation. Molecular analyses indicate that point mutations (for CEO involving AT and GC pairs) may predominate over deletion mutations. In mammalian cells, the potential of acrylonitrile to induce clastogenicity has been investigated in human peripheral blood lymphocytes, CHO, CHL and metabolically competent rat liver RL4 cell lines. Many studies have reported positive results for the induction of structural aberrations, with most requiring metabolic activation. There is no evidence for the induction of numerical aberrations.

In vivo Studies

Investigation of mutagenicity and clastogenicity in appropriate animal models is of most relevance in terms of carcinogenic potential; the models used generally incorporate

relevant toxicokinetic, toxicodynamic and metabolic factors all of which could potentially influence the genetic toxicity potential of the test substance.

Exposure of rats by inhalation to acrylonitrile at concentrations of up to 500 ppm for 90 days did not result in observable effects on cells of the bone marrow (Johnson et al., 1978). No effects were observed in the bone marrow cells of mice administered acrylonitrile by gavage at dose levels of up to 21 mg/kg bw/d for up to 30 days, following intraperitoneal injection with dose levels of up to 20 mg/kg bw/d for up to 30 days; similarly no effects were seen in the bone marrow of rats administered acrylonitrile by gavage at a dose level of 40 mg/kg bw/d for 16 days (Rabello-Gay & Ahmed, 1980). Leonard et al., (1981) showed no induction of bone marrow micronuclei or chromosomal aberrations following the intraperitoneal injection of a single dose of acrylonitrile at a dose level of 20 or 30 mg/kg bw. No increase in the proportion of bone marrow cells was demonstrated in mice following inhalation exposure to dose levels of up to 140 mg/kg bw/d equivalent (Zhurkov et al., 1983) or following a single intraperitoneal injection of up to 60 mg/kg bw (Sharief et al., 1986). Similar negative effects were seen in mice administered acrylonitrile by single or repeated intraperitoneal injection (10 mg/kg bw) or by single (5, 10 mg/kg bw) or repeated (20 mg/kg bw) gavage dosing (Nesterova et al., 1999). The high quality NTP study (NTP, 2001) also showed no evidence of increased micronuclei formation in the peripheral blood normo-chromatic erythrocytes (NCEs) of mice in a 14-week gavage study at dose levels of up to 60 mg/kg bw/d.

A small number of dominant lethal studies performed with acrylonitrile have reported negative results following administration by intraperitoneal injection in mice (Leonard et al., 1981), inhalation exposure of mice (Zurkov et al., 1983) and in rats following gavage administration (Working et al., 1987).

An unpublished abstract of a study of the induction of hypoxanthine-guanine phosphoribosyltransferase (Hprt) mutations in the splenic lymphocytes of mice administered acrylonitrile by gavage for 6 weeks (Walker & Ghanayem, 2003) reports positive results in normal mice at the highest dose level tested of 20 mg/kg bw/d and in CYPE2E1 knock-out mice at the highest dose level tested of 60 mg/kg bw/d (which was lethal to normal mice). Results indicate the requirement for metabolic (or enhancement by) oxidative metabolic activation of mutagenicity and also the involvement of mechanisms other than direct DNA-reactive mutagenicity. An study of Lac Z mutagenicity in the Mutamouse model using administration of acrylonitrile in the drinking water at dose levels of up to 750 ppm for 4 weeks and with a 7-week expression period reports negative findings in all tissues investigated (bone marrow, lung, splenic lymphocytes, male germ cells and brain). This assay detects point mutations, therefore indicating that the positive response in the previous study is attributable to large scale changes.

G. Carcinogenicity

The carcinogenicity of acrylonitrile has been investigated in a large number of studies in rats and mice, using oral (gavage, drinking water) and inhalation exposure. The body of literature is much too broad to summarize here, but the results of the studies indicate that acrylonitrile is a multi-site carcinogen in rodent species. However, the IARC downgraded its carcinogenicity classification of acrylonitrile to Group 2B (possibly carcinogenic to humans). This assessment was based on a consideration of the genotoxicity data, animal carcinogenicity and human epidemiological data. It was concluded that, while acrylonitrile was mutagenic in vitro, the results of studies in vivo were largely negative. The clear evidence of carcinogenicity in studies in experimental animals was not considered to be reflected in the epidemiology. The IARC concluded that, on balance, and given the largely unsupportive findings from the other epidemiology studies, the evidence of an increased incidence of lung cancer reported in exposed workers in one early study was not considered to be sufficiently strong to conclude that there was a credible association between acrylonitrile exposure and lung cancer. The earlier indications of an increased cancer risk in workers exposed to acrylonitrile were therefore not confirmed by the more recent studies, which were also considered to be more informative.

Kirman et al (2005) were able to show the link between occupational human exposure and the results of the rodent cancer assays by modelling the exposure concentrations of the metabolite (2-cyanoethylene oxide or CEO, cyanide). A cancer dose–response assessment was conducted for acrylonitrile (AN) using updated information on mechanism of action, epidemiology, toxicity, and pharmacokinetics. Although more than 10 chronic bioassays indicate that AN produces multiple tumors in rats and mice, a number of large, well-conducted epidemiology studies provide no evidence of a causal association between AN exposure and cancer mortality of any type. The epidemiological data include early industry exposures that are far higher than occur today and that approach or exceed levels found to be tumorigenic in animals. Despite the absence of positive findings in the epidemiology data, a dose–response assessment was conducted for AN based on brain tumors in rats. Mechanistic studies implicate the involvement of oxidative stress in rat brain due to CEO, but do not conclusively rule out a potential role for the direct genotoxicity of CEO. A PBPK model was used to predict internal doses (peak CEO in brain) for 12 data sets, which were pooled together to provide a consistent characterization of the dose–response relationship for brain tumor incidence in the rat. The internal dose corresponding to a 5% increase in extra risk (ED05 D 0.017 mg/L brain) and its lower confidence limit (LED05 D 0.014 mg/L brain) was used as the point of departure. The ED05 and LED05 correspond to human equivalent concentrations of 25.9 and 21.3 mg/m^3, respectively, for inhalation exposures, and to human equivalent doses of 2.1 and 1.7 mg/kg-day, respectively, for oral exposures.

H. Reproductive and Developmental Toxicity

The reproductive toxicity of acrylonitrile has been investigated in a number of studies. A two-generation inhalation toxicity study (Nemec et al., 2008) study is considered to be key to the assessment of the reproductive toxicity of acrylonitrile as it includes a comprehensive investigation of a number of relevant parameters and uses an appropriate route of exposure. Sprague-Dawley rats (25/sex/group) were exposed (whole body) by inhalation (6 hours/day) to acrylonitrile vapour at concentrations of 0, 5, 15, 45 or 90 ppm. F0 animals were exposed for 10 weeks prior to mating and throughout mating, gestation and lactation of the subsequent F1 litters. Selected F1 offspring were then similarly exposed following weaning and mated to produce F2 litters. In addition to standard reproductive indices, the study included assessment of oestrus cyclicity and sperm parameters. Postmortem investigations of parental animals included detailed histopathological assessment of the reproductive system and associated organs/tissues, detailed histopathological assessment of brain and nasal tissues. Offspring were additionally investigated for developmental ontogeny. F1 animals exposed to 90 ppm acrylonitrile showed excessive toxicity, therefore this exposure level was not investigated further. Mortality was unaffected by exposure. Systemic toxicity in exposed adult rats was limited to reduced weight gain and food consumption and increased liver weights at 45 and 90 ppm. Local toxicity (nasal irritation) was apparent during and immediately following exposure to 90 ppm; histopathological effects on the nasal tissues consistent with local irritation were also seen in some animals in all exposure groups in the F1 generation, although a NOAEC of 15 ppm for this effect was apparent in the F0 generation. The difference for this effect is attributable to the age at first exposure (8 weeks for F0, 4 weeks for F1) and may be related to differences in nasal morphology, dosimetry There was no evidence of any effect on reproductive parameters, tissues or organs of the reproductive system. Effects on offspring were limited to bodyweight effects.

Neal et al. (2009) provided a review of published and unpublished animal reproductive toxicity studies, human epidemiology studies, other non-standard investigative studies and relevant endpoints from other toxicology studies and discuss the potential of acrylonitrile to cause reproductive toxicity in exposed humans. The authors concluded that no data were seen in animal studies supporting an increased incidence of stillbirths, pre-term or post-term deliveries or maternal mortality following exposure to acrylonitrile at dose levels producing other evidence of systemic toxicity. There was very weak support in the animal data for increased infant mortality, with pup deaths increased only at the high dose level in a single generation of a three-generation reproductive toxicity study. The pup deaths may have been contributed to by decreased water intake of the dams. No evidence of increased pup mortality was seen in the two-generation inhalation reproductive toxicity study, considered to have the highest confidence level. There is no robust evidence for male-mediated toxicity, with only one equivocal study of poor quality reporting a positive result (Ahmed et al., 1992), and other studies, including a well-conducted dominant lethal study (Working et al., 1987) showing no effects. Effects on male reproductive toxicity (changes in sperm parameters or testicular degeneration) were reported in three studies, one of moderate quality

(Tandon et al., 1988) and two of very poor quality. However, several other high- or moderate-quality evaluations showed no effects on the testes or on andrology data, including the Nemec et al. (2008) inhalation reproductive toxicity study, which included the most comprehensive evaluation of these parameters.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for acrylonitrile 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). Drinking water guidelines have been developed using the Reference dose (RfD) approach and the drinking water guidance value. Because acrylonitrile is considered carcinogenic to humans via the oral route of exposure, drinking water guidance value using the guidelines will be developed based on cancer endpoints, which traditionally do not follow this approach. For the purposes of this evaluation, given that drinking water is not a realistic route of exposure for workers, the RfD approach was adapted for acrylonitrile.

Kirman et al (2005) conducted a cancer dose–response assessment for acrylonitrile using updated information on mechanism of action, epidemiology, toxicity, and pharmacokinetics. A PBPK model was used to predict internal doses (peak CEO in brain) for 12 data sets, which were pooled together to provide a consistent characterization of the dose–response relationship for brain tumor incidence in the rat. The internal dose corresponding to a 5% increase in extra risk (ED05, 0.017 mg/L brain) and its lower confidence limit (LED05; 0.014 mg/L brain) was used as the point of departure. For this evaluation, LED05, which corresponds to 1.7 mg/kg-day for oral exposures was used as the NOAEL.

Oral Reference Dose based on Cancer Endpoint (oral RfDc)

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

Where:
NOAEL = LED05 from Kirman et. al. 2005
UF_A (interspecies variability) = 3.2
UF_H (intraspecies variability) = 6.4
UF_L (LED05 = LOAEL to NOAEL) = 10
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1

The values for these uncertainty factors were described in Kirman et al. (2005) and summarized here.

- UF_A: Consistent with the UF_A value used for the oral RfD, the default value of 10 for UF_A can be treated as two specific factors of 3.2 for kinetic variation and 3.2 for dynamic variation. Because PBPK models were used to account for kinetic differences between rats and humans, thereby improving the confidence in the interspecies extrapolation, the kinetic component of UF_A was set equal to one. For the dynamic component of UF_A, a value of 3.2 was used nonlinear approach to account for potential dynamic differences between rats and humans.
- UF_H: The default value of 10 can also be treated as two specific factors of 3.2 for kinetic variation and 3.2 for dynamic variation. A factor of 2.0 was combined with the default factor of 3.2 for human variation in toxicodynamics to yield an UF_H value of 6.4 to account for the use of a PBPK model and variability analysis to address human variation for peak CEO in brain following oral exposure.
- UF_L: The authors conclude that a 5% response level reflects a fairly significant response and cannot be treated as a NOAEL for an effect of this severity. A UF_L of 10 was selected to account for the 5% increase in risk.

Applying the RfDc and the uncertainty factors results in an the oral reference dose of 0.009 mg/kg-day.

Oral RfDc = 1.7/(3.2 x 6.4 x 10 x 1 x 1) = 1.7/200 = 0.009 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 RfDc,

Drinking water guidance value = (oral RfDc) 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 = (0.009 x 70 x 0.1)/2 = 0.03 mg/L

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

The substance does not exhibit the following physico-chemical properties:

· Explosivity
· Flammability

· Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Acute toxicity studies for algae, invertebrates, and fish were reviewed . The invertebrate, *Daphnia magna* appeared to be the most sensitive species with a 48 hr LC50 of 2.5 mg/L while the the EC50 for the algae, *Pseudokirchneriella subcapitata* was determined to be 10 mg/L.

Details of test results are provided below.

B. Aquatic Toxicity

Acute Studies

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

Table 2: Acute Aquatic Toxicity Studies on Acrylonitrile

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oryzias latipes	96-hr LC_{50}	5.1	1	ECHA
Daphnia magna	48-hr EC_{50}	2.5	1	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	10	1	ECHA

Chronic Studies

The 30-day LOEC to *Pimephales promelas* in a fish early life stage test was 0.34 mg/L. A NOEC of 0.17 mg/L is derived by LOEC/2. (ECHA) [Kl. score = 2].

The 21-day NOEC from a *Daphnia* reproduction test is 0.5 mg/L (ECHA) [Kl. score = 2].

The 72-hr NOEC to *Pseudokirchneriella subcapitata* is 0.95 mg/l based on growth rate (ECHA) [Kl. score = 1].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for acrylonitrile 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 (0.17 mg/L), invertebrates (2.5 mg/L), and algae (10 mg/L). Results from chronic studies are available for fish (0.34 mg/L), invertebrates (0.5 mg/L), and algae (0.95 mg/L). On the basis that the data consists of short-term studies for three trophic levels and long-term results studies for three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC of 0.17 mg/L for fish. The $PNEC_{water}$ is 0.017 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 $PNEC_{soil}$ is 0.002 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.17/1500) \times 1000 \times 0.017$
$= 0.002$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 8.511 \times 0.02$
$= 0.17$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for acrylonitrile based on the molecular connectivity index (MCI) is 8.511 L/kg (EPA, 2018).
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).

Acrylonitrile is inherently biodegradable; thus, it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of 1.04, acrylonitrile does not meet the screening criteria for bioaccumulation.

The lowest chronic NOEC for acrylonitrile is >0.1 mg/L. The acute E(L)C_{50} values are >1 mg/L. Thus, acrylonitrile does not meet the criteria for toxicity.

The overall conclusion is that acrylonitrile is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable liquid – category 2
Carcinogenicity – category 1B
Acute toxicity – category 3
Acute toxicity – category 3
Specific target organ toxicity (single exposure) – category 3
Skin irritation – category 2
Eye damage – category 1
Hazardous to the aquatic environment (chronic) – category 2
Skin sensitisation – category 1

B. Labelling

Danger

C. Pictogram

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

A. First Aid

Eye Contact
Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a poison control center or doctor/physician

Skin Contact
Remove all contaminated clothing. Rinse skin with water/shower. Call a poison center or doctor/physician if you feel unwell. Wash contaminated clothing before reuse. If skin irritation or rash occurs: Get medical advice/attention

Inhalation
Remove victim to fresh air and keep at rest in a position comfortable for breathing. Call a poison center or doctor/physician

Ingestion
Do not induce vomiting. Call a physician or Poison Control Center immediately. Rinse mouth.

Notes to Physician
Causes severe eye damage. May cause allergic skin reaction. Inhalation of high vapor concentrations may cause symptoms like headache, dizziness, tiredness, nausea and vomiting: Symptoms of allergic reaction may include rash, itching, swelling, trouble breathing, tingling of the hands and feet, dizziness, lightheadedness, chest pain, muscle pain or flushing. Treat symptomatically.

Medical Conditions Aggravated by Exposure
Asthma or other respiratory conditions may be aggravated by exposure to the substance

Emergency Personnel Protection
Avoid contact with – or ingestion of – the chemical. Acrylonitrile is flammable; take precautionary measures against static discharge.

B. Fire Fighting Information

Extinguishing Media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide. Cool closed containers exposed to fire with water spray.

Specific Exposure Hazards
In advanced or massive fires, fire-fighting should be done from a safe distance or a protected location. Isolate for 1/2 mile in all directions if tank car or truck is involved in fire.

Vapors may form explosive mixtures with air. Vapors are heavier than air and may travel to source of ignition and flash back. Liquid may float on water.
Containers may explode when heated.

Hazardous Combustion Products: Nitrogen oxides (NOx) Carbon monoxide (CO) Carbon dioxide (CO2) Hydrogen cyanide (hydrocyanic acid)

Special Protective Equipment for Firefighters
Materials are too dangerous to health to expose fire fighters. A few whiffs of vapor could cause death or vapour or liquid could be fatal on penetrating the fire fighter's normal full protective clothing. The normal full protective clothing and breathing apparatus available to the average fire department will not provide adequate protection against inhalation or skin contact with these materials. Explosion hazard is moderate. It is flammable and explosive at normal room temperatures. Can react violently with strong acids, amines, strong alkalis. Vapors may travel considerable distance to source of ignition and flash back. Dilute solutions are also hazardous (flash point of a solution of 2 percent in water is 70F). When heated or burned, toxic hydrogen cyanide gas and oxides of nitrogen are formed. As in any fire, wear self-contained breathing apparatus and full protective gear. Thermal decomposition can lead to release of irritating gases and vapors.

C. Accidental Release Measures

Personal Precautions
Ensure adequate ventilation. Use personal protective equipment. Keep people away from and upwind of spill/leak. Evacuate unprotected persons. Remove all sources of ignition. Take precautionary measures against static discharges.

Environmental Precautions
Do not flush into surface water or sanitary sewer system.

Steps to be Taken if Material is Released or Spilled
Keep in suitable, closed containers for disposal. Soak up with inert absorbent material. Remove all sources of ignition. Use spark-proof tools and explosion-proof equipment.

D. Storage and Handling

General Handling
Wear personal protective equipment. Do not get in eyes, on skin, or on clothing. Use only under a chemical fume hood. Do not breathe vapors or spray mist. Do not ingest. Keep away from open flames, hot surfaces and sources of ignition. Use only non-sparking tools. To avoid ignition of vapors by static electricity discharge, all metal parts of the equipment must be grounded. Take precautionary measures against static discharges.

Other Handling Precautions
Respiratory protection required if ventilation is not sufficient.
Chemical is flammable and explosive at normal room temperatures.

Storage
Keep away from heat and sources of ignition. Keep away from direct sunlight. Keep container tightly closed in a dry and well-ventilated place.

Can react violently with strong acids, amines, strong alkalis. Avoid strong acids, amines, alkalis. Incompatible with strong oxidizers
(especially bromine) copper and copper alloys. Unstable, moderate hazard is possible when it is exposed to flames, strong acids, amines and alkalis.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
The workplace exposure standard for acrylonitrile in Australia is 2 ppm (4.3 mg/m3) as an 8-hr TWA. No STEL is listed.

Engineering Controls
Ensure adequate ventilation, especially in confined areas. Use explosion-proof electrical/ventilating/lighting/equipment. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protection Equipment
Respiratory Protection:
Use approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Hand Protection:
Protective gloves; inspect before use.

Skin Protection:
Long sleeved clothing.

Eye protection:

Wear appropriate protective eyeglasses or chemical safety goggles

Other Precautions:

Explosion hazard is moderate. It is flammable and explosive at normal room temperatures.
The vapour is heavier than air and may travel along the ground; distant ignition possible.

F. TRANSPORT INFORMATION

UN Number 1093
Hazard Class 3

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

AICS: Listed

XIII. REFERENCES

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ALCOHOLS, C6-12, ETHOXYLATED PROPOXYLATED

This dossier on alcohols, C_{6-12}, ethoxylated propoxylated presents the most critical studies pertinent to the risk assessment of alcohols, C_{6-12}, ethoxylated propoxylated 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 Human & Environmental Risk Assessment on Ingredients of European Household Cleaning Products: Alcohol Ethoxylates (HERA, 2009) 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): Alcohols, C_{6-12}, ethoxylated propoxylated

CAS RN: [redacted]

Molecular formula: Not available (UVCB substance)

Molecular weight: Not available (UVCB substance)

Synonyms: (C6-C12) Alkyl alcohol ethoxylate propoxylate; Ethoxylated propoxylated alcohols (C6-12)

SMILES: Not available (UVCB substance)

Alcohol ethoxylates (AE) are a class of non-ionic surfactants that have the basic structure $C_{x-y}AE_n$. The subscript (x-y) following the 'C' indicates the range of carbon chain units. The hydrocarbon chain can be either linear or branched. AEs also contain an ethylene oxide (E) chain attached to the alcohol. The degree of ethylene oxide polymerization is indicated by the subscript (n), which indicates the average number of ethylene oxide units. In household products, the average EO chain length ranges between 3 and 12 units (HERA, 2009).

II. PHYSICO-CHEMICAL PROPERTIES

No information is available for alcohols, C_{6-12}, ethoxylated propoxylated. Key physical and chemical properties for read-across AEs are shown in Table 1.

Table 1: Overview of the physico-chemical properties of alcohols, C_6-C_8-(even numbered, linear) ethoxylated (<2.5 EO) [CAS RN [redacted]

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Colourless, viscous liquid	1	ECHA
Melting Point	≤30°C @ 101.3 kPa	1	ECHA
Boiling Point	105°C @ 101.3 kPa	1	ECHA
Density	947 kg/m^3@ 20°C	1	ECHA
Vapour Pressure	1400 Pa @ 20°C	1	ECHA

Property	Value	Klimisch Score	Reference
Partition Coefficient (log K_{ow})	1.5 @ 23°C	1	ECHA
Water Solubility	4 g/L @ 20°C	1	ECHA
Flash Point	111°C	1	ECHA
Auto flammability	230°C	1	ECHA
Viscosity	13.3 mPa s @ 20°C	1	ECHA
Henry's Law Constant	Not available	-	

Table 2: Overview of the Physico-chemical Properties of Alcohols, C_{9-11}, Branched and Linear, Ethoxylated (1 – 2.5 moles ethoxylated) [CAS RN [redacted]

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Colourless to light yellow liquid	2	ECHA
Melting Point	≤20°C @ 101.3 kPa	1	ECHA
Boiling Point	260° @ 101.3 kPa	2	ECHA
Density	940 kg/m³ @ 20°C	1	ECHA
Vapour Pressure	Negligible	-	ECHA
Partition Coefficient (log K_{ow})	3.74 @ 25°C	2	ECHA
Water Solubility	Moderately soluble	2	ECHA
Flash Point	125°C	1	ECHA
Auto flammability	311°C	1	ECHA
Viscosity	0.01112 mPa s @ 40°C	1	ECHA
Henry's Law Constant	Not available		A

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Alcohols, C_{6-12}, ethoxylated propoxylated is expected to be readily biodegradable. It has a low potential for bioaccumulation and a moderate potential for absorption to soil and sediment.

B. Biodegradation

In an OECD 301 B test, degradation of alcohols, C_{6-8} alkyl-(even, linear), ethoxylated (<2.5 EO) [CAS RN [redacted] was 63% in 28 days. The 10-day window was met (ECHA) [KI.score=1].

An alcohol ethoxylate, C_{9-11}, branched (2.5 EO) [CAS RN [redacted] was readily biodegradable, as indicated by degradation of 72% in 28 days in an ultimate aerobic biodegradability (CO_2 headspace) ISO 14593 water quality test (ECHA) [KI.score=2].

An alcohol ethoxylate, C_{9-11}, branched (3 EO) [CAS RN [redacted] was readily biodegradable, as indicated by degradation of 101% in 28 days in an ultimate aerobic biodegradability (CO_2 headspace) ISO 14593 water quality test (ECHA) [KI.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 alcohols, C_{6-12}, ethoxylated propoxylated. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value for alcohols, C_{6-12}, ethoxylated propoxylated is 10.1 L/kg (MCI) and 5.946 L/kg (K_{ow}).

D. Bioaccumulation

The 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 × kg/d) and elimination rates varied from 3.3 to 59 per day (Toll et al., 2000). The high concentrations in fish are thought to be prevented by an efficient biotransformation of the alcohol ethoxylates, leading to a high elimination rate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of alcohols, C_{6-12}, ethoxylated is expected to be low by the oral and dermal routes. The skin irritation with alcohols, C_{12-16}, ethoxylated have shown mixed results in rabbits, but human patch studies on these alcohol ethoxylates do not support a skin irritant classification. Alcohols, ethoxylated are expected to be irritating to the eyes of rabbits. Alcohols, ethoxylated do not appear to be skin sensitisers. Repeated dose toxicity studies on alcohol ethoxylates similar to alcohols, C_{12-16}, ethoxylated in rats do not indicate any target organ effects. These alcohol ethoxylates are not genotoxic or carcinogenic and have a low potential for reproductive and developmental toxicity.

B. Acute Toxicity

The oral LD_{50} in rats for $C_{7-9}AE_6$ is >2,000 mg/kg (HERA, 2009) [KI.score=2]. The oral LD_{50} in rats for $C_{11}AE_9$ is 1,100 mg/kg (HERA, 2009) [KI.score=2]. The oral LD_{50} in rats for $C_{9-11}AE_{2.5}$ is between 4,000 and 10,000 mg/kg (HERA, 2009) [KI.score=2]. The oral LD_{50} in rats for $C_{9-11}AE_8$ is 1,200 mg/kg (HERA, 2009) [KI.score=2]. The oral LD_{50} in rats for $C_{12-13}AE_{6.5}$ is 2,100 mg/kg (HERA, 2009) [KI.score=2].

The 4-hour inhalation LC_{50} value for $C_{9-11}AE_5$ is >0.22 mg/L as a mist. The mass median aerodynamic diameter (MMAD) were 3.4 mm and 3.0 mm in the two exposure tests (HERA, 2009) [KI.score=2].

The acute dermal LD_{50} of $C_{7-9}AE_6$ is >2,000 mg/kg (HERA, 2009) [KI.score=2]. The acute dermal LD_{50} of $C_{9-11}AE_6$ is >2,000 mg/kg (HERA, 2009) [KI.score=2]. An acute dermal LD_{50} values of >2,000 mg/kg were determined for $C_{12-14}AE_3$ and $C_{12-14}AE_6$ in two separate studies (HERA, 2009) [KI.score=2].

C. Irritation

Skin

Application of $C_{9-11}AE_9$ to the skin of rabbits for 4 hours under semi-occlusive conditions was found to be slightly irritating (HERA, 2009) [Kl.score=2]. Application of $C_{11}AE_9$ to the skin of rabbits for 4 hours under occluded conditions was found to be slightly irritating (HERA, 2009) [Kl.score=2]. Application of $C_{9-11}AE_6$ to the skin of rabbits for 24 hours under occluded conditions was found to be severely irritating (HERA, 2009) [Kl.score=2].

Eye

Instillation of $C_{7-9}AE_{12}$ into the eyes of rabbits was minimally irritating (HERA, 2009). Instillation of $C_{9-11}AE_6$ into the eyes of rabbits was moderately to severely irritating (HERA, 2009). Instillation of $C_{7-9}AE_6$ into the eyes of one rabbit was severely irritating (HERA, 2009).

D. Sensitisation

In a guinea pig maximization test, alcohols, C_{6-C8}-(even numbered, linear)-ethoxylated (<2.5 EO) was not found to be a skin sensitizer (ECHA) [Kl.score=1].

In a guinea pig maximization test, $C_{12-13}AE<2.5$ (CAS RN [redacted] was not found to be a skin sensitizer (ECHA) [Kl.score=2].

E. Repeated Dose Toxicity

Oral

Male and female CFE (SPF) rats were given in their feed 0, 125, 250, 500, 1,000 or 3,000 ppm (0, 6.25, 12.5, 25, 50 and 150 mg/kg-day) $C_{9-11}AE_6$ for 13 weeks. There was no mortality and no treatment-related clinical signs. Body weights were significantly lower in the >250 ppm males throughout the study; body weights of the 125 ppm males were lower for only the first half of the study. Feed consumption was lower in treated males with the change being statistically significant in the >1,000 ppm males. This reduction in feed consumption was thought to be a palatability issue; the feed conversion efficiency values were similar for treated and control males, and so it is not possible to attribute the reduced body weights to the toxicity of the test material alone. The female rats showed no differences in body weights and feed consumption. There were no treatment-related changes in hematology parameters, and the clinical chemistry parameters and organ weights showed no changes that were of toxicological significance. Gross pathology showed no treatment-related changes. The NOAEL for this study was 3,000 ppm, which corresponds to 150 mg/kg-day (ECHA) [Kl.score=2].

Rats were given in their feed 0, 0.04, 0.2 or 1% $C_{9-11}AE_8$ for 90 days. There were no deaths or treatment-related clinical signs during the study. There was reduced body weight gain and decreased feed consumption in the 1% animals and in the 0.2% females throughout the study. Additional statistical analysis indicated a significant decrease in mean body weight gain in the 1% females and decreased feed consumption in the 1% males and females. The reduced body weight gain of the 0.2% females was not statistically significant. The study authors considered these changes to be due to the poor palatability of the test material in the feed. Organ weights and gross and microscopic pathology were similar across groups. The NOAEL for this study is 1% in the diet, which corresponded to 400 mg/kg-day (HERA, 2009) [Kl.score=2].

Rats were given in their feed 0, 125, 250 or 500 mg/kg $C_{10}AE_5$ for 90 days. There were no deaths or treatment-related clinical signs during the study. The only treatment-related effect noted was a slight increase in absolute liver weights, with the 500 mg/kg animals showing statistical significance. However, there were no corresponding histopathologic changes in the liver. The NOAEL is 500 mg/kg-day, the highest dose tested (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 based on 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].

Rats were given in their diet 0, 0.1, 0.5 or 1% $C_{12\text{-}13}AE_{6.5}$ 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 incidence 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].

Inhalation

There are no studies available.

Dermal

Male and female F344 rats were given dermal applications of 0, 1, 10 or 25% $C_{9\text{-}11}AE_6$ solutions 3 days/week for 13 weeks. There were no deaths during the study and no clinical signs of toxicity. Body weights, clinical chemistry and hematology parameters, and urinalysis showed no differences between treated and control animal. The 25% animals showed a slight increase in kidney weights, although no histopathologic findings were noted in the kidney. There were no histopathologic changes that were considered to be treatment related. The NOAEL for this study is 25% (Gingell & Lu, 1991; ECHA) [Kl.score=2].

F. Genotoxicity

In Vitro Studies

The genotoxicity studies conducted on alcohol ethoxylates are reviewed in HERA (2009). Representative results of the *in vitro* genotoxicity studies on alcohol ethoxylates similar to alcohols, $C_{6\text{-}12}$, ethoxylated propoxylated are presented in Table 3.

Table 3: *In vitro* genotoxicity studies on selected alcohol ethoxylates

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (S. typhimurium strains)	-	-	2	HERA, 2009

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (S. typhimurium strains)	-	-	2	HERA, 2009
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 $C_{12-15}AE_3$ or $C_{12-14}AE_9$. There were no increases in the frequency of micronuclei in the bone marrow cells (Talmage, 1994) [Kl.score=2].

G. Carcinogenicity

Oral

Male and female Sprague-Dawley rats were given in their diet $C_{12-13}AE_{6.5}$ 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 with the control group. No treatment-related histopathology was found, and no increase in tumour incidence was observed (HERA, 2009) [Kl.score=2].

Inhalation

There are no studies available.

Dermal

There are no studies available.

H. Reproductive Toxicity

A two-generation reproductive toxicity study was conducted on $C_{9-11}AE_6$. Male and female F344 rats were given dermal applications of 0, 1, 10 or 25% solutions of $C_{9-11}AE_6$ (0, 10, 100 or 250 mg/kg-day) 3 days/week; the F_0 and F_1 generations were treated for 119 and 133 days, respectively, before mating. There were no deaths in the F_0 generation, but there were 5 deaths in the F_1 generation (controls and treatment groups) that were not considered to be treatment related. Animals in either generation showed no skin reactions. Body weights of the 25% F_0 and F_1 parental animals were lower during certain periods of the study; however, maternal body weights in both generations were similar across groups during the gestational and lactational periods. The organ weights in the F_0 animals were similar between treated and control animals; the F_1 parental animals showed sporadic organ weight changes but were not no toxicological significance. There were no histopathologic changes that correlated with the organ weight changes in the F_1 parental animals. Mating and fertility indices were similar across groups in both generations. There were no treatment-related effects on testicular weights, testicular pathology, serum counts and LDH-X activity toxicity in either generation. Macroscopic and microscopic evaluations of the reproductive organ showed no treatment-related effects. The NOAEL for reproductive toxicity for toxicity is 25% test concentration, which corresponded to 250 mg/kg-day, the highest dose tested (Gingell & Lu, 1991; ECHA) [Kl.score=2].

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 with 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].

I. Developmental Toxicity

Oral

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 fetal 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 $C_{12}AE_6$ 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 fetuses or 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].

Inhalation

There are no studies available.

Dermal

A two-generation reproductive toxicity study was conducted on $C_{9\text{-}11}AE_6$. Male and female F344 rats were given dermal applications of 0, 1, 10 or 25% solutions 3 days/week; the F_0 and F_1 generations were treated for 119 and 133 days, respectively, before mating. There were no deaths in the F_0 generation, but there were 5 deaths in the F_1 generation (controls and treatment groups) that were not considered to be treatment related. Animals in either generation showed no skin reactions. Body weights of the 25% F_0 and F_1 parental animals were lower during certain periods of the study; however, maternal body weights in both generations were similar across groups during the gestational and lactational periods. The organ weights in the F_0 animals were similar between treated and control animals; the F_1 parental animals showed sporadic organ weight changes but were not no toxicological significance. There were no histopathologic changes that correlated with the organ weight changes in the F_1 parental animals. There was no effect on litter size, survival index, sex ratio or body weights of the pups in either the F_1 or F_2 generation. The NOAEL for developmental toxicity is 25% test concentration, which corresponded to 250 mg/kg-day, the highest dose tested (Gingell & Lu, 1991; ECHA) [Kl.score=2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for alcohols, $C_{6\text{-}12}$, ethoxylated propoxylated 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

A two-year dietary study in rats has been conducted on $C_{12\text{-}13}AE_{6.5}$ (HERA, 2009). The NOAEL from this study 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, $C_{6\text{-}12}$, ethoxylated propoxylated.

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) = 1
- UF_D (database uncertainty) = 1
- Oral RfD = 50/(10 × 10 × 1 × 1 × 1) = 50/100 = 0.5 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 = (0.5 × 70 × 0.1)/2 = 1.8 mg/L

B. Cancer

The alcohol ethoxylate $C_{12\text{-}13}AE_{6.5}$ was not carcinogenic to rats in a two-year dietary study. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Alcohols, C_{6-12}, ethoxylated propoxylated does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

There are no aquatic toxicity studies for alcohols, C_{6-12}, ethoxylated propoxylated. The aquatic toxicity of other AEs has been extensively evaluated in numerous studies on fish, daphnids and algae as well as microorganisms. A review of the acute studies indicates that invertebrates are somewhat more sensitive to AEs than fish and algae. AEs have moderate chronic toxicity to aquatic life.

B. Aquatic Toxicity

Acute Studies

There are no acute aquatic toxicity studies for alcohols, C_{6-12}, ethoxylated propoxylated. The aquatic toxicity of other AEs has been extensively evaluated in numerous studies on fish, daphnids and algae as well as microorganisms. Table 4 lists the results of acute aquatic toxicity studies on read across substance alcohols, C12-C15, ethoxylated (1 to 2.5 EO) [CAS RN [redacted] alcohols, C12-C14, ethoxylated (2 EO) [CAS RN [redacted] and alcohols, C12-C15, branched and linear, ethoxylated [CAS RN [redacted]

Table 4: Acute aquatic toxicity studies on ethoxylated C12-C16 alcohol[a,b,c]

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Oncorhynchus mykiss (Rainbow Trout)	96-hr LC_{50}	1.3 – 1.7[a]	2	ECHA
Danio Rio	96-hr LC_{50}	1.2[b]	2	ECHA
Danio Rio	96-hr LC_{50}	2[b]	2	ECHA
Zebrafish	96-hr LC_{50}	>2[c]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.14[a]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.23[a]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.53[b]	2	ECHA
Daphnia magna	48-hr EC_{50}	2.84[b,d]	2	ECHA
Daphnia magna	48-hr EC_{50}	1.2[e]	1	ECHA
Daphnia magna	48-hr EC_{50}	>2[b]	2	ECHA
Daphnia magna	48-hr EC_{50}	>2[c]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.23	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	0.75[a]	2	ECHA

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Pseudokirchneriella subcapitata	72-hr EC_{50}	>2[c]	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	0.41[b]	2	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	0.778[b]	2	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	0.87[e]	1	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	1.3[e]	1	ECHA

a: Read across to alcohols, C12-C15, ethoxylated (1 to 2.5 EO) CAS RN [redacted]
b: Read across to alcohols, C12-C14, ethoxylated (EO 2) CAS RN [redacted]
c: Read across to alcohols, C12-C15, branched and linear, ethoxylated (CAS RN [redacted]
d: Alcohols, C12-C14, ethoxylated (EO 1) CAS RN [redacted] as WAF (water accommodated fraction)
e: Alcohols, C12-C14, ethoxylated (EO 4 or EO 6) CAS RN [redacted]

A review of the acute studies indicates that invertebrates are somewhat more sensitive to AEs than fish and algae. As concluded in HERA (2009), the Danish EPA (2001) found that the acute toxicity of AEs to invertebrates varies, with EC_{50} values from 0.1 mg/L to more than 100 mg/L for linear AE and from 0.5 mg/L to 50 mg/L for branched AEs. The toxicity is species specific and may vary between 0.29 mg/L and 270 mg/L for the same linear AEs (Lewis & Suprenant 1983, quoted in Danish EPA, 2001). The most commonly used invertebrates for testing are *Daphnia magna* and *Daphnia pulex*, and they are also among the most sensitive invertebrates to AEs. The Danish EPA (2001) found that some AEs are very toxic to invertebrates, i.e., linear AEs of C12-15 EO1-8 and branched AEs with a low degree of branching, i.e. < 10–25%. They concluded that branching of the alkyl chain reduces the toxicity of AEs to invertebrates, as also observed for algae (Danish EPA, 2001). However, the data used for this conclusion were from specially synthesized AE, which have a significantly higher toxicity than AEs used commercially (Kaluza & Taeger, 1996).

Chronic Studies

In developing a water quality guideline for AEs (ANZG, 2018), the toxicity data were normalised for a specific alkyl chain length or a specific number of EO groups. The NOECs listed below were normalised to an alkyl chain length of C13.3 and EO of 8.2. There were chronic data for 13 species that belonged to 7 taxonomic groups (fish, crustacea, blue alga, diatoms, green alga, protozoa and worms).

Freshwater fish: 2 species, 720 to 1,500 µg/L.

Freshwater crustaceans: 2 species, 590 to 860 µg/L.

Freshwater rotifers: 1 species, *Brachionus calyciflorus*, 1,300 µg/L.

Freshwater algae, diatoms and blue-green algae: 6 species, 200 to 8,700 µg/L.

Freshwater mesocosms: 4 NOEC data for multiple species tests were 80, 80, 320 and 330 µg/L, although replication was insufficient to meet OECD (1992) requirements. Normalised data were 380, 380, 320 and 1,520 µg/L.

C. Terrestrial Toxicity

No studies are available. The substance is readily biodegradable. Therefore, soil is not expected to be a compartment of concern. Thus, the risk to terrestrial macroorganisms is regarded to be negligible (ECHA).

D. Calculation of PNEC

The PNEC calculations for alcohols, $C_{6\text{-}12}$, ethoxylated propoxylated follow the methodology discussed in DEWHA (2009).

PNEC Water

The ANZG water quality guideline (2018) in freshwater is: "A high reliability trigger value of 140 µg/L was derived for AE (normalized data) using the statistical distribution method with 95% protection."

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 0.11 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.994/1280) \times 1000 \times 0.14$
$= 0.11$ 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]

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]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.404/1000 \times 2400]$
$= 0.994\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 10.1 \times 0.04$
$= 0.404$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for alcohols, $C_{6\text{-}12}$, ethoxylated propoxylated calculated from EPISUITE™ using the MCI is 10.1 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 0.019 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.202/1500) \times 1000 \times 0.14$
$= 0.019$ 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]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 10.1 \times 0.02$
$= 0.202\ m^3/m^3$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for alcohols, C6-12, ethoxylated propoxylated calculated from EPISUITE™ using the MCI is 10.1 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 (IChEMS, 2022; ECHA, 2023).

Alcohols, C_{6-12}, ethoxylated propoxylated is readily biodegradable and thus does not meet the screening criteria for persistence.

The bioconcentration factors (BCF) in fish for ethoxylated alcohols (which includes alcohols, C_{6-12}, ethoxylated propoxylated) have been reported to range from <5 to 387.5. Thus, alcohols, C_{6-12}, ethoxylated propoxylated does not meet the criteria for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on alcohols, C_{6-12}, ethoxylated propoxylated are > 0.1 mg/L. Thus, alcohols, C_{6-12}, ethoxylated propoxylated does not meet the criteria for toxicity.

The overall conclusion is that alcohols, C6-12, ethoxylated propoxylated is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not Classified

B. Labelling

None

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

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. Firefighting 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 area.

Steps to be Taken if Material is Released or Spilled

Absorb spill with inert absorbent material, and 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

The workplace exposure standards for alcohols, C6-12, ethoxylated propoxylated in Australia has not been established.

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

Alcohols, C6-12, ethoxylated propoxylated 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.

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ALCOHOLS, C10-16, ETHOXYLATED PROPOXYLATED

This dossier on alcohols, C_{10-16}, ethoxylated propoxylated presents the most critical studies pertinent to the risk assessment of alcohols, C_{10-16}, ethoxylated propoxylated 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 Human & Environmental Risk Assessment on Ingredients of European Household Cleaning Products: Alcohol Ethoxylates (HERA, 2009), 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): Alcohols, C_{10-16}, ethoxylated propoxylated

CAS RN: [redacted]

Molecular formula: Not available (UVCB substance)

Molecular weight: Not available (UVCB substance)

Synonyms: Ethoxylated propoxylated C_{10-16} alcohols

SMILES: Not available (UVCB substance)

Alcohol ethoxylates (AE) are a class of non-ionic surfactants that have the basic structure $C_{x-y}AE_n$. The subscript (x-y) following the 'C' indicates the range of carbon chain units. The hydrocarbon chain can be either linear or branched. AEs also contain an ethylene oxide (EO) chain attached to the alcohol. The degree of ethylene oxide polymerization is indicated by the subscript (n) which indicates the average number of ethylene oxide units. In household products, the average EO chain length ranges between 3 and 12 units (HERA, 2009).

II. PHYSICO-CHEMICAL PROPERTIES

No information is available for alcohols, C_{10-16}, ethoxylated propoxylated. Key physical and chemical properties for read-across AEs are shown in Table 1.

Table 1: Overview of the physico-chemical properties of alcohols, C_{12-15}, ethoxylated (1 to 2.5 moles ethoxylated) [CAS RN [redacted]

Property	Value	Klimisch Score	Reference
Physical state at 20oC and 101.3 kPa	Clear liquid with a rancid odor*	2	ECHA
Melting Point	7.22°C @ 101.3 kPa	2	ECHA
Boiling Point	287°C @ 101.3 kPa	1	ECHA
Density	926 kg/m^3@ 15.56°C	1	ECHA
Vapour Pressure	Negligible	-	ECHA
Partition Coefficient (log K_{ow})	5.06 @ 25°C	2	ECHA

Property	Value	Klimisch Score	Reference
Water Solubility	0.007-0.063 g/L @ 25°C	2	ECHA
Flash Point	165.56°C	2	ECHA
Auto flammability	235°C	2	ECHA
Viscosity	28.1 mPa s @ 20°C	2	ECHA
Henry's Law Constant	Not available	-	ECHA

*Based on alcohols, C_{12-14}, ethoxylated (1 to 2.5 EO) [CAS RN [redacted]

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Alcohols, C_{10-16}, ethoxylated propoxylated is expected to be readily biodegradable. It has a low potential for bioaccumulation and a moderate potential for adsorption to soil and sediment.

B. Biodegradation

An alcohol ethoxylate, C_{9-11}, branched (2.5 EO) [CAS RN [redacted] was readily biodegradable, as indicated by degradation of 72% in 28 days in an ultimate aerobic biodegradability (CO_2 headspace) ISO 14593 water quality test (ECHA) [KI.score=2].

An alcohol ethoxylate, C_{9-11}, branched (3 EO) [CAS RN [redacted] was readily biodegradable, as indicated by degradation of 101% in 28 days in an ultimate aerobic biodegradability (CO_2 headspace) ISO 14593 water quality test (ECHA) [KI.score=2].

Alcohols, C_{12-15}, ethoxylated is readily biodegradable. In an OECD 301B test, degradation was 72% in 28 days but failed the 10-day window (ECHA) [KI.score=1].

An alcohol, C_{12-15}, ethoxylated (7 EO) was readily biodegradable, as indicated by degradation of 80 to 88% in 28 days when tested using a shake-flask CO_2-evolution test method (ECHA) [KI.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 alcohols, C_{10-16}, ethoxylated propoxylated. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value for alcohols, C_{10-16}, ethoxylated propoxylated is 1,180 L/kg (MCI) and 3,882 L/kg (K_{ow}).

D. Bioaccumulation

The 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 × kg/d) and elimination rates varied from 3.3 to 59 per day (Toll et al., 2000). The high concentration in fish is thought to be prevented by an efficient biotransformation of the alcohol ethoxylates, leading to a high elimination rate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The substance displays a relatively low order of acute toxicity. It is expected to be absorbed via the gastrointestinal tract following oral absorption and minor amounts are expected to be absorbed via the skin. Most of the absorbed dose is rapidly excreted via urine and faeces with a minor amount being expired via CO_2.Tests with similar substances indicate irritation in animal evaluations while human patch tests suggest relatively minimal irritation post exposure. Additionally, the weight of evidence suggests ethoxylates are likely to be irritating to the eyes. Ethoxylates are not expected to be sensitizers.

While no inhalation studies were found, oral and dermal repeat dose studies with similar substances do not indicate significant toxicity.

Similar substances do not demonstrate genotoxicity according to *in vitro* and *in vivo* studies and there was no evidence for any in vivo carcinogenic activity after long term oral dosing.

Relatively high NOAELs obtained from 2-generation oral dosing do not support a conclusion that the ethoxylates are reproductively and developmentally toxic.

B. Metabolism

100% of the ^{14}C-labelled alcohol ethoxylates (AE) are assumed to be absorbed via the gastrointestinal tract after oral ingestion and distributed widely in the body. Only minor amounts of the AE are directly absorbed via the skin (2%). The majority of the absorbed dose is rapidly excreted via urine and feces and minor parts via expired CO_2 with more of the AE being excreted via the feces and expired in air as the ethoxy (EO) chain length increased. Moreover, the length of the alkyl chain is assumed to have an impact on AE with longer alkyl chains being excreted at a higher proportion into expired air and less into the urine and faeces. A maximum of 1% of the administered dose was found in liver and kidneys, respectively. Metabolism is shown to be rapid and complete. The most likely pathway of AE metabolism is expected to be the hydrolysis of the ether linkage and subsequent oxidation of the alcohols to finally form C_2-fragments and shorter alkyl chains and ultimately carbon dioxide and water. The lower molecular weight polyethylene glycol-like compounds are further broken down via ether hydrolysis or are subjected to renal excretion (ECHA).

C. Acute Toxicity

The oral LD_{50} in rats for $C_{11}AE_9$ is 1,100 mg/kg (HERA, 2009) [Kl.score=2].

The oral LD_{50} in rats for $C_{9\text{-}11}AE_{2.5}$ is between 4,000 and 10,000 mg/kg (HERA, 2009) [Kl.score=2]. The oral LD_{50} in rats for $C_{9\text{-}11}AE_8$ is 1,200 mg/kg (HERA, 2009) [Kl.score=2]. The oral LD_{50} in rats for $C_{12\text{-}13}AE_{6.5}$ is 2,100 mg/kg (HERA, 2009) [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 4-hour inhalation LC_{50} value for $C_{9\text{-}11}AE_5$ is >0.22 mg/L as a mist. The mass median aerodynamic diameters (MMAD) were 3.4 mm and 3.0 mm in the two exposure studies (HERA, 2009) [Kl.score=2].

The acute dermal LD_{50} of $C_{9\text{-}11}AE_6$ is >2,000 mg/kg (HERA, 2009) [Kl.score=2]. 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].

D. Irritation

Skin

Application of $C_{9\text{-}11}AE_9$ to the skin of rabbits for 4 hours under semi-occlusive conditions was found to be slightly irritating (HERA, 2009) [KI.score=2]. Application of $C_{11}AE_9$ to the skin of rabbits for 4 hours under occluded conditions was found to be slightly irritating (HERA, 2009) [KI.score=2]. Application of $C_{9\text{-}11}AE_6$ to the skin of rabbits for 24 hours under occluded conditions was found to be severely irritating (HERA, 2009) [KI.score=2].

Application of 0.5 mL isotridecanol, ethoxylated (3 EO) to the skin of rabbits for 4 hours under occlusive conditions was considered irritating (ECHA) [KI. score = 2]. Application of 0.5 mL isotridecanol, branched, ethoxylated (3-4 EO) to the skin of rabbits for 24 hours under occlusive conditions was considered irritating (ECHA) [KI. 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) [KI. score = 2]. Application of 0.5 mL $C_{12\text{-}13}AE<2.5$ (CAS RN [redacted] to the skin of rabbits for 24 hours under occlusive conditions was considered irritating (ECHA) [KI.score=2].

Application of 0.5 mL alcohols $C_{12\text{-}13}$, branched and linear, <2.5 EO to the skin of rabbits for 4 hours under occlusive conditions was not considered irritating (ECHA) [KI.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 edema in any subjects (HERA, 2009) [KI.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) [KI.score=2]. Nonetheless, current classification according to ECHA recommends classification as an irritant.

Eye

Instillation of $C_{9\text{-}11}AE_6$ into the eyes of rabbits was moderately to severely irritating (HERA, 2009).

Instillation of 0.1 mL isotridecanol, ethoxylated (3 EO) (CAS RN [redacted] into the eyes of rabbits was severely irritating. The means of the 24, 48, and 72 hour scores were 1.6 for corneal opacity, 0.6 for iridial lesions, 2.2 for conjunctival redness, and 0.7 for chemosis. The effects were not fully reversible within 21 days (ECHA) [KI.score=2].

Instillation of 0.1 mL isotridecanol, branched, ethoxylated (3-4 EO) (CAS RN [redacted] into the eyes of rabbits was severely irritating. The means of the 24, 48, and 72 hour scores were 1.0 for corneal opacity, 0.1 for iridial lesions, 1.7 for conjunctival redness, and 0.6 for chemosis. The effects were not fully reversible within 8 days (ECHA) [KI.score=2].

Instillation of 0.1 mL alcohols $C_{12\text{-}13}$, branched and linear, <2.5 EO (CAS RN [redacted] into the eyes of rabbits was not irritating. The means of the 24, 48, and 72 hour scores were 0.00 for corneal opacity, 0.00 for iridial lesions, 0.83 for conjunctival redness, and 0.50 for chemosis (ECHA) [KI.score=2].

Instillation of 0.1 mL $C_{12\text{-}13}AE<2.5$ (CAS RN [redacted] into the eyes of rabbits was not irritating. The means of the 24, 48, and 72 hour scores were 0.00 for all endpoints (ECHA) [KI.score=2].

E. Sensitisation

In a guinea pig maximization test, $C_{12\text{-}13}AE<2.5$ (CAS RN [redacted] was not considered a skin sensitizer (ECHA) [KI.score=2].

F. Repeated Dose Toxicity

Oral

Male and female CFE (SPF) rats were given in their feed 0, 125, 250, 500, 1,000, or 3,000 ppm (0, 6.25, 12.5, 25, 50, and 150 mg/kg-day) $C_{9\text{-}11}AE_6$ for 13 weeks. There was no mortality and no treatment-related clinical signs. Body weights were significantly lower in the ≥250 ppm males throughout the study; body weights of the 125 ppm males were lower for only the first half of the study. Feed consumption was lower in treated males with the change being statistically significant in the ≥1,000 ppm males. This reduction in feed consumption was thought to be related to palatability; the feed conversion efficiency values were similar for treated and control males, and so it is not possible to attribute the reduced body weights to the toxicity of the test material alone. The female rats showed no differences in body weights and feed consumption. There were no treatment-related changes in hematology parameters, and the clinical chemistry parameters and organ weights showed no changes that were considered to be of toxicological significance. Gross pathology showed no treatment-related changes. The NOAEL for this study was considered to be 3,000 ppm, which corresponds to150 mg/kg-day (ECHA) [KI.score=2].

Rats were given in their feed 0, 0.04, 0.2, or 1% $C_{9\text{-}11}AE_8$ for 90 days. There were no deaths or treatment-related clinical signs during the study. There was reduced body weight gain and decreased feed consumption in the 1% animals and in the 0.2% females throughout the study. Additional statistical analysis indicated a significant decrease in mean body weight gain in the 1% females and decreased feed consumption in the 1% males and females. The reduced body weight gain of the 0.2% females was not statistically significant. The study authors considered these changes to be due to the poor palatability of the test material in the feed. Organ weights, gross and microscopic pathology were similar across groups. The NOAEL for this study is 1% in the diet, which corresponded to 400 mg/kg-day (HERA, 2009) [KI.score=2].

Rats were given in their feed 0, 125, 250, or 500 mg/kg $C_{10}AE_5$ for 90 days. There were no deaths or treatment-related clinical signs during the study. The only treatment-related effect noted was a slight increase in absolute liver weights with the 500 mg/kg animals showing statistical significance. However, there were no corresponding histopathologic changes in the liver. The NOAEL is 500 mg/kg-day, the highest dose tested (HERA, 2009) [KI.score=2].

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) [KI.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].

Rats were given 0, 0.1, 0.5 or 1% $C_{12\text{-}13}AE_{6.5}$ in their diet 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 incidence in the treated animals was higher than in the controls. The NOAEL was established at 0.1% or 50 mg/kg-day (HERA, 2009) [Kl.score=2]

Inhalation

There are no studies available.

Dermal

Male and female F344 rats were given dermal applications of 0, 1, 10, or 25% $C_{9\text{-}11}AE_6$ solutions 3 days/week for 13 weeks. There were no deaths during the study and no clinical signs of toxicity. Body weights, clinical chemistry and hematology parameters, and urinalysis showed no differences between treated and control animal. The 25% animals showed a slight increase in kidney weights, although no histopathologic findings were noted in the kidney. There were no histopathologic changes that were considered to be treatment related. The NOAEL for this study is 25% (Gingell and Lu, 1991; ECHA) [Kl.score=2].

G. Genotoxicity

In Vitro Studies

The genotoxicity studies conducted on alcohol ethoxylates are reviewed in HERA (2009). The results of few of the *in vitro* genotoxicity studies on similar alcohol ethoxylates to alcohols $C_{10\text{-}16}$, ethoxylated propoxylated are presented in Table 2.

Table 2: *In vitro* genotoxicity studies on selected alcohol ethoxylates

``Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (S. typhimurium strains)	-	-	2	HERA, 2009
Bacterial reverse mutation (S. typhimurium strains)	-	-	2	HERA, 2009
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 $C_{12-15}AE_3$ or $C_{12-14}AE_9$. 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 $C_{14-15}AE_7$. There were no increases in chromosomal aberrations in the bone marrow cells (HERA, 2009 [Kl.score=2].

H. Carcinogenicity

Oral

Male and female Sprague-Dawley rats were given in their diet $C_{12-13}AE_{6.5}$ 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 tumor incidence was observed (HERA, 2009) [Kl.score=2].

Male and female Charles River rats were given 0, 0.1, 0.5 or 1% $C_{14-15}AE_7$ in their diet for two years. There were no treatment-related changes in general behavior 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 tumor incidence (HERA, 2009) [Kl.score=2]

Male and female Sprague-Dawley rats were given in their diet $C_{14-15}AE_7$ 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].

Inhalation

There are no studies available.

Dermal

There are no studies available.

I. Reproductive Toxicity

A two-generation reproductive toxicity study was conducted on $C_{9-11}AE_6$. Male and female F344 rats were given dermal applications of 0, 1, 10, or 25% solutions of $C_{9-11}AE_6$ (0, 10, 100, or 250 mg/kg-day) 3 days/week; the F_0 and F_1 generations were treated for 119 and 133 days, respectively, before mating. There were no deaths in the F_0 generation, but there were 5 deaths in the F_1 generation (controls and treatment groups) that were not considered to be treatment related. Animals in either generation showed no skin reactions. Body weights of the 25% F_0 and F_1 parental animals were lower during certain periods of the study; however, maternal body weights in both generations were similar across groups during the gestational and lactational periods. The organ weights in the F_0 animals were similar between treated and control animals; the F_1 parental animals showed sporadic organ weight changes but were not no toxicological significance. There were no histopathologic changes that correlated with the organ weight changes in the F_1 parental animals. Mating and

fertility indices were similar across groups in both generations. There were no treatment-related effects on testicular weights, testicular pathology, serum counts and LDH-X activity toxicity in either generation. Macroscopic and microscopic evaluations of the reproductive organ showed no treatment-related effects. The NOAEL for reproductive toxicity for toxicity is 25% test concentration, which corresponded to 250 mg/kg-day, the highest dose tested (Gingell and Lu, 1991; ECHA) [Kl.score=2].

CD rats were given 0, 0.05, 0.1 or 0.5% (approximately 0, 25, 50 or 250 mg/kg-day) $C_{12}AE_6$ in their diet 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 F1 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 F0 and F1 generations. The NOAEL for reproductive toxicity is 0.5% in the diet or 250 mg/kg-day (HERA, 2009) [Kl.score=2].

J. Developmental Toxicity

Oral

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) C12AE6. 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 $C_{12}AE_6$ 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].

Inhalation

There are no studies available.

Dermal

A two-generation reproductive toxicity study was conducted on $C_{9\text{-}11}AE_6$. Male and female F344 rats were given dermal applications of 0, 1, 10, or 25% solutions 3 days/week; the F_0 and F_1 generations were treated for 119 and 133 days, respectively, before mating. There were no deaths in the F_0 generation, but there were 5 deaths in the F_1 generation (controls and treatment groups) that were not considered to be treatment related. Animals in either generation showed no skin reactions. Body weights of the 25% F_0 and F_1 parental animals were lower during certain periods of the study; however, maternal body weights in both generations were similar across groups during the gestational and lactational periods. The organ weights in the F_0 animals were similar between treated and control animals; the F_1 parental animals showed sporadic organ weight changes but were not no toxicological significance. There were no histopathologic changes that correlated with the organ weight changes in the F_1 parental animals. There was no effect on litter size, survival index, sex ratio, or body weights of the pups in either the F_1 or F_2 generation. The NOAEL for developmental toxicity is 25% test concentration, which corresponded to 250 mg/kg-day, the highest dose tested (Gingell and Lu, 1991; ECHA) [Kl.score=2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for alcohols, $C_{10\text{-}16}$, ethoxylated propoxylated 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

A two-year dietary study in rats has been conducted on $C_{12\text{-}13}AE_{6.5}$ (HERA, 2009). The NOAEL from this study 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 $C_{10\text{-}16}$, ethoxylated propoxylated.

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) = 1
UF_D (database uncertainty) = 1
Oral RfD = 50/(10 × 10 × 1 × 1 × 1) = 50/100 = 0.5 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 = (0.5 × 70 × 0.1)/2 = <u>1.8 mg/L</u>

B. Cancer

The alcohol ethoxylates $C_{12\text{-}13}AE_{6.5}$ and $C_{14\text{-}15}AE_{7}$ were not carcinogenic to rats in a two-year dietary study. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Alcohols, $C_{10\text{-}16}$, ethoxylated propoxylated does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

There are no aquatic toxicity studies for alcohols, $C_{10\text{-}16}$, ethoxylated propoxylated. The aquatic toxicity of other AEs has been extensively evaluated in numerous studies on fish, daphnids and algae as well as microorganisms. A review of the acute studies indicates that invertebrates are somewhat more sensitive to AEs than fish and algae. AEs have moderate chronic toxicity to aquatic life.

B. Aquatic Toxicity

<u>Acute Studies</u>

There are no acute aquatic toxicity studies for alcohols, $C_{10\text{-}16}$, ethoxylated propoxylated. The aquatic toxicity of other AEs has been extensively evaluated in numerous studies on fish, daphnids and algae as well as microorganisms. Table 3 lists the results of acute aquatic toxicity studies on read across substance alcohols, C12-C15, ethoxylated (1 to 2.5 EO) [CAS RN [redacted] alcohols, C12-C14, ethoxylated (2 EO) [CAS RN [redacted] and alcohols, C12-C15, branched and linear, ethoxylated [CAS RN [redacted]

Table 3: Acute Aquatic Toxicity Studies on Ethoxylated C12-C16 Alcohol[a,b,c]

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Oncorhynchus mykiss (Rainbow Trout)	96-hr LC_{50}	1.3 – 1.7[a]	2	ECHA
Danio Rio	96-hr LC_{50}	1.2[b]	2	ECHA

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Danio Rio	96-hr LC_{50}	2[b]	2	ECHA
Zebrafish	96-hr LC_{50}	>2[c]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.14[a]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.23[a]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.53[b]	2	ECHA
Daphnia magna	48-hr EC_{50}	2.84[b,d]	2	ECHA
Daphnia magna	48-hr EC_{50}	1.2[e]	1	ECHA
Daphnia magna	48-hr EC_{50}	>2[b]	2	ECHA
Daphnia magna	48-hr EC_{50}	>2[c]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.23	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	0.75[a]	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	>2[c]	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	0.41[b]	2	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	0.778[b]	2	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	0.87[e]	1	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	1.3[e]	1	ECHA

a: Read across to alcohols, C12-C15, ethoxylated (1 to 2.5 EO) CAS RN [redacted]
b: Read across to alcohols, C12-C14, ethoxylated (EO 2) CAS RN [redacted]
c: Read across to alcohols, C12-C15, branched and linear, ethoxylated (CAS RN [redacted]
d: Alcohols, C12-C14, ethoxylated (EO 1) CAS RN [redacted] as WAF (water accommodated fraction)
e: Alcohols, C12-C14, ethoxylated (EO 4 or EO 6) CAS RN [redacted]

A review of the acute studies indicates that invertebrates are somewhat more sensitive to AEs than fish and algae. As concluded in HERA (2009), the Danish EPA (2001) found that the acute toxicity of AEs to invertebrates varies, with EC_{50} values from 0.1 mg/l to more than 100 mg/l for linear AE and from 0.5 mg/l to 50 mg/l for branched AEs. The toxicity is species specific and may vary between 0.29 mg/l and 270 mg/l for the same linear AEs (Lewis and Suprenant 1983, quoted in Danish EPA 2001). The most commonly used invertebrates for testing are Daphnia magna and Daphnia pulex, and they are also among the most sensitive invertebrates to AEs. The Danish EPA (2001) found that some AEs are very toxic to invertebrates, i.e., linear AEs of C12-15 EO1-8 and branched AEs with a low degree of branching, i.e. < 10-25%. They concluded that branching of the alkyl chain reduces the toxicity of AEs to invertebrates, as also observed for algae (Danish EPA 2001). However, the data used for this conclusion was from specially synthesized AE, which have a significantly higher toxicity than AEs used commercially (Kaluza and Taeger, 1996).

Chronic Studies

In developing a water quality guideline for AEs (ANZG, 2018), the toxicity data was normalised for a specific alkyl chain length or a specific number of EO groups. The NOECs listed below were normalised to an alkyl chain length of C13.3 and EO of 8.2. There were chronic data for 13 species that belonged to 7 taxonomic groups (fish, crustacea, blue alga, diatoms, green alga, protozoa, and worms).

Freshwater fish: 2 species, 720 to 1,500 µg/L.

Freshwater crustaceans: 2 species, 590 to 860 µg/L.

Freshwater rotifers: 1 species, *Brachionus calyciflorus*, 1,300 µg/L.

Freshwater algae, diatoms and blue-green algae: 6 species, 200 to 8,700 µg/L.

Freshwater mesocosms: 4 NOEC data for multiple species tests were 80, 80, 320 and 330 µg/L, although replication was insufficient to meet OECD (1992) requirements. Normalised data were 380, 380, 320 and 1,520 µg/L.

C. Terrestrial Toxicity

No studies are available. The substance is readily biodegradable. Therefore, soil is not expected to be a compartment of concern. Thus, the risk to terrestrial macroorganisms is regarded to be negligible (ECHA).

D. Calculation of PNEC

The PNEC calculations for alcohol, $C_{10\text{-}16}$, ethoxylated propoxylated follow the methodology discussed in DEWHA (2009).

PNEC Water

The ANZG water quality guideline (2018) in freshwater is: “A high reliability trigger value of 140 µg/L was derived for AE (normalized data) using the statistical distribution method with 95% protection.”

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 2.57 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (23.5/1280) \times 1000 \times 0.14$
$= 2.57$ 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]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 47.2/1000 \times 2400]$
$= 23.5\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 1180 \times 0.04$
$= 47.2$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for alcohols, $C_{10\text{-}16}$, ethoxylated propoxylated calculated from EPISUITE™ using the MCI value is 1,180 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 $PNEC_{soil}$ value is 2.20 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (23.6/1500) \times 1000 \times 0.14$
$= 2.20$ 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]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 1180 \times 0.02$
$= 23.6\ m^3/m^3$

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for alcohols, $C_{10\text{-}16}$, ethoxylated propoxylated calculated from EPISUITE™ using the MCI value is 1,180 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).

Alcohols, $C_{10\text{-}16}$, ethoxylated propoxylated is readily biodegradable and thus does not meet the screening criteria for persistence.

The bioconcentration factors (BCF) in fish for ethoxylated alcohols (which includes alcohols, C_{10-16}, ethoxylated propoxylated) have been reported to range from <5 to 387.5. Thus, alcohols, C_{10-16}, ethoxylated propoxylated does not meet the screening criteria for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on alcohols, C_{10-16}, ethoxylated propoxylated are > 0.1 mg/L. Thus, alcohols, C_{10-16}, ethoxylated propoxylated does not meet the criteria for toxicity.

The overall conclusion is that alcohols, C_{10-16}, ethoxylated propoxylated is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

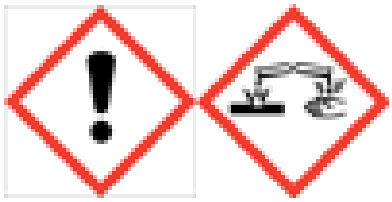
A. Classification

Eye Irritant Category 2

B. Labelling

Warning

C. Pictogram



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

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. Firefighting 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 area.

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

The workplace exposure standards for alcohols, $C_{10\text{-}16}$, ethoxylated propoxylated in Australia has not been established.

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

Alcohols, $C_{10\text{-}16}$ ethoxylated propoxylated 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

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ALCOHOLS, C12-15, ETHOXYLATED

This dossier on alcohols, C12-15, ethoxylated presents the most critical studies pertinent to the risk assessment of alcohols, C12-15, ethoxylated 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 Human & Environmental Risk Assessment on Ingredients of European Household Cleaning Products: Alcohol Ethoxylates (HERA, 2009), 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: Alcohols, C12-15, ethoxylated

CAS RN: [redacted]

Molecular formula: (C2H4O)1-3(CH2)10-13C2H6O

Molecular weight: Not available

Synonyms: Alcohols, C12-15, ethoxylated

SMILES: Not available

Alcohol ethoxylates (AE) are a class of non-ionic surfactants that have the basic structure $C_{x-y}AE_n$. The subscript (x-y) following the 'C' indicates the range of carbon chain units. The hydrocarbon chain can be either linear or branched. AEs also contain an ethylene oxide (E) chain attached to the alcohol. The degree of ethylene oxide polymerization is indicated by the subscript (n) which indicates the average number of ethylene oxide units. Alcohols, C12-15, ethoxylated (CAS No. [redacted] has an average number of 1 to 2.5 moles of ethylene oxide units.

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the 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 odor*	2	ECHA
Melting Point	7.22°C	2	ECHA
Boiling Point	ca. 287°C	1	ECHA

Property	Value	Klimisch score	Reference
Density	0.926 g/cm^3 @ 15.56°C	1	ECHA
Vapor 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]
**Weight-averaged log K_{oc} of whole substance based on normalized composition

III. 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™ (EPA, 2019), 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 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.

IV. 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 sensitizer. 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 edema 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. Sensitization

No sensitization studies are available on alcohols, C12-15, ethoxylated.

In a guinea pig maximization test, $C_{12\text{-}13}AE_{<2.5}$ (CAS No. [redacted] was not considered a skin sensitizer (ECHA) [Kl. score = 2].

In a guinea pig maximization tests, $C_{12\text{-}15}AE_3$, $C_{12\text{-}15}AE_7$, and $C_{14\text{-}15}AE_7$ were not considered skin sensitizers (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 $\geq$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 $\geq$0.5% male rats and $\geq$0.25% females. Histopathologic examination showed hepatocytic enlargement in the $\geq$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 $\geq$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 $\geq$0.5% male rats and $\geq$0.25% females. Histopathologic examination showed hepatocytic enlargement in the $\geq$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 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 $\geq$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 hemoglobin were identified in one or both sexes fed in the $\geq$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 $\geq$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 $\geq$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
$C_{14\text{-}15}AE_7$	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 tumor

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 behavior 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 tumor 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 behavior, 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 behavior 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 behavior, 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 fetal 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 fetuses 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].

V. 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

Oral

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 = 0.5 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 = (0.5 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.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Alcohols, C12-15, ethoxylated does not exhibit the following physico-chemical properties:

· Explosivity
· Flammability
· Oxidizing potential

VII. 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, 2000), the toxicity data was normalized for a specific alkyl chain length or a specific number of ethoxylate (EO) groups. The NOECs listed below were normalized 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. Normalized 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 (normalized 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 III.C).
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).

Alcohols, C12-15, ethoxylated is readily biodegradable and thus does not meet the screening criteria for persistence.

The bioconcentration factors (BCF) 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.

IX. CLASSIFICATION AND LABELLING

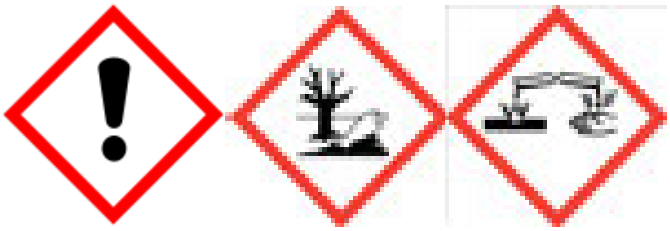
A. Classification

Acute Toxicity Category 4 [Oral]
Eye Irritant Category 2
Aquatic Chronic Toxicity Category 3

B. Labelling

Warning

C. Pictogram



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

A. First Aid

Eye Contact
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 area

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 isotridecanol, ethoxylated.

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.

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

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ALCOHOLS, C12-16, ETHOXYLATED
POLY(OXY-1,2-ETHANEDIYL), α-HYDRO-ω-HYDROXY-, MONO-C10-14 ALKYL ETHERS, PHOSPHATES

This dossier on alcohols, C12-16, ethoxylated and similar alcohol ethoxylate poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates, a similar alcohol ethoxylate, present 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 information presented in this dossier was obtained primarily from the Human & Environmental Risk Assessment on Ingredients of European Household Cleaning Products: Alcohol Ethoxylates (HERA, 2009), 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).

For the purpose of this dossier, alcohols, C12-15, ethoxylated (CAS RN [redacted] has been reviewed as a surrogate chemical for ethoxylated C12-C16 alcohol (CAS RN [redacted] and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates (CAS RN [redacted] where appropriate.

I. SUBSTANCE IDENTIFICATION

Chemical Name: Alcohols, C12-16, ethoxylated

CAS RN: [redacted]

Molecular formula: $H–(CH_2)_{12–16}–(OCH_2CH_2)_n–OH$ (where n is the average number of EO units)

Molecular weight: Not available (UVCB substance)

Synonyms: Alcohols, C12-16, ethoxylated, Ethoxylated C12-16 alcohols; polyethylene glycol, dodecyl, tetradecyl, hexadecyl ether

SMILES: Not available (UVCB substance)

Chemical Name (IUPAC): Poly(oxy-1,2-ethanediyl), a-hydro-w-hydroxy-, mono-C10-14-alkyl ethers, phosphates

CAS RN: [redacted]

Molecular formula: No data

Molecular weight: No data

Synonyms: Poly(oxy-1,2-ethanediyl), .alpha.-hydro-.omega.-hydroxy-, mono-C10-14 (even numbered)-alkyl ethers, phosphates

SMILES: No data

Alcohol ethoxylates (AE) are a class of non-ionic surfactant polymers that have the basic structure $C_{x-y}AE_n$. The subscript (x-y) following the 'C' indicates the range of carbon chain units. The hydrocarbon

chain can be either linear or branched. AEs also contain an ethylene oxide (EO) chain attached to the alcohol. The degree of EO polymerization is indicated by the subscript (n) which indicates the average number of EO units. Ethoxylated C12-C16 alcohol (CAS RN [redacted] has an average number of 1 to 6 moles of EO units.

II. PHYSICO-CHEMICAL PROPERTIES

No information is available on alcohols, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates. Therefore, data were read across from a similar substance, alcohols, C12-15, ethoxylated (CAS RN [redacted] as shown below.

Table 1: Overview of the 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° (pressure not provided)	2	ECHA
Boiling Point	271.11–516.11°C (pressure not provided)	2	ECHA
Density	ca. 930 kg/m^3 @ 20°C	2	ECHA
Vapor Pressure	<1 Pa@ 25°C	2	ECHA
Partition coefficient (log K_{ow})	5.06** @ 25°C	2	ECHA
Water Solubility	0.021 g/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°	2	ECHA

*Based on alcohols, C12-15, ethoxylated (1 to 2.5 EO) [CAS RN [redacted]
**Weight-averaged log K_{oc} of whole substance based on normalized composition

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Based on a review of read-across substances, alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates are readily biodegradable. They have a low potential for bioaccumulation and a moderate potential for adsorption to soil and sediment.

B. Biodegradation

There are no studies available for alcohol, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates.

AE homologues with linear hydrocarbon chain lengths from C8 to C15 and mean values ranging from 3-20 EO units are readily biodegradable (HERA, 2009).

Alcohols, C12-C14, ethoxylated (7-8) degraded to 100% in 28 days in a die away screening test (HERA, 2009) [KI.score=2].

Alcohols, C12-15, ethoxylated is readily biodegradable. In an OECD 301B test, degradation of 10 mg/L of alcohols, C12-15. ethoxylated was 72% after 28 days but it failed the 10-day window (ECHA) [KI.score=1].

In an OECD 301B test, degradation of 20 mg/L of alcohols, C12-15. ethoxylated was 61% after 28 days but it failed the 10-day window (ECHA) [KI.score=1].

A 240 mg/L concentration of alcohol, C12-15, ethoxylated (7 EO) degraded 80- 88% in 28 days when tested using a shake-flask CO_2-evolution test method (ECHA) [KI.score=2].

If a chemical is found to be readily biodegradable, it is categorized as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

C. Environmental Distribution

There are no experimental data are available for alcohols, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates. Using KOCWIN in EPISuite™ (EPA, 2018), the estimated K_{oc} values for surrogates of alcohols, C12-16, ethoxylated are: K_{oc} for C12-C16 linear alcohol, ethoxylated (2 EO): 3,920 L/kg (molecular connectivity index, MCI) and 13,530 L/kg (K_{ow}).

Based on these K_{oc} values, if released to soil, the alcohols, C12-C16 ethoxylated and similar AE poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates are expected to adsorb strongly to soil and it is expected to have a low potential for mobility.

D. Bioaccumulation

The potential for bioaccumulation of AEs is considered low due to the biotransformation and excretion of the substance. The various studies present considerable evidence that AEs are rapidly eliminated and metabolised (ECHA).

The BCF values for alcohol ethoxylates in fathead minnows have been reported to range from <5 to 387.5 L/kg (Toll et al., 2000; as cited in ECHA) [KI.score=2]. The uptake rates varied from 330 to 1660 (L × kg/d) and elimination rates varied from 3.3 to 59 per day (Toll et al., 2000; as cited in ECHA) [KI. score=2]. The high concentration in fish is thought to be prevented by an efficient biotransformation of the alcohol ethoxylates, leading to a high elimination rate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates is low by the oral and dermal routes. Skin irritation studies in rabbits on alcohols, C12-16, ethoxylated have shown mixed results, but human patch studies on these alcohol ethoxylates do not support a skin irritant classification. Alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates is expected to be irritating to the eyes of rabbits. Alcohols, C12-16, ethoxylated is not a skin sensitiser. Repeated dose toxicity studies on alcohol ethoxylates similar to alcohols, C12-16, ethoxylated in rats

do not indicate any target organ effects. These alcohol ethoxylates are not genotoxic, carcinogenic, and they have a low potential for reproductive and developmental toxicity.

B. Acute Toxicity

There are no acute toxicity studies are available on alcohols, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), a-hydro-w-hydroxy-, mono-C10-14-alkyl ethers, phosphates.

Oral

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).

The acute oral LD_{50} for alcohols, C12-C15, ethoxylated in male and female Wistar rats is >5000-<10,000 mg/kg bw (ECHA) [KI. score = 2].

Inhalation

The 4-hour LC_{50} for alcohols, C12-C15, ethoxylated in male and female Sprague-Dawley rats is > 1,600 mg/m^3 (>1.6 mg/L) (ECHA) [KI. score =2].

Dermal

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].

The acute dermal LD_{50} for alcohols, C12-C15, ethoxylated in male and female Wistar rats >2000 mg/kg bw (ECHA) [KI.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 edema 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]. Nonetheless, the substance is classified by ECHA as an irritant (see Section IX).

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 $C_{12-14}AE_3$, $C_{12-14}AE_6$, $C_{13}AE_6$, and $C_{12-14}AE_{10}$ were found to be moderately to severely irritating to the eyes of rabbits (HERA, 2009). In another study, $C_{12-15}AE_{11}$ 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: $C_{12-15}AE_3$, $C_{14-15}AE_7$, $C_{12-14}AE_{15}$, $C_{14-15}AE_{18}$, and $C_{13}AE_{20}$ (HERA, 2009).

D. Sensitisation

There are no sensitisation studies are available on alcohols, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates.

In a guinea pig maximization test, $C_{12-13}AE_{<2.5}$ (CAS RN [redacted] was not considered a skin sensitiser (ECHA) [KI.score=2].

In guinea pig maximization tests, $C_{12-15}AE_3$, $C_{12-15}AE_7$, and $C_{14-15}AE_7$ were not considered skin sensitisers (HERA, 2009) [KI.score=2].

E. Repeated Dose Toxicity

Oral

There are no repeated dose toxicity studies are available on alcohols, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates. Data for similar ethoxylates are presented below.

Rats were given 0%, 0.0313%, 0.0625%, 0.125, 0.25, 0.5 or 1.0% $C_{12-15}AE_7$ in their diet 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 based on 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) [KI.score=2].

Rats were fed $C_{12-14}AE_7$ 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 based on 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) [KI.score=2].

Male and female Wistar rats given in their diet 0, 300, 1,000, 3,000, and 10,000 ppm $C_{14-15}AE_7$ 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 hemoglobin 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 0, 0.1, 0.5, or 1% $C_{14\text{-}15}AE_7$ in their diet 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 0, 0.1, 0.5 or 1% $C_{12\text{-}13}AE_{6.5}$ or $C_{14\text{-}15}AE_7$ in their diet 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 incidence 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 $C_{14\text{-}15}AE_7$ at 0.1, 0.5 and 1% in their diet 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 0.5% in the diet, which corresponded to 162 and 190 mg/kg-day for males and females, respectively (HERA, 2009) [Kl.score=2].

An OECD guideline 422 (Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test) was conducted in male and female Wistar rats exposed to a daily (7 days a week) dose of 100, 300, and 1,000 mg/kg bw/day of alcohols, C12-C15, ethoxylated by oral gavage for 29 (males) -64 days (females). Slightly increased plasma albumin concentrations were observed in males at the 300 and 1000 mg/kg bw/day dose levels, increased plasma urea concentrations were observed in males at the 1000 mg/kg bw/day dose level, decreased plasma cholesterol concentrations in males at the 300 and 1000 mg/kg bw/day levels and increased bile acid concentrations in females at the 1000 mg/kg bw/day dose level were considered as non-adverse since these changes were not associated with any adverse pathological alterations. Non-adverse test item-related morphologic alterations were present in males and females at the 1000 mg/kg bw/day dose level in the liver (macroscopically enlarged liver, centrilobular hypertrophy, increased weights starting at 100 mg/kg bw/day in males and 300 mg/kg bw/day in females), forestomach (squamous cell hyperplasia) and jejunum (vacuolation in the lamina propria), in males starting at 100 mg/kg bw/day in the thyroid gland (follicular cell hypertrophy and increased weights at 1000 mg/kg bw/day) and in females at 1000 mg/kg/day in the adrenal gland (macroscopically enlarged adrenal gland, diffuse cortical hypertrophy, and increased weights at 1000 mg/kg bw/day). There were no toxicologically significant changes were noted in any of the remaining parameters investigated in this study, i.e., mortality, clinical appearance, functional

observations (motor activity, grip strength, hearing ability, pupillary reflex and static righting reflex), body weight, food consumption, hematology and clotting parameters, male T4 thyroid hormone. A systemic NOAEL of ≥1000 mg/kg bw/day and a reproductive toxicity NOAEL of ≥1000 mg/kg bw/day was established for this study (ECHA) [KI. score = 1].

Inhalation

There are no studies are available.

Dermal

There are 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, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates 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
$C_{14\text{-}15}AE_7$	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) [KI.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) [KI.score=2].

G. Carcinogenicity

There are no studies are available on alcohols, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates. Therefore, data from similar substances are presented below.

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) [KI.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) [KI.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) [KI.score=2].

H. Reproductive Toxicity

There are studies are available on alcohols, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates.

CD rats were given 0, 0.05, 0.1 or 0.5% (approximately 0, 25, 50 or 250 mg/kg-day) $C_{12}AE_6$ in their diet 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) [KI.score=2].

In a two-generation developmental and teratogenicity study, CD rats were given 0, 0.05, 0.1 or 0.5% $C_{14\text{-}15}AE_7$ (approximately 0, 25, 50 or 250 mg/kg-day) in their diet. 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) [KI.score=2].

A sub-acute reproductive and developmental toxicity screening study was completed using male and female Wistar rats exposed to 100, 300, and 1,000 mg/kg bw/day of alcohols, C12-15, ethoxylated via oral gavage for 29 (males)-64 (females) days. All the females had regular cycles of 4 to 5 days. Extended di-oestrous occurred during the mating period in three females of the control group and two females of the mid-dose group (300 mg/kg bw/day) with a regular cycle during premating. One female at 300 mg/kg bw/day had an inconclusive cycle determination during the premating phase. Given their absence of a dose-related incidence, this finding did not indicate a relation with

treatment. Length and regularity of the oestrous cycle were considered not to have been affected by treatment with the test item up to 1000 mg/kg bw/day. Mating index was not affected by treatment. The mating indices were 90, 100, 100 and 100% for the control, 100, 300 and 1000 mg/kg bw/day groups, respectively. One female of the control group did not mate. All paired females showed evidence of mating within 4 days, except one female at 300 mg/kg bw/day for which mating took 13 days. Hence, precoital time was not affected by treatment with the test item. Number of implantation sites was considered not to be affected by treatment. The mean number of implantation sites were 11.0, 8.9, 12.9 and 12.1 for the control, 100, 300 and 1000 mg/kg bw/day, respectively. The relatively low mean number of implantation sites at 100 mg/kg bw/day was attributed to the low number of implantation sites in three females (4, 1 and 2 implantation sites, respectively). In the absence of a dose-related incidence, the relatively low mean number of implantation sites at 100 mg/kg bw/day was considered not to be related to treatment with the test item. One female at 100 mg/kg bw/day and one female at 1000 mg/kg bw/day were not pregnant. In the absence of a dose-related incidence of non-pregnancy, this was considered not to be related to treatment with the test item. The fertility indices were 100, 90, 100 and 90% for the control, 100, 300 and 1000 mg/kg bw/day groups, respectively. It was considered not to be affected by treatment of the animals. Gestation index and duration of gestation were not affected by treatment with the test item up to 1000 mg/kg bw/day. The gestation indices were 100% for all groups. All pregnant females had 21-22 days gestation, except for one female at 100 mg/kg bw/day which only had 19 days of gestation (her litter consisted of 1 pup only). Given the incidental occurrence and lack of a dose-related trend, no toxicological relevance was attributed to this early delivery. No signs of difficult or prolonged parturition and no deficiencies in maternal care were noted among the pregnant females. A NOAEL for systemic toxicity was reported to be ≥1000 mg/kg bw/day ECHA) [KI. score =1].

A two-generation reproductive toxicity study was completed using male and female Fischer 344 rats exposed to 10, 100, and 250 mg/kg bw/day alcohols, C12-15, ethoxylated via dermal exposure. No mortalities were observed in the parental generation, and the five deaths in the F_1 adult males and females in the control and treatment groups were not considered to be compound related. In the highest dose group, body weights of both males and females in both treated generations were sporadically decreased compared to controls. There was no effect on maternal body weight during gestational and lactational periods in both generations. At necropsy organ weight differences in liver, lung, kidney, and heart were observed in the F_1 generation. However, there were no pathological findings that were associated with these affected organs. There were no compound-related effects on mating and fertility indices and mean gestational length in both generations. No effects on testicular weights, sperm counts and LDH-X activities in F_0 and F_1 male adults were observed. Macroscopic and microscopic examination of the reproductive organs did not reveal significant differences in the treated groups compared to the controls. A NOAEL for systemic toxicity was reported to be ≥ 250 mg/kg bw/day based on changes in body and organ weights that were not associated with histopathological findings. A reproductive toxicity NOAEL was reported to be ≥ 250 mg/kg bw/day (ECHA)[KI. score = 2].

I. Developmental Toxicity

There are no studies are available on alcohols, C12-16, ethoxylated or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates.

In a two-generation reproductive toxicity study, Charles River rats were given 0, 0.05, 0.1 or 0.5% (about 0, 25, 50 or 250 mg/kg-day) $C_{12}AE_6$ in their diet. 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) [KI.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) [KI.score=2].

A developmental toxicity study was conducted using Fischer 344 rats exposed to 10,100,250 mg/kg bw/day alcohols, C12-15 ethoxylated via dermal exposure three days a week from gestation day 0 until weaning. In the highest dose, body weights of both males and females in both treated generations were sporadically and not always statistically significant decreased compared to controls. At necropsy organ weight differences in liver, lung, kidney, and heart were observed in the F1 generation, but no pathological findings were associated with the affected organs. There were no treated related effects reported for the foetuses. The NOAEL for developmental toxicity was reported to be ≥ 250 mg/kg bw/day and the NOAEL for maternal toxicity was reported to be ≥ 250 mg/kg bw/day. The NOAEL for fetotoxicity was reported to be ≥250 mg/kg bw/day (ECHA) [KI.score=2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates 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

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, C12-16, ethoxylated.

Oral Reference Dose (oral RfD)

$$\text{Oral RfD} = \text{NOAEL} / (UF_A \times UF_H \times UF_L \times UF_{Sub} \times UF_D)$$

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

Oral RfD = 50/(10 × 10 × 1 × 1 × 1) = 50/100 = 0.5 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 = (0.5 × 70 × 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.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Alcohols, C12-16, ethoxylated does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

There are no aquatic toxicity studies for ethoxylated C12-C16 alcohol or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates. The aquatic toxicity of other AEs has been extensively evaluated in numerous studies on fish, daphnids and algae as well as microorganisms. A review of the acute studies indicates that invertebrates are somewhat more sensitive to AEs than fish and algae. AEs have moderate chronic toxicity to aquatic life.

B. Aquatic Toxicity

There are no acute aquatic toxicity studies for ethoxylated C12-C16 alcohol or poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates. The aquatic toxicity of other AEs has been extensively evaluated in numerous studies on fish, daphnids and algae as well as microorganisms. Table 3 lists the results of acute aquatic toxicity studies on read across substance alcohols, C12-C15, ethoxylated (1 to 2.5 EO) [CAS RN [redacted] alcohols, C12-C14, ethoxylated (2 EO) [CAS RN [redacted] and alcohols, C12-C15, branched and linear, ethoxylated [CAS RN [redacted]

Table 3: Acute aquatic toxicity studies on ethoxylated C12-C16 alcohol[a,b,c]

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Oncorhynchus mykiss (Rainbow Trout)	96-hr LC_{50}	1.3 – 1.7[a]	2	ECHA
Danio Rio	96-hr LC_{50}	1.2[b]	2	ECHA
Danio Rio	96-hr LC_{50}	2[b]	2	ECHA
Zebrafish	96-hr LC_{50}	>2[c]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.14[a]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.23[a]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.53[b]	2	ECHA
Daphnia magna	48-hr EC_{50}	2.84[b,d]	2	ECHA
Daphnia magna	48-hr EC_{50}	1.2[e]	1	ECHA
Daphnia magna	48-hr EC_{50}	>2[b]	2	ECHA
Daphnia magna	48-hr EC_{50}	>2[c]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.23	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	0.75[a]	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	>2[c]	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	0.41[b]	2	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	0.778[b]	2	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	0.87[e]	1	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	1.3[e]	1	ECHA

a: Read across to alcohols, C12-C15, ethoxylated (1 to 2.5 EO) CAS RN [redacted]
b: Read across to alcohols, C12-C14, ethoxylated (EO 2) CAS RN [redacted]
c: Read across to alcohols, C12-C15, branched and linear, ethoxylated (CAS RN [redacted]
d: alcohols, C12-C14, ethoxylated (EO 1) CAS RN [redacted] as WAF (water accommodated fraction)
e: alcohols, C12-C14, ethoxylated (EO 4 or EO 6) CAS RN [redacted]

A review of the acute studies indicates that invertebrates are somewhat more sensitive to AEs than fish and algae. As concluded in HERA (2009), the Danish EPA (2001) found that the acute toxicity of AE to invertebrates varies, with EC50 values from 0.1 mg/l to more than 100 mg/l for linear AE and from 0.5 mg/l to 50 mg/l for branched AE. The toxicity is species specific and may vary between 0.29 mg/l and 270 mg/l for the same linear AE (Lewis and Suprenant 1983, quoted in Danish EPA 2001). The most commonly used invertebrates for testing are Daphnia magna and Daphnia pulex, and they are also among the most sensitive invertebrates to AE. The Danish EPA (2001) found that some AE are very toxic to invertebrates, i.e., linear AE of C12-15 EO1-8 and branched AE with a low degree of branching, i.e. < 10-25%. They concluded that branching of the alkyl chain reduces the toxicity of AE to invertebrates, as also observed for algae (Danish EPA, 2001). However, the data used to reach this conclusion is from specially synthesized AE which have been shown to have a significantly higher toxicity than the AE made from a technical alcohol which are used commercially (Kaluza and Taeger, 1996).

Chronic studies

In developing a water quality guideline for AEs (ANZG, 2018), the toxicity data was normalized for a specific alkyl chain length or a specific number of EO groups. The NOECs listed below were normalized to an alkyl chain length of C13.3 and EO of 8.2. There were chronic data for 13 species that belonged to 7 taxonomic groups (fish, crustacea, blue alga, diatoms, green alga, protozoa, and worms).

Freshwater fish: 2 species, 720 to 1,500 µg/L.

Freshwater crustaceans: 2 species, 590 to 860 µg/L.

Freshwater rotifers: 1 species, Brachionus calyciflorus, 1,300 µg/L.

Freshwater algae, diatoms and blue-green algae: 6 species, 200 to 8,700 µg/L.

Freshwater mesocosms: 4 NOEC data for multiple species tests were 80, 80, 320 and 330 µg/L, although replication was insufficient to meet OECD (1992) requirements. Normalized data were 380, 380, 320 and 1,520 µg/L.

C. Terrestrial Toxicity

There are no studies are available. The substance is readily biodegradable. Therefore, soil is not expected to be a compartment of concern. Thus, the risk to terrestrial macroorganisms is regarded to be negligible (ECHA).

D. Calculation of PNEC

The PNEC calculations for ethoxylated C12-C16 and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates alcohol follow the methodology discussed in DEWHA (2009).

PNEC water

The ANZG water quality guideline (2018) in freshwater is: "A high reliability trigger value of 140 µg/L was derived for AE (normalized data) using the statistical distribution method with 95% protection."

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Nonetheless, a $PNEC_{sed}$ was calculated using the equilibrium partitioning method. The $PNEC_{sed}$ is 0.0875 mg/kg sediment wet weight.

The calculations are as follows:
$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= 0.800/1280 \times 1000 \times 0.140$
$= 0.0875$ 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 kg/m^3[default]
$PNEC_{water}$ = 0.002 mg/L

$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 156.8)/1000 \times 2400]$
$= 0.800\ m^3/m^3$

And:
Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 kg/m^3[default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 3920 \times 0.04$
$= 156.8$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for alcohols, C12-16, ethoxylated based on the molecular connectivity index (MCI) is 3,920 L/kg (USEPA, 2018).
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 7.32 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (78.4/1500) \times 1000 \times 0.14$
$= 7.32$mg/kg

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 kg/m^3 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 3920 \times 0.02$
$= 78.4\ m^3/m^3$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for alcohols, C12-16, ethoxylated based on the molecular connectivity index (MCI) is 3,920 L/kg (USEPA, 2018).
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).

Based on a review of similar read-across substances, alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates are considered to be readily biodegradable and thus do not meet the screening criteria for persistence.

The bioconcentration factors (BCF) in fish for ethoxylated alcohols (which includes alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers,

phosphates) have been reported to range from <5 to 387.5. Thus, alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates does not meet the screening criteria for bioaccumulation.

The chronic NOEC values for alcohols ethoxylates are >0.1 mg/L. Thus, alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates do not meet the criteria for toxicity.

The overall conclusion is that alcohols, C12-16, ethoxylated and poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-, mono-C10-14-alkyl ethers, phosphates are not PBT substances.

IX. CLASSIFICATION AND LABELLING

A. Classification

H400: Very toxic to aquatic life
H412: Harmful to aquatic life with long lasting effects

B. Labelling

Warning

C. Pictogram

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

A. First Aid

Eye Contact

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. Firefighting 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 area

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 alcohols, C12-16, ethoxylated.

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

UN: UN 1993

Class:3

Packaging Group: II

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

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AMIDES, TALL OILS FATTY, N,N-BIS(HYDROXYETHYL)

This dossier on amides, tall oils fatty, N,N-bis(hydroxyethyl) presents the most critical studies pertinent to the risk assessment of amides, tall oils fatty, N,N-bis(hydroxyethyl) 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; Kl).

I. SUBSTANCE IDENTIFICATION

Chemical Name: Amides, tall oils fatty, N,N-bis(hydroxyethyl)

CAS RN: [redacted]

Synonyms:

Synonyms for oleamide DEA listed below.

While no specific composition data are available on amides, tall oils fatty, N,N-bis(hydroxyethyl), it is expected to be a mixture of diethanolamides of the fatty acids that constitute tall oil, which is composed of predominantly C18 unsaturated fatty acids: 48% oleic acid, 35% linoleic acid, 7% conjugated linoleic acid (REF).

As there are no available studies on CAS [redacted] this dossier is based on information on Amides, C18-unsatd, N,N-bis(hydroxyethyl) [CAS No. [redacted] This is justified because amides, tall oils fatty, N,N-bis(hydroxyethyl) is predominantly diethanolamides of unsaturated C18 fatty acids similar to the composition of the target substance CAS [redacted]

AMIDES, C18-UNSATURATED, N,N-BIS(HYDROXYETHYL)

Chemical Name: Oleamide DEA

CAS RN: [redacted]

Molecular formula: $C_{22}H_{43}NO_3$ (UVCB substance)

Molecular weight: 369.6 g/mol (UVCB substance)

Synonyms for oleamide DEA:
Oleyl diethanolamide;(9Z)-N,N-Bis(2-hydroxyethyl)-9-octadecenamide; (z)-n,n-bis(2-hydroxyethyl)-9-octadecenamide; 9-Octadecenamide, N,N-bis(2-hydroxyethyl)-, (Z)-; Alkamide DO-280;
N,N-Bis(2-hydroxyethyl)-9-octadecenamide; Alrosol O; Amisol ode; Clindrol 2000; Clindrol 2020, Comperlan OD; Diethanololeamide; EMID 6545; Emulsifier WHC; Lauridit OD; Mackamide O, Marlamid D 1885, N,N-Diethanololeamide, Nitrene NO, Oleamide, N,N-bis(2-hydroxyethyl)-, Oleic acid diethanolamide, Oleic acid diethanolamine condensate, Oleic diethanolamide, Schercomid ODA, Stafoam DO, Steinamid DO 280SE, Witcamide 511C

SMILES: CCCCCCCC\C=C/CCCCCCCC(=O)N(CCO)CCO

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Amides, C18-unsatd, N,N-bis(hydroxyethyl) [CAS No. [redacted]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Liquid	2	ECHA
Melting point	ca. -80°C	1	ECHA
Boiling point	>300°C	1	ECHA
Density	0.967 g/cm^3@ 20°C	1	ECHA
Vapor pressure	0 Pa @ 25°C	1	ECHA
Partition coefficient (log K_{ow})	>6 (experimental)	1	ECHA
Water solubility	<1 mg/L @ 20°C	1	ECHA
Flash point	218°C	1	ECHA
Auto flammability	350°C	1	ECHA
Viscosity	805.87 mPa s @ 20°C	1	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

According to ECHA, hydrolysis studies were not conducted; “the study does not need to be conducted because the substance is readily biodegradable.” (ECHA)

B. Biodegradation

Amides, C18-unsatd, N,N-bis(hydroxyethyl) is readily biodegradable. In an OECD 301 D test, degradation was 70% after 28 days (ECHA) [Kl. score = 1]. In an OECD 301 B test, degradation was 79% after 14 days and 86% after 28 days (ECHA) [Kl. score = 1].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for amides, C18-unsatd, N,N-bis(hydroxyethyl). Using KOCWIN v2.00, the estimated K_{oc} values for the individual components were calculated using the molecular connectivity index (MCI) approach. The final K_{oc} value was calculated on a weighted-average basis using the mole fractions of the individual components. The final K_{oc} value is 1,717 L/kg.

D. Bioaccumulation

There are no bioaccumulation studies on amides, C18-unsatd, N,N-bis(hydroxyethyl). The bioaccumulation potential of amides, C18-unsatd, N,N-bis(hydroxyethyl) was estimated using BCFBAF v3.01. The final BCF was calculated on a weighted-average basis using the mole fractions of all individual components. The calculated BCF was 112.53 L/kg, indicating a low potential for bioaccumulation (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

Human health toxicity data were obtained from ECHA, unless another source is explicitly cited.

A. Summary

Amides, C18-unsatd, N,N-bis(hydroxyethyl) are considered acutely toxic and an skin and eye irritant. It is not considered a skin sensitizer or toxic via repeated doses, and has no reported reproductive or developmental effects. It is not considered genotoxic or carcinogenic.

B. Acute Toxicity

Amides, C18-unsatd, N,N-bis(hydroxyethyl) is considered acutely toxic via oral route of exposure, with an LD50 of 10,000 mg/kg in male Sprague-Dawley rats (Kl = 2).

C. Irritation

Based on the available data, the test substance is considered irritating to both the skin and eyes. The available in vivo studies demonstrate:

- Clear irritation response following semi-occlusive exposure to the test substance for 24 h. The data support a classification as Skin Irrit. 2 - H315 (causes skin irritation) according to CLP (EC 1272/2008) criteria (Kl =1).
- Undiluted test substance showed irritation to rabbit eyes and supports classification as Eye Irrit. 2 – H319 (causes serious eye irritation) according to CLP (EC 1272/2008) criteria (Kl = 1).

D. Sensitization

The test substance is not expected to be a skin sensitiser based on a negative in vivo skin sensitisation study conducted on a structurally similar substance (Kl=1). Therefore no classification is required for sensitisation according to CLP (EC 1272/2008) criteria. There are no data on the respiratory sensitization potential of the substance.

E. Repeated Dose Toxicity

Based on the NOAEL derived from an oral subacute study in rat (>750 mg/kg bw/day) in which no treatment-related effects were observed, and observed effects in a chronic dermal study in rat (NOAEL of 50 mg/kg bw/day for systemic effects and LOAEL of 50 mg/kg bw/day for local effects), the test substance is not considered to meet the requirements for repeated dose toxicity classification according to CLP (EC 1272/2008) criteria. There are no data to evaluate the repeated dose toxicity classification for the inhalation exposure route.

F. Genotoxicity

The test substance and read across substance (amides, C8-18 (even numbered) and C18-unsatd. N,N bis(hydroxyethyl) were negative in short-term in vitro and in vivo genotoxicity tests. Therefore no classification is required for this endpoint according to CLP (EC 1272/2008) criteria.

In Vitro Studies
The *in vitro* studies conducted for this substance are described in Table 2. The referenced studies indicate that the substance is not mutagenic or genotoxic *in vitro*.

Table 2: *In vitro* Genotoxicity Studies

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
In vitro gene mutation study in bacteria (*S. typhimurium* TA97, TA98, TA100 and TA1535)	-	-	2	Irwin, 1999**
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	-	1	Irwin, 1999**
Bacterial reverse mutation (S. typhimurium and E. coli strains)	-	-	1	Verspeek-Rip, 2014**

*+, positive; -, negative. ** As cited in ECHA.

In Vivo Studies

A study was conducted to evaluate the potential of the test material to induce micronuclei in B6C3F1 mice. Under the conditions of the study, the test substance did not increase the frequencies of micronucleated normochromatic erythrocytes (NCEs) in peripheral blood of both male and female mice at the end of 13 weeks (KI =1).

G. Carcinogenicity

No studies are available for assessing the carcinogenicity of this substance via the oral or inhalation routes of exposure.

Rodent tests indicate that the substance is not carcinogenic by the dermal route. A study was conducted to evaluate the effects of chronic exposure to the test substance in B6C3F1 mice. Under the test conditions, no evidence of carcinogenic activity was observed with the test substance at any tested dose levels in mice (KI =1). A study was conducted to evaluate the effects of chronic exposure to the test substance in F344/N rats. Under the test conditions, no evidence of carcinogenic activity was observed with the test substance at any tested dose levels in rats (KI =1).

H. Reproductive and Developmental Toxicity

No studies were available to assess the effects of the substance on reproduction. No adverse developmental effects were observed following administration of 1,000 mg/kg bw day to pregnant Sprague-Dawley rats (KI = 2).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed 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 lowest NOAEL from these studies is a 750 mg/kg bw/day based on bodyweight, hematology, clinical chemistry, urinalysis, gross and microscopic pathology in male and female rats from a 28-day oral gavage study (Potokar, 1983). The NOAEL of 750 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 = 750/(10 x 10 x 1 x 10 x 1) = 750/1000 = 7.5 mg/kg-day

Drinking water guidance value

The drinking water guidance value is calculated as:

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

Using the oral RfD, the drinking water guidance value is calculated as:

(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 = (7.5 x 70 x 0.1)/2 = 26.3 mg/L

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on amides, C18-unsatd, N,N-bis(hydroxyethyl).

Table 3: Acute Aquatic Toxicity Studies on Amides, C18-unsatd, N,N-bis(hydroxyethyl)

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Danio rerio	96-hr LC_{50}	5.1	1	ECHA
Daphnia magna	48-hr EC_{50}	3.2	2	ECHA
Desmodesmus subspicatus	72-hr EC_{50}	18.6	2	ECHA

Chronic Studies

The 28-day NOEC to *Oncorhynchus mykiss* in a fish chronic toxicity study is 0.32 mg/L [nominal] and 0.26 mg/L [measured] (ECHA) [Kl. score = 2].

The 21-d NOEC in a *Daphnia* reproduction test is 0.1 mg/L [nominal] and 0.07 mg/L [measured] (ECHA) [Kl. score = 2].

The 72-hr EC_{10} to *Desmodesmus subspicatus* is 1.4 mg/L (ECHA) [Kl. score = 2].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for amides, C18-unsatd, N,N-bis(hydroxyethyl) 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 (5.1 mg/L), invertebrates (3.2 mg/L), and algae (18.6 mg/L). Results from chronic studies are available for fish (0.26 mg/L), invertebrates (0.07 mg/L), and algae (1.4 mg/L). On the basis that the data consists of short-term and long-term results for three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC or EC_{10} value of 0.07 mg/L for invertebrates. The $PNEC_{water}$ is 0.007 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 $PNEC_{soil}$ is 0.16 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (34.34/1500) \times 1000 \times 0.007$
$= 0.16$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 1717 \times 0.02$
$= 34.34$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for Amides, C18-unsatd, N,N-bis(hydroxyethyl) based on the molecular connectivity index (MCI) is 1,717 L/kg (ECHA).
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).

Amides, C18-unsatd, N,N-bis(hydroxyethyl) is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Based on an estimated BCF value of 113 L/kg, amides, C18-unsatd, N,N-bis(hydroxyethyl) does not meet the criteria for bioaccumulation.

The lowest chronic NOEC or EC_{10} value for amides, C18-unsatd, N,N-bis(hydroxyethyl) is <0.1 mg/L. Thus, amides, C18-unsatd, N,N-bis(hydroxyethyl) meets the criteria for toxicity.

The overall conclusion is that amides, C18-unsatd, N,N-bis(hydroxyethyl) is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Skin Irritant Category 2
Eye Irritant Category 2
Aquatic Chronic Toxicity Category 2

May cause respiratory tract irritation.

B. Labelling

Danger.

C. Pictogram

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

A. First Aid

Eye Contact
Rinse thoroughly for at least 15 minutes and consult a physician.

Skin Contact
Remove contaminated clothing. Wash with soap and plenty of water. Consult a physician immediately.

Inhalation
Move the person to fresh air.

Ingestion
Rinse mouth with water; consult a physician immediately. Do not induce vomiting.

Notes to Physician
No data available

Medical Conditions Aggravated by Exposure
No data available

Emergency Personnel Protection
No additional notes

B. Fire Fighting Information

Extinguishing Media
Water spray, alcohol-resistant foam, dry chemical, or carbon dioxide.

Specific Exposure Hazards
May be combustible at high temperatures; container explosion may occur under fire conditions or if heated. Hazardous combustion products include carbon oxides and nitrogen oxides.

Special Protective Equipment for Firefighters
As in any fire, wear self-contained breathing apparatus and full protective gear.

C. Accidental Release Measures

Personal Precautions
Remove all sources of ignition. Ensure adequate ventilation. Use personal protective equipment. Avoid dust formation. Avoid breathing vapours, mist, or gas. Evacuate unprotected persons.

Environmental Precautions
Stop the spill if possible and safe. Prevent from reaching drains, sewers, or waterways.

Steps to be Taken if Material is Released or Spilled
Contain spill material by diking or using inert absorbent such as vermiculite, dry sand, or earth. Transfer to a disposal or recovery container.

D. Storage And Handling

General Handling
Avoid contact with skin and eyes. Avoid formation of dust and aerosols.

Other Handling Precautions
Provide appropriate exhaust ventilation at places where dust is formed. Do not eat or drink while working with chemical substances.

Storage
Store in a cool, dry, well-ventilated place. Keep container tightly closed.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
No data available.

Engineering Controls
Provide ventilation.

Personal Protection Equipment

Respiratory Protection:
Wear dust mask when handling large quantities

Hand Protection:
Wear impervious gloves, inspect gloves before use.

Skin Protection:
Wear impervious clothing; PPE is to be selected according to the concentration and amount of the substance to be handled.

Eye protection:
Safety glasses with side-shields conforming to EN166. Use equipment for eye protection tested and approved under appropriate government standards such as NIOSH (US) or EN 166(EU).

Other Precautions:
No data available

F. Transport Information

UN Number: Not regulated

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS
AICS: Listed

XIII. REFERENCES

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AMINE OXIDES, COCOALKYLDIMETHYL

This dossier on amine oxides, cocoalkyldimethyl presents the most critical studies pertinent to the risk assessment of amine oxides, cocoalkyldimethyl 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 amine oxides (OECD, 2006). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Coco alkyldimethylamine oxides

CAS RN: [redacted]

Molecular formula: $CH_3.(CH_2)_R.N(CH_3)_2$:O where R is 9-17 (UVCB substance)

Molecular weight: Unspecified (UVCB substance)

Synonyms: Cocamine oxide; coco dimethylamine oxide; coconutdimethylamineoxide; N-(cocoalkyl)-dimethylamine oxide; N,N-dimethylcocamino oxide

SMILES: Not available (UVCB substance)

The typical alkyl chain length distribution of amine oxides, cocoalkyldimethyl is:

<1-3 C_{10}; 64-74 C_{12}; 21-30 C_{14}; 2-13 C_{16}; and <1-9 C_{10}. The average alkyl chain is 13.0 (OECD, 2006).

II. PHYSICO-CHEMICAL PROPERTIES

Specific physico-chemical properties on amine oxides, cocoalkyldimethyl are unavailable. Therefore, key physical and chemical properties for the surrogate substance Amines, C10-16- Alkyldimethyl, N-oxides, Average Chain Length 12.6* (CAS RN [redacted] are shown in Table 1.

Table 1: Overview of the physico-chemical properties of Amines, C10-16- Alkyldimethyl, N-oxides, Average Chain Length 12.6* [CAS No. [redacted] (OECD, 2006)

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Liquid (commercially available in water at 25–35% activity)	-	OECD, 2006
Melting Point	Average: 130.5°C @ 101.3 kPa	2	OECD, 2006
Boiling Point	Decomposes before boiling***	2	OECD, 2006
Density	Not available	-	-
Vapour Pressure	Negligible	2	OECD, 2006
Partition Coefficient (log K_{ow})	<2.7 (temperature not available)	2	OECD, 2006
Water Solubility	409.5 g/L (temperature not available)	2	OECD, 2006
Flash Point	Not available	-	-

Property	Value	Klimisch Score	Reference
Auto flammability	Not available	-	-
Viscosity	Not available	-	-
Henry's Law Constant	Not available	-	-

*Except melting point.
**Aliphatic amine oxides undergo thermal decomposition between 90° and 200°C, so melting point is likely to be accompanied with decomposition; all boiling points are predicted to be far above the decomposition temperature

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

The substance is not expected to persist, adsorb, or bioaccumulate. Specific data are discussed below.

B. Biodegradation

Amine oxides, cocoalkyldimethyl is readily biodegradable. In an OECD 301 D test, degradation was 89% after 14 days and 93% after 28 days (OECD, 2006) [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 amine oxides, cocoalkyldimethyl. Based on read-across from amines, C12-14 (even numbered)-alkyldimethyl, N-oxides (CAS RN [redacted] a normalised organic carbon to water partition coefficient (K_{oc}) value of 1,525 L/kg was identified (ECHA). Based on this estimated value, amine oxides, cocoalkyldimethyl is expected to have low mobility in soil. If released to water, based on the K_{oc} value and its water solubility, it is expected to adsorb to suspended solids and sediment.

D. Bioaccumulation

There are no bioaccumulation studies on amine oxides, cocoalkyldimethyl. Amine oxides, cocoalkyldimethyl is not expected to bioaccumulate based on a log K_{ow} of <2.7 (OECD, 2006).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

In general, amine oxides, cocoalkyldimethyl does not exhibit significant acute oral or dermal toxicity. It appears to be a skin and eye irritant but not a skin sensitiser. It is not a reproductive or developmental toxicant, genotoxic or expected to be a carcinogen.

B. Toxicokinetics/Metabolism

Following an oral dose to male and female rats, approximately 75% of the radioactivity was excreted within 24 hours. Excretion was primarily in the urine (>50%), followed by feces and expired CO_2. The amount of test compound recovered in liver was 1.1 to 1.5%; 1.9 to 4.8% of the dose was retained in

the carcass, with the remaining tissues <0.1% of the dose. Degradation of the alkyl chain to 4-carbon acid metabolites was more efficient in rabbits (OECD, 2006).

In two human volunteers, the uptake and excretion of 1-dodecanamine, N,N-dimethyl-, N-oxide (CAS No. [redacted] was rapid, with 37 to 50% of the administered radioactivity collected in urine and 18 to 22% in the expired air within two hours after dosing. Humans were more efficient than rats in metabolizing the alkyl chain to 4-carbon acid metabolites (Turan & Gibson, 1981).

C. Acute Toxicity

The oral LD_{50} in rats of amine oxides, cocoalkyldimethyl was 1,236 mg/kg in males and 846 in females (OECD, 2006) [Kl. score = 2]. In another study, the oral LD50 in rats of amine oxides, cocoalkyldimethyl was 3,873 mg/kg (OECD, 2006) [Kl.score=2].

No inhalation studies available.

The dermal LD_{50} values of amines, C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] were >520 mg/kg (OECD, 2006) [Kl.score=2]

D. Irritation

Application of amine oxides, cocoalkyldimethyl (30% solution) to the skin of rabbits for 4 hours under semi-occlusive conditions was irritating (OECD, 2006) [Kl.score=1].

Instillation of a 30% solution of 1-dodecanamine, N,N-dimethyl-, N-oxide (CAS No. [redacted] into the eyes of rabbits was slightly irritating (OECD, 2006) [Kl.score=2].

Instillation of 28% solution of C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] into the eyes of rabbits was moderately to severely irritating (OECD, 2006) [Kl.score=2]. In another study, instillation of 27.84% solution of C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] into the eyes of rabbits was moderately irritating (OECD, 2006) [Kl.score=2].

E. Sensitisation

No studies are available on amine oxides, cocoalkyldimethyl.

C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] was not considered to be a skin sensitizer in a guinea pig Buehler test (OECD, 2006) [Kl.score=2].

F. Repeated Dose Toxicity

No studies are available on amine oxides, cocoalkyldimethyl.

Oral

Male and female SD rats were given 0, 0.1, 0.2, or 0.4% C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] in their diet for 13 weeks. The estimated daily intakes were 0, 63, 112 and 236 mg/kg-day for males, and 0, 80, 150 and 301 mg/kg-day for females. Mean body weights were significantly lower in the 0.4% males and ≥0.2% females. The opthalmoscopic examination showed lenticular opacities in the posterior cortex of the ≥0.2% males. There were no treatment-related effects in the clinical chemistry and hematology parameters nor was there any histopathologic changes in the treated animals compared to controls. The NOAEL for this study is 0.1% in the diet, which corresponds to 63 and 80 mg/kg-day for males and females, respectively (OECD, 2006) [Kl.score=2].

Male and female New Zealand rabbits were given 0, 0.1, 0.5 or 1.0% C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] in their diet for 32 weeks. The estimated daily intakes were 0, 40, 196 and 390 mg/kg-day for males and 0, 39, 195 and 380 mg/kg-day for females. There were no opthalmoscopic effects. The 0.5% males had decreased alkaline phosphatase levels and increased relative liver weights. Histopathologic examination showed no treatment-related effects. The NOAEL for this study is 1% in the diet, which corresponds to 390 and 380 mg/kg-day for males and females, respectively (OECD, 2006) [Kl.score=2].

Male and female rats were given 0, 0.1, 0.1 or 0.2% C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] in their diet for 104 weeks. The estimated daily intakes were 0, 4.24, 42.3 or 87.4 mg/kg-day for males, and 0, 5.23, 52.6 or 107 mg/kg-day for females. Survival, clinical chemistry, opthalmoscopic exams, clinical signs, gross pathology, and histopathology were similar across groups. The 0.2% animals had reduced body weights of >10%. The NOAEL for this study is 0.1% in the diet, which corresponds to 42 and 53 mg/kg-day for males and females, respectively (OECD, 2006) [Kl.score=2].

Inhalation

No studies are available.

Dermal

Male and female ICR Swiss mice received dermal applications of an aqueous solution of C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] 3 times/week for 104 weeks. The average daily dose was 0, 1.1, 2.8 or 5.6 mg/kg-day. The high-dose mice showed microscopic signs of skin irritation. There were no other treatment-related effects (OECD, 2006) [Kl.score=2].

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on amine oxides, cocoalkyldimethyl and similar substances are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Amine Oxides, Cocoalkyldimethyl

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (S. typhimurium strains)	-	-	2	ECHA
Mammalian cell gene mutation (Chinese hamster fibroblasts)**	-	-	1	ECHA

*+, positive; -, negative
**Read-across from C10-16 alkyldimethyl, N-oxides (CAS No. [redacted]

In Vivo Studies

In a dominant lethal test, male mice were given in their drinking water 0, 10, 100 or 1,000 mg/kg 1-dodecanamine, N,N-dimethyl-, N-oxide (CAS No. [redacted] There was no evidence of a mutagenic effect (OECD, 2006) [Kl.score=2].

H. Carcinogenicity

No carcinogenicity studies are available on amine oxides, cocoalkyldimethyl.

Oral

Male and female rats were given 0, 0.1, 0.1 or 0.2% C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] in their diet for 104 weeks. The estimated daily intakes were 0, 4.24, 42.3 or 87.4 mg/kg-day for males, and 0, 5.23, 52.6 or 107 mg/kg-day for females. The incidence of tumours was similar between treated and control animals (OECD, 2006) [Kl.score=1].

Inhalation

There are no studies available.

Dermal

Male and female ICR Swiss mice received dermal applications of an aqueous solution of C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] 3 times/week for 104 weeks. The average daily dose was 0, 1.1, 2.8 or 5.6 mg/kg-day. The high-dose mice showed microscopic signs of skin irritation. There was no evidence of skin tumors at any dose level (OECD, 2006) [Kl.score=2].

I. Reproductive Toxicity

A two-generation reproductive toxicity study has been conducted in CD rats on 1-dodecanamine, N,N-dimethyl-, N-oxide (CAS No. [redacted] The dietary levels were 0, 750, 1,500 and 3,000 ppm for 6.5 weeks, and 0, 188, 375 and 750 ppm for the remainder of the study. The dietary levels were reduced because of the reduced body weight gain in the mid- and high-dose groups. There were slight reductions in body weight gain of both the parental animals and offspring, but mating performance and fertility were unaffected by treatment in either generation. Macroscopic and microscopic pathologic examinations showed no differences between treated and control groups. The NOAEL for reproductive and developmental toxicity is 750 ppm, which corresponded to 40 mg/kg-day (OECD, 2006) [Kl.score=1].

J. Developmental Toxicity

Oral

Pregnant female CD rats were dosed by oral gavage with 0, 50, 100 or 200 mg/kg 1-dodecanamine, N,N-dimethyl-, N-oxide (CAS No. [redacted] on GD 7 to 17. One-half of the females/group were sacrificed on GD 20, and the other half were allowed to deliver; the pups were weaned at PND 25, and the F_1 animals were paired at 10 weeks of age. Body weights and water consumption were lower (<10%) in the 200 mg/kg group. Mean fetal weights were lower and associated with slight retardation of fetal ossification in the 200 mg/kg group that were sacrificed in GD 20. However, pup survival and pup growth were unaffected in the offspring of the 200 mg/kg group that were allowed to deliver. The subsequent growth, mating performance and fertility of the F_1 animals were similar between treated and control groups; F_1 females from the 200 mg/kg F_0 group had slightly elevated fetal and placental weights. There were no macroscopic changes seen in the F_1 animals at terminal necropsy that were considered to be treatment-related. The NOAEL for maternal and developmental toxicity is 100 mg/kg-day (OECD, 2006) [Kl.score=1] suggesting that observations of developmental toxicity are related to maternal effects.

Pregnant female SD rats were dosed by oral gavage with 0, 25, 100 or 200 mg/kg C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] on GD 6-19. There was one death in the 200 mg/kg group. The ≥100 mg/kg groups had reduced body weight gain and relative feed consumption. In the 200 mg/kg group, early resorptions were increased, and liver litter sizes and fetal body weights were decreased. The reduced fetal body weights were associated with fetal variations consisting of delays in skeletal ossifications. The 100 mg/kg group also showed some delays in ossification. There was no indication of fetal malformations at any dose level. The NOAEL for maternal and developmental toxicity is 25 mg/kg-day (OECD, 2006) [Kl.score=2] suggesting that observations of developmental toxicity are related to maternal effects.

Pregnant female New Zealand rabbits were dosed by oral gavage with 0, 40, 80 or 160 mg/kg 1-dodecanamine, N,N-dimethyl-, N-oxide (CAS RN [redacted] on GD 6-18. Three of the 80 mg/kg and three of the 160 mg/kg dams died or were killed in extremis. These deaths were not considered to be treatment related. Body weight gain was reduced in all treated groups, although 40 mg/kg dams achieved similar body weights to controls at study termination. Feed consumption was reduced compared with the pre-treatment period, during the second half of the treatment period in the 40 and 80 mg/kg animals, and for the entire treatment period in the 160 mg/kg animals. Water consumption was also decreased in all treated groups. There was no indication of developmental toxicity. The NOAEL for maternal toxicity was > 160 mg/kg-day based on decreased body weight. The NOAEL for developmental toxicity is > 160 mg/kg-day, the highest dose tested (OECD, 2006) [Kl.score=1].

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 amine oxides, cocoalkyldimethyl 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

In a two-year rat dietary study, the lowest NOAEL was 42 mg/kg-day (OECD, 2006). The NOAEL of 42 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 / ($UF_A \times UF_H \times UF_L \times UF_{Sub} \times UF_D$)

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 = 42/(10 × 10 × 1 × 1 × 1) = 42/100 = <u>0.4 mg/kg/day</u>

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 = (0.42 × 70 × 0.1)/2 = <u>1.5 mg/L</u>

B. Cancer

There are no carcinogenicity studies on amine oxides, cocoalkyldimethyl. However, C_{10-16} alkyldimethyl, N-oxides (CAS No. [redacted] was not carcinogenic to rats in a 2-year dietary study; nor was there any evidence of skin tumors in mice in a 104-week dermal study. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Amine oxides, cocoalkyldimethyl does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Overall, amine oxides, cocoalkyldimethyl is moderately toxic to aquatic organisms. Based on hazard data, freshwater green algae are considered the most sensitive species, for acute and chronic endpoints. Acute toxicity is affected by chain length for fish and invertebrates.

B. Aquatic Toxicity

<u>Acute Studies</u>

Table 3 lists the results of acute aquatic toxicity studies conducted on amine oxides, cocoalkyldimethyl.

Table 3: Acute Aquatic Toxicity Studies on Amine Oxides, Cocoalkyldimethyl

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Salmo gairdneri	96-hr LC_{50}	13	1	OECD, 2006
Brachydanio rerio	96-hr LC_{50}	1.0	2	OECD, 2006
Leuciscus idus melanotus	96-hr LC_{50}	4.3	2	OECD, 2006
Daphnia magna	48-hr EC_{50}	2.9	1	OECD, 2006
Selenastrum capricornutum	72-hr EC_{50}	0.29	2	OECD, 2006

Chronic Studies

The 302-d NOEC for C10-16 alkyldimethyl, N-oxides (CAS No. [redacted] to *Pimephales promelas* was 0.42 mg/L; this value is 0.31 mg/L when normalized to a $C_{12.9}$ amine oxide (OECD, 2006) [Kl.score=2].

The 21-day NOEC for 1-dodecanamine, N,N-dimethyl-, N-oxide (CAS No. [redacted] in a *Daphnia* reproduction test is 0.36 mg/L; this value is 0.28 mg/L when normalized to a $C_{12.9}$ amine oxide (OECD, 2006) [Kl.score=1].

As noted with acute toxicity, green algae are the most sensitive for chronic endpoints with a 72-hr EC_{20} value of 0.09 mg/L for *Selenastrum capricornutum*. (The geometric mean of 12 studies for the group was 0.11 mg/L) (OECD, 2006) [Kl.score=2].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for amine oxides, cocoalkyldimethyl 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 (1.0 mg/L), invertebrates (2.9 mg/L) and algae (0.29 mg/L). Results from chronic studies are available for fish (0.31 mg/L), invertebrates (0.28 mg/L) and algae (0.09 mg/L). On the basis that the data consists of short-term and long-term studies for three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC value of 0.09 mg/L for algae. The $PNEC_{water}$ is 0.009 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 0.21 mg/kg sediment wet weight.

The calculations are as follows:

$$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$$

= (30.1/1280) × 1000 × 0.009
= 0.21 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]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
= $0.8 + [(0.2 \times 61.0/1000 \times 2400]$
= 30.1 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]
$Kp_{sed} = K_{oc} \times f_{oc}$
= 1525×0.04
= 61.0 L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for amine oxides, cocoalkylmethyl is 1525 L/kg based on read-across from C12-14 (even numbered)-alkyldimethyl, N-oxides (CAS RN [redacted] (ECHA).

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 0.18 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
= $(30.5/1500) \times 1000 \times 0.009$
= 0.18 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]
$Kp_{soil} = K_{oc} \times f_{oc}$
= 1525×0.02
= 30.5 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for amine oxides, cocoalkylmethyl is 1525 L/kg based on read-across from C12-14 (even numbered)-alkyldimethyl, N-oxides (CAS No. [redacted] (ECHA)
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).

Amine oxides, cocoalkyldimethyl is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Based on a predicted log K_{ow} of <2.7, amine oxides, cocoalkyldimethyl does not meet the screening criteria for bioaccumulation.

The lowest NOEC from chronic aquatic toxicity studies conducted on amine oxides, cocoalkyldimethyl and similar substances is <0.1 mg/L. Thus, amino oxides, cocoalkyldimethyl meets the screening criteria for toxicity.

The overall conclusion is that amine oxides, cocoalkyldimethyl is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H315: Skin Irritant Category 2

H318:Eye Damage Category 1

H400: Aquatic Acute Category 1

B. Labelling

Danger!

According to the classification provided by companies to ECHA in CLP notifications, this substance is very toxic to aquatic life, causes serious eye damage, is harmful if swallowed and causes skin irritation

C. Pictogram

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.

<u>Eye Contact</u>

In the case of contact with eyes, rinse immediately with plenty of water. Seek medical advice. Call a physician immediately.

Skin Contact

After contact with skin, wash immediately with plenty of soap and water. Consult a physician.

Inhalation

Remove to fresh air. If breathing is irregular or stopped, administer artificial respiration.

Ingestion

Call a physician immediately. Clean mouth with water and drink afterwards plenty of water. Do not induce vomiting without medical advice. Never give anything by mouth to an unconscious person.

Medical Conditions Aggravated by Exposure

Exposure to substance may aggravate individuals with asthma or other respiratory conditions.

Emergency Personnel Protection

CAUTION!

Wear appropriate protective equipment and respiratory protection where dusts or airborne particulates of unknown concentrations may be generated.

LARGE SPILLS: Self-contained breathing apparatus preferred.

B. Firefighting Information

Extinguishing Media

Dry powder, Water spray, Foam.

Specific Exposure Hazards

Heating or fire can release toxic gas.

Special Protective Equipment for Firefighters

In the event of fire, wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

CAUTION!

Wear appropriate protective equipment and respiratory protection where dusts or airborne particulates of unknown concentrations may be generated. For large spills, self-contained breathing apparatus preferred.

Environmental Precautions

Do not release to drains or flush into surface water or sanitary sewer system.

Steps to be Taken if Material is Released or Spilled

Carefully shovel spills into appropriate containers for disposal. Avoid generating dust. Wet residue with water and absorb with inert material (sand, earth, etc.). Transfer into appropriate containers for recovery or disposal. Keep spill out of sewers and open bodies of water.

D. Storage and Handling

General Handling

Provide sufficient air exchange and/or exhaust in work rooms. Avoid contact with skin and eyes.

Other Handling Precautions

Take precautionary measures against static discharges.

Storage

Keep container tightly closed. To maintain product quality, do not store in heat or direct sunlight. Keep in a dry, cool and well-ventilated place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for amine oxides, cocoalkyldimethyl.

Engineering Controls

Ensure adequate ventilation, especially in confined areas. Use explosion-proof electrical/ventilating/lighting/equipment. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protection Equipment

Respiratory Protection: In the case of vapor formation use a respirator with an approved filter.

Hand Protection: Suitable material: Nitrile rubber.

Skin Protection: Choose protection according to amount/concentration of dangerous substance. No special protective equipment required.

Eye protection: Tightly fitting safety goggles.

Other Precautions: Avoid contact with skin, eyes and clothing. Wash hands before breaks and immediately after handling the product.

F. Transport Information

Australian Transportation Codes

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

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BENZALDEHYDE

This dossier on benzaldehyde presents the most critical studies pertinent to the risk assessment of benzaldehyde 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): Benzaldehyde

CAS RN: [redacted]

Molecular formula: C_7H_6O

Molecular weight: 106.12 g/mol

Synonyms: Artificial Almond Oil; Benzaldehyde FFC; Benzenecarbonal; Benzenecarboxaldehyde; Benzoic aldehyde; Phenylmethanal; Almond artificial essential oil; Phenylmethanal benzenecarboxaldehyde; NCI-C56133; Oil of Bitter Almond; Artificial essential oil of almond; Benzene carbaldehyde; NA 1989; Artificial essential oil of almond; Artificial bitter almond oil; Benzene methylal; Benzoyl hydride; Ethereal oil of bitter almonds; Benzyaldehyde

SMILES: c1(C=O)ccccc1

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of benzaldehyde

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Colourless liquid, becoming yellowish on keeping; almond odour	2	ECHA
Melting Point	-26°C @ 101.3 kPa	2	ECHA
Boiling Point	179°C @ 101.3 kPa	2	ECHA
Density	1.042 (relative density) 25°C	2	ECHA
Vapour Pressure	169 Pa @ 25°C	2	ECHA
Partition Coefficient (log K_{ow})	1.4 @ 25°C	1	ECHA
Water Solubility	6.95 g/L @ 25°C	2	ECHA
Flash Point	62°C	2	ECHA
Auto flammability	192°C	2	ECHA
Viscosity	1.321 mPa s @ 25°C	2	ECHA
Henry's Law Constant	Not available	-	

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Benzaldehyde is readily biodegradable. It is not expected to bioaccumulate. It has a low potential to adsorb to soil or sediment.

B. Biodegradation

Benzaldehyde is readily biodegradable. In an activate sludge test, degradation was approximately 100% after 19 days as measured by DOC removal (ECHA) [Kl.score=2].

In a BOD test, degradation was >60% after 28 days as measured by O_2 consumption (ECHA) [Kl.score=2]. In a CO_2 evolution test, degradation was about 60% in 7 days and 100% in 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 benzaldehyde. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value from log K_{ow} is 32.69 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 11.09 L/kg. If released to soil, based on these K_{oc} values, the substance is expected to have very high mobility. If released to water, based on the K_{oc} values and its water solubility, benzaldehyde is not expected to adsorb to suspended solids and sediment.

D. Bioaccumulation

There are no bioaccumulation studies on benzaldehyde. Benzaldehyde is not expected to bioaccumulate based on a log Kow of 1.4 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

The following sections detail the available and relevant literature on the toxicity of benzaldehyde. The information described below was obtained from NICNAS IMAP if available and the ECHA database.

A. Summary

Benzaldehyde is hazardous and considered harmful if swallowed. It has low acute dermal toxicity and moderate acute inhalation toxicity potential. It is not irritating to the skin but may be an eye and respiratory irritant. It is not a skin sensitiser. Based on the data available, the chemical is not considered to cause serious damage to health from repeated oral exposure or through inhalation. No data are available to evaluate exposure via the dermal pathway. The substance is not genotoxic when tested in both *in vitro* and *in vivo* assays. There is no indication that this substance will cause malformations or have an adverse effect on reproduction and development.

B. Acute Toxicity

Oral

The oral LD_{50} of the test substance in rats is between 300 and 2000 mg/kg bw/day. In the key OECD 401 Guideline Study (Acute Oral Toxicity), an acute LD_{50} value for rats appeared to be approximately 1430 mg/kg bw (ECHA) [Kl.score=2].

In a supportive study, a LD_{50} value of 1300 mg/kg bw in rats and 1000 mg/kg bw for guinea pigs was derived. In another limitedly reported supporting study, an LD_{50} value of 800–1600 mg/kg bw was reported for both rats and mice. In an acute oral toxicity study in rats, an oral LD_{50} of > 2170 mg/kg (> 2000 mg/kg) was reported (ECHA) [Kl.score=4].

The chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). In humans, a lethal oral dose of 600–900 mg/kg bw was calculated for the chemical in the absence of prompt treatment (NICNAS, 2016).

Dermal

Although limited information is available, the chemical is likely to have low acute dermal toxicity in animal tests following dermal exposure. In the key study, four rabbits were dermally exposed (semi-occlusive) for 24 hours to the test substance (2000 mg/kg). No mortality was observed. The LD_{50} was > 2,000 mg/kg bw (ECHA) [Kl.score=2]. In an acute dermal toxicity study in rabbits with limited available data, an LD50 of >1250 mg/kg bw was reported (ECHA) [Kl.score=4].

Inhalation

Although limited data are available, the available information indicates that the chemical has moderate acute toxicity in animal tests. Based on an acute inhalation toxicity study in rats, the inhalation LC50 is 1000–5000 mg/m^3 (ECHA) [Kl.score=1].

Based on two studies on sensory irritation (Babiuk, 1984; Steinhagen, 1983), it cannot be excluded that benzaldehyde induces sensory irritation in rodents. The data are, however, not sufficient to set an effect level in humans (ECHA) [Kl.score=4].

An increased incidence of respiratory symptoms was noted among workers exposed to vapour of the chemical at atmospheric concentrations of >5 mg/m^3 (NICNAS, 2016).

C. Irritation

Although limited data are available, the available information indicates that the chemical is not likely to be a skin irritant. However, it has been reported to be an eye irritant in animal and human studies and a respiratory irritant in humans.

Skin

The shaved skin of guinea pigs was exposed to undiluted benzaldehyde with a gauze pad for 24 hours. The concentration of the test substance ranged from 5 to 20 mL/kg. The test substance was moderately irritating to the guinea pig skin in this test (ECHA) [Kl.score=4].

A read-across study was conducted using benzoic acid in New Zealand White Rabbits. The test substance caused very slight erythema in two animals at 60 minutes after removal of the dressings.

The erythema resolved by day 2. Twenty-four hours after test substance removal, one animal showed very slight oedema, which resolved within 24 hours. No signs of systemic intoxication were observed in any of the rabbits. The test substance was considered minimally irritating to the skin (ECHA) [Kl.score=2].

Eyes

In an OECD 405 Guideline Study (Acute Eye Irritation/Corrosion), New Zealand White Rabbits were dosed with 100 microliter of benzaldehyde in the eye and observed for 7 days. The test substance was slightly irritating to the rabbit eye in this test. Immediate irritation effects were noted at 1 hour and within 24 hours; the anterior portion of the cornea was damaged. The cornea was cleared within 48 hours and only erythema of the conjunctiva and nictitating membrane was noted at this stage. Although the rabbit died on the sixth day, the death was not related to the application of the chemical (ECHA) [Kl.score=2].

In an inhalation toxicity study, human volunteers were exposed to 4.5 ppm (19.5 mg/m^3) of the chemical for one minute. Irritation of the eyes and upper respiratory tract were observed. In an occupational study, workers exposed to the chemical vapour at atmospheric concentrations of >5 mg/m^3 reported symptoms of slight eye irritation and considerable skin irritation (NICNAS, 2016).

D. Sensitisation

Overall, it is concluded that the test substance is not a skin sensitiser (ECHA).

The test substance was determined not to be a contact sensitiser using the Magnusson-Kligmann method [Kl. Score = 2] and the open epicutaneous test [Kl.score=4]. However, it was reported positive for allergenicity in guinea pigs in the Draize test, the maximisation test and a test with Freund's complete adjuvant (ECHA) [Kl.score=4].

Supportive evidence from Opdyke (1976) showed no evidence of sensitisation in a maximisation test with 25 human volunteers. In this test, a concentration of 4% in petrolatum was used. Furthermore, in a human patch test using 5% of the test substance in Vaseline, positive reactions were noted in 10 of 100 patients. Positive reactions occurred in patients with sensitivity to benzoic acid or vanillin.

Although the chemical has produced skin sensitisation reactions in some tests, based on the weight of evidence, the chemical is not likely to be a skin sensitiser. It is also noted that the chemical is rapidly metabolised to benzoic acid in the skin. Clinical reports of allergy to the chemical are rare, and benzoic acid has also been reported not to produce sensitisation in clinical trials in humans (NICNAS, 2016).

E. Repeated Dose Toxicity

Oral

In a sub-chronic oral toxicity study, male and female Fischer 344 rats and B6C3F1 mice were treated daily with the test substance by gavage for 90 days in several doses. Groups of 10 male and 10 female F344 rats were given gavage doses of benzaldehyde of 50, 100, 200, 400 and 800 mg/kg body weight (dissolved in corn oil). Groups of 10 male and 10 female B6C3F1 mice were given benzaldehyde doses of 75, 150, 300, 600 or 1200 mg/kg body weight per day. Both groups were dosed 5 days/week for a period of 13 weeks (90 days).

The symptoms of intoxication observed in the rats of the 800 mg/kg group were increased activity, trembling or periodic inactivity. Six males and three females of this group and one female animal of

the 400 mg/kg group and the control group died in the second half of the experiment. In the male animals of the 800 mg/kg group, body weight gains and the absolute and relative weights (relative to the brain weight) of the thymus and testes were reduced. The female animals of this group were found to have slightly increased liver, kidney, thymus and heart weights. In most of the animals of the 800 mg/kg group and two males of the 400 mg/kg group, slight hyperplasia and hyperkeratosis of the forestomach epithelium, accompanied by increased mitotic activity in the basement membrane, were detected. This study yielded a NOEL for rats of 400 mg/kg body weight per day as the damage to the forestomach is likely due to the application methodology.

No clinical symptoms of intoxication were observed in mice. All male animals and one female from the 1200 mg/kg group died during the first 4 weeks of the experiment. The body weight gains were reduced in the female animals after doses of 1200 mg/kg and in the male animals after doses as low as 600 mg/kg. At the end of the experiment the body weights of the male animals of the 600 mg/kg group were reduced by 9% relative to those of the controls. The organ weights did not differ from the control values. In the gross pathological and microscopic examinations, weak to moderate degeneration of the renal tubules was detected in all male animals of the 1200 mg/kg group and one male of the 600 mg/kg group. This study, therefore, yielded a NOEL of 300 and 600 mg/kg body weight per day for male and female mice, respectively (Kluwe et al. 1983; NTP, 1990, cited in ECHA) [Kl.score=2].

Inhalation

In a short-term inhalation study, groups of 14 Sprague-Dawley rats per sex and group were exposed in whole animal exposure chambers on 14 consecutive days, for 6 hours a day, to benzaldehyde vapour in concentrations of 0, 500, 750 and 1000 mL/m^3 (about 2200, 3300 and 4400 mg/m^3). During the experiment, 11 animals from the 1000 mL/m^3 group (10 females, 1 male) and 3 female animals from the 750 mL/m^3 group died. In all animals exposed to benzaldehyde, tremor, piloerection, diuresis, decreased respiration rates, hypothermia, reduced motor activity and concentration-dependent symptoms of eye and nose irritation occurred in the first week of the experiment. Since effects were observed at all test levels, this study did not yield a NOEL (ECHA) [Kl.score=2].

Albino rats were exposed to 26 mg/m^3 (about 6.0 mL/m^3) of benzaldehyde for a period of 4 months for 5 hours a day under dynamic conditions. After 3 months of exposure, changes were detected in haematological parameters (hypoglobulinaemia, erythrocytosis, leukocytosis, initial lymphocytosis followed by lymphopenia) and delays in body weight gain. At the end of the experiment, all the parameters were within the normal range (ECHA) [Kl.score=4].

Exposure to benzaldehyde concentrations of 6 mg/m^3 (about 1.4 mL/m^3) under otherwise identical conditions was tolerated by albino rats without symptoms (no further details) (Peresedov, 1974, cited in ECHA) [Kl.score=4].

F. Genotoxicity

Overall, the data indicate that the chemical has no mutagenic or genotoxic potential. Although there is no mutagenic activity in bacterial systems, the chemical does have weak clastogenic effects in some mammalian cell assays.

The genotoxicity of benzaldehyde has been investigated in many *in vitro* test systems (ECHA). In Salmonella typhimurium, in mutagenicity studies with the strains TA98, TA100, TA102, TA104, TA1535, TA1537 and TA2637, and in a DNA repair test with and without metabolic activation,

genotoxic activity was not detected. In a mutagenicity test with Escherichia coli WP2 uvrA and the mutagen 4-nitroquinoline-1-oxide, benzaldehyde from concentrations of 2120 µg/p1ate was found to have an antimutagenic effect (Watanabe et al., 1988). In Bacillus subtilis, DNA-damaging effects were observed at high concentrations only after metabolic activation. An increase in the incidence of mutants in the mouse Lymphoma test occurred only in the high, cytotoxic concentration range, and the finding is therefore questionable. Evidence of a weak clastogenic potential in the chromosomal aberration test and in the sister chromatid exchange test was also found only with high concentrations. Therefore, there is unreliable evidence of benzaldehyde having weak genotoxic activity.

In an *in vivo* test, a sex-linked recessive lethal test with *Drosophila melanogaster*, benzaldehyde administered in a concentration of 1500 ppm with the diet and injection of 2500 ppm was inactive (NTP, 1990; Woodruff et al., 1985, cited in ECHA) [Kl.score=2].

G. Carcinogenicity

H. Reproductive Toxicity and Developmental Toxicity

Benzyl derivatives, including benzaldehyde, have not been reported to produce reproductive and developmental toxicity. Benzyl derivatives generally follow similar metabolic pathways; therefore, studies conducted on benzyl derivatives are sufficient to support benzaldehyde (ECHA).

In one available study, 10 female rats were given oral doses of 2 mg benzaldehyde per animal (about 5 mg/kg body weight and day) every second day for a period of 223 days and were mated with untreated males on days 75 and 108 after the beginning of treatment. The number of offspring, weight of the pups (after 1 and 3 weeks) and pup survival were in the range of the control values. The number of pregnant females in the lest group was decreased relative to that in the control group (Sporn et al., 1967, as cited in ECHA). The study design (small number of treated animals, only one dose group) does not meet present-day standards and cannot, therefore, be regarded as evidence of impairment of female fertility (ECHA) [Kl.score=2].

The key study evaluating effects on fertility were by Kieckebusch and Lang (1960), which evaluated the effects of benzoic acid over four generations in rats via feeding. While this study does have some limitations, supplemental data on reproductive organs/tissues (sperm parameters, including epididymis/cauda epididimys/testis weights, sperm motility/density/abnormal sperm; Estrous cyclicity in females) from a 13-week repeated dose study of benzyl acetate (a substances that is metabolized completely to benzoic acid) (Morrissey et al., 1988), the apparent gaps in data from the current OECD 443 study design are filled. Overall, taking into consideration both the Kieckebusch and Lang (1960), and Morrissey et al. (1988) studies, no effects on reproductive performance and offspring were reported at 1% the test substance in feed (500 mg/kg bw). Therefore, the NOAEL for toxicity to reproduction is set at 500 mg/kg bw. (ECHA) [Kl.score=2].

Sodium benzoate is the sodium salt of benzoic acid and is completely metabolized to benzoic acid prior to excretion via the hippuric acid pathway. In a sub-acute developmental toxicity study conducted in rats and mice using sodium benzoate, dose levels applied showed no evidence of maternal toxicity. No effects on foetal development were reported. A NOAEL of 175 mg/kg bw/day was established. This level is considered to be very conservative, and rats and mice seem to be the most sensitive species (ECHA) [Kl.score=2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for benzaldehyde 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 lowest NOAEL is 175 mg/kg-day, which is based on the absence of reproductive effects in a sub-acute developmental toxicity study in rats and mice. The NOAEL of 175 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 / ($UF_A \times UF_H \times UF_L \times UF_{Sub} \times UF_D$)

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 = 175/(10 × 10 × 1 × 10 × 1) = 175/1000 = 0.175 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 = (0.175 × 70 × 0.1)/2 = 0.61 mg/L

B. Cancer

There was no evidence of carcinogenicity in rat and mouse chronic studies conducted on benzaldehyde. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Benzaldehyde does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Benzaldehyde has moderate toxicity to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

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

Table 3: Acute aquatic toxicity studies on benzaldehyde

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Fathead minnow	96-hr LC_{50}	12.4	2	ECHA
Rainbow trout	96-hr LC_{50}	11.2	2	ECHA
Goldfish	96-hr LC_{50}	13.8	2	ECHA
Channel catfish	96-hr LC_{50}	5.39	2	ECHA
Bluegill	96-hr LC_{50}	1.07	2	ECHA
Daphnia magna	48-hr EC_{50}	19.7	1	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	33.1 (growth) 8.05 (yield)	1	ECHA

Chronic Studies

In a juvenile growth test, the 7-day NOEC to 1- day *Pimephales promelas* larvae was 0.12 mg/L (measured) based on growth rate and mortality (ECHA) [KI.score=2].

The 8-day NOEC to *Scenedesmus quadricauda* is 34 mg/L (ECHA) [KI.score=4].

The 72-hr EC_{10} for Raphidocelis subcapitata was reported as 0.039 mg/L (ECHA) [KI.score=1].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for benzaldehyde 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 (1.07 mg/L), invertebrates (19.7 mg/L) and algae (8.05 mg/L). Results from chronic studies are available for fish (0.12 mg/L) and algae (0.039 mg/L). 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 NOEC of 0.039 mg/L for algae. The $PNEC_{water}$ is 0.0008 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 0.00063 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (1.0129/1280) \times 1000 \times 0.0008$
$= 0.0.00063$ 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]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.4436/1000 \times 2400]$
$= 1.0129\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 11.09 \times 0.04$
$=0.4436$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for benzaldehyde calculated from EPISUITE™ using the MCI is 11.09 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 0.0003 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.22/1500) \times 1000 \times 0.002$
$= 0.0003$ 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]

$Kp_{soil} = K_{oc} \times f_{oc}$

$= 11.09 \times 0.02$

$= 0.22\ m^3/m^3$

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for benzaldehyde calculated from EPISUITE™ using the MCI is 11.09 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).

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

Based on a measured log K_{ow} of 1.4, benzaldehyde does not meet the screening criteria for bioaccumulation.

The lowest chronic NOEC for benzaldehyde is <0.1 mg/L. Thus, benzaldehyde meets the screening criteria for toxicity.

The overall conclusion is that benzaldehyde is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H302: Acute toxicity – oral and dermal – Category 4

H332: Respiratory sensitization Category 1

B. Labelling

Warning

C. Pictogram

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

Rinse thoroughly with plenty of water for at least 15 minutes and consult a physician.

Skin Contact

Wash off with soap and plenty of water. Consult a physician.

Inhalation

Move person to fresh air. If not breathing, give artificial respiration. Consult a physician.

Ingestion

Do NOT induce vomiting. Rinse mouth with water. Consult a physician.

Notes to Physician

Symptoms may occur even after several hours. Medical observation for at least 48 hours is recommended.

Benzaldehyde may cause allergy or asthma symptoms or breathing difficulties if inhaled.

Medical Conditions Aggravated by Exposure

No data available.

Emergency Personnel Protection

Avoid breathing dust/fume/gas/mist/vapours/spray.

B. Firefighting Information

Extinguishing Media

Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

Specific Exposure Hazards

No data available.

Special Protective Equipment for Firefighters

No special measures required; wear self-contained breathing apparatus for firefighting if necessary.

C. Accidental Release Measures

Personal Precautions

Use personal protective equipment. Respiratory protection and/or ventilation may be necessary to avoid breathing vapours, mist or gas. Remove all sources of ignition. Evacuate unprotected persons. Beware of vapours accumulating to form explosive concentrations. Vapours can accumulate in low areas.

Environmental Precautions

Do not allow to enter sewers, drains or waterways. Discharge into the environmental must be avoided.

Steps to be Taken if Material is Released or Spilled

Contain spillage, and then collect with an electrically protected vacuum cleaner or by wet-brushing and place in container for disposal according to local regulations. Keep in suitable, closed containers for disposal.

D. Storage and Handling

General Handling

Avoid contact with skin and eyes. Avoid inhalation of vapour or mist. No smoking.

Other Handling Precautions

Keep away from sources of ignition. Take measures to prevent the build-up of electrostatic charge.

Storage

Keep container tightly closed in a dry and well-ventilated place. Containers that are opened must be carefully resealed and kept upright to prevent leakage. Storage under nitrogen if necessary.

Sensitive to light. Store in light-resistant containers.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Australia: No specific exposure standards are available.

The chemical has an exposure standard of 5 mg/m^3 time weighted average (TWA) in Bulgaria, Hungary, Latvia and Russia; 10 mg/m^3 in Poland; and 2 ppm in the USA.

Short-term exposure limits (STEL) of 4 ppm in the USA and Canada; 10 mg/m^3 in Hungary; and 40 mg/m^3 in Poland have been reported.

Engineering Controls

Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapours below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection Equipment

Respiratory Protection: Vapour respirator.

Hand Protection: Impervious gloves. Inspect gloves before use.

Skin Protection: Protective clothing as required by the situation.

Eye protection: Splash goggles or face shield and safety glasses.

Other Precautions: Use other PPE as required by the situation.

F. Transport Information

UN Number: 1990

Class 9

XI. DISPOSAL MANAGMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

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BISMUTH OXIDE

This dossier on bismuth oxide presents the most critical studies pertinent to the risk assessment of bismuth oxide 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): [(oxobismuthanyl)oxy]bismuthanone

CAS RN: [redacted]

Molecular formula: Bi2O3

Molecular weight: 465.96 g/mol

Synonyms: Dibismuth trioxide, Bismuth sesquioxide, Bismuth trioxide, Bismuthous oxide, Wismutoxid

SMILES: O=[Bi]O[Bi]=O

II. PHYSICAL and CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Bismuth Oxide

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Yellow monoclinic crystals or a yellow powder with no odor.	2	ECHA
Melting point	825°C	2	ECHA
Boiling point	1,890°C	2	ECHA
Density	8.93 g/cm^3 @ 20°C	2	ECHA
Water solubility	Slightly soluble. See below*	1	ECHA

*5.887 and 0.777 mg/L @ 21.3°C at a flow rates of 23.45 12.33/6.15 mL/hour, respectively. Measurements were bismuth oxide in water.

III. ENVIRONMENTAL FATE PROPERTIES

Biodegradation is not applicable to bismuth oxide. It is an inorganic mineral that is slightly soluble in water; thus, it is not expected to be bioaccumulative.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Bismuth oxide is not acutely toxic via oral, dermal or inhalation route or irritating to the skin or eyes. The findings indicate that it does not need to be classified as a skin sensitizer. There were no findings of toxicity in repeated dose testing. Bismuth is not expected to be genotoxic or carcinogenic, as oxides of bismuth are not soluble and testing with soluble bismuth salts were not found to be genotoxic. There are no reported reproductive or developmental effects for bismuth.

B. Acute Toxicity

Bismuth oxide is not acute toxic via oral, dermal or inhalation route. A 28-day oral gavage administration study in rats (Kl =2) found no mortality, abnormal clinical signs, body weight changes or abnormal histopathological findings at a maximum dose of 2000 mg/kg bw for both sexes (Sano et al., 2005).

Administration of a dry aerosol of dibismuth trioxide at a gravimetricly determined concentration of 5.07±0.09 mg dibismuth trioxide/L air for 4 hours by inhalation using a dynamic nose-only exposure chamber to rats found no mortality or change in weight gain over the course of the study. Slight ataxia and slight dyspnea was noted in 2 of 3 male and 3 of 3 female rats.

No studies were listed to evaluate the dermal toxicity of bismuth oxide.

C. Irritation

Dibismuth trioxide is not considered to be irritating to skin or to eyes. Dibismuth trioxide was tested for its potential to induce skin irritation in a human skin model (Kl =1). 3 tissues of the human skin model EpiSkin™ were treated with either the test item, the negative or the positive control for 15 minutes. 15 µL of either the negative control (deionised water) or the positive control (5% Sodium lauryl sulfate) were applied to each tissue. The test item is not considered to possess an irritant potential. In this study and under the experimental conditions reported, the test item was concluded to be a non-irritant to skin.

D. Sensitization

No published data or studies for determination the sensitisation properties of dibismuth trioxide are available. In an available guideline study with the more bioavailable substance, bismuth hydroxide nitrate oxide, the sensitising potential was determined in the LLNA in mice. Results show that bismuth hydroxide nitrate oxide does not reveal any sensitising properties and should not be classified and labelled according to regulation (EC) No.1272/2008. Based on read across from this much more bioavailable substance, it can be considered that dibismuth trioxide does not need to be classified for sensitisation.

E. Repeated Dose Toxicity

A 90-day repeated dose oral toxicity study (Kl = 2) was conducted in accordance with OECD Guideline 408 with the read-across substance, bismuth subnitrate. There was no adverse effect of treatment on body weight development and dietary intake in animals of either sex. Hematology, blood chemistry, testosterone hormone assessment, estrus cycle assessment in females, sperm analysis in males and microscopic examination of the selected tissues did not identify any findings of toxicological relevance. A dose level of 1000 mg/kg bw/day is therefore considered to be the NOAEL for systemic toxicity within the confines of this type of study. Based on read across to the results of this study, classification for repeated dose toxicity under the CLP Regulation is not required.

No reliable or relevant studies or data are available for dibismuth trioxide. Dermal repeated dose toxicity is considered to be scientifically unjustified. No data are available; classification concerning repeated dermal toxicity is not required.

F. Genotoxicity

No published data or studies for determination the mutagenicity of dibismuth trioxide is available. Due to the low solubility of the substance in water, it would not allow a study to be conducted in accordance with guidelines. However, there are publications available in which soluble bismuth salts were tested. Colloidal bismuth subcitrate was tested to induce sister chromatid exchanges or chromosome aberrations and bismuth subsalicylate and bismuth nitrate were both tested to induce gene mutation in bacterial cells. There is no indication for genotoxic/mutagenic effects of either colloidal bismuth subcitrate, bismuth subsalicylate or bismuth nitrate in these available publications.

In addition, in an available guideline study with the soluble bismuth hydroxide nitrate oxide the gene mutation potential was determined in the hprt locus of L5178Y mouse lymphoma cells. The study included treatments up to the maximum practicable concentration, 140 µg/mL (limited by solubility in the primary vehicle), in two independent experiments in the absence and presence of a rat liver metabolic activation system (S9).

G. Carcinogenicity

There are no studies available to evaluate carcinogenicity of bismuth oxide. Based on the lack of genotoxicity of soluble bismuth salts and the general insolubility of bismuth oxide, it is likely that bismuth oxides are not carcinogenic.

H. Reproductive and Developmental Toxicity

In a 90 day repeated dose oral toxicity study with additional reproductive toxicity endpoints conducted in accordance with OECD Guideline 408, the read-across substance, bismuth subnitrate had no toxicological effects on sperm or on testosterone levels in male rats or on the estrous cycle in female rats. The NOAEL in this study was 1000 mg/kg bw/day. By read across, dibismuth trioxide is not predicted to have any toxic effects on fertility.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for bismuth oxide 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 lowest NOAEL from the available studies is 1000 mg/kg-day based on a lack of effect on clinical signs and mortality, body weight, haematology, clinical chemistry and other clinical endpoints. This NOAEL for bismuth oxide was adjusted using the molecular weight of bismuth oxide (466 g/mol, Bi2O3) and the molecular weight of bismuth subnitrate (397 g/mol, BiH2N3O9), resulting in a NOAEL of 1174 mg/kg-day. The NOAEL of 1174 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) = 3

UF_D (database uncertainty) = 1
Oral RfD = 1174/(10 x 10 x 1 x 3 x 1) = 1174/300 = 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 = (4 x 70 x 0.1)/2 = 14 mg/L

B. Cancer

Bismuth oxide is not a carcinogen, therefore no drinking water guideline for cancerous endpoints is developed.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Bismuth oxide does not exhibit the following physico-chemical properties:

· Explosivity
· Flammability
· Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

While there are no aquatic toxicity studies on bismuth oxide, studies with bismuth subnitrate suggest a relatively low order of aquatic toxicity for bismuth compounds.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies conducted on bismuth subnitrate.

Table 2: Acute Aquatic Toxicity Studies on Bismuth Subnitrate ($Bi_5O(OH)_9(NO_3)_4$)

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Brachydanio rerio	96-hr LC_{50}	>137 [WAF] >100 [WAF]*	2	ECHA
Daphnia magna	48-hr EC_{50}	>137 [WAF] >100 [WAF]*	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	>137 [WAF] >100 [WAF]*	2	ECHA

*As bismuth. The value for bismuth oxide is 223 mg/L (the molecular weight is 266 g/mol).

Chronic Studies
No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

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

PNEC water
Experimental results on bismuth subnitrate are available for three trophic levels. Acute $E(L)C_{50}$ values (as bismuth oxide) are available for fish (>223 mg/L WAF), invertebrates (>223 mg/L WAF), and algae (>223 mg/L WAF). On the basis that the data consists of short-term data for three trophic levels, an assessment factor of 100 has been applied to the $E(L)C_{50}$ values of 223 for fish, invertebrates, and algae. The $PNEC_{water}$ is 2.2 mg/L (for bismuth oxide).

PNEC soil
There are no toxicity data for terrestrial or soil organisms. The $PNEC_{soil}$ cannot be derived using the equilibrium partitioning method.

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).

Bismuth oxide is an inorganic mineral. Biodegradation is not applicable to bismuth oxide. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to bismuth oxide.

Bismuth oxide is an inorganic substance that is a slightly soluble powder. Bioaccumulation of bismuth oxide is generally unlikely to occur, given its low bioavailability.

There are no chronic toxicity studies on bismuth oxide. The acute E(L)C_{50} values of another inorganic bismuth substance (bismuth subnitrate) are >1 mg/L for fish, invertebrates, and algae. Thus, bismuth oxide is not expected to meet the criteria for toxicity.

The overall conclusion is that bismuth oxide is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

This substance does not meet the criteria for classification in accordance with Regulation No 1272/ 2008/EC. It Is not a dangerous substance or mixture according to the Globally Harmonized System (GHS).

B. Labelling

Not required. This substance does not meet the criteria for classification; it is not a dangerous substance according to the Globally Harmonized System.

C. Pictogram

Not required.

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

A. First Aid

Eye Contact
Rinse cautiously with water for several minutes. In all cases of doubt, or when symptoms persist, seek medical advice.

Skin Contact
Rinse skin with water/shower. In all cases of doubt, or when symptoms persist, seek medical advice.

Inhalation
Provide fresh air. In all cases of doubt, or when symptoms persist, seek medical advice.

Ingestion
Rinse mouth. Call a doctor if you feel unwell.

Notes to Physician
Treat symptomatically.

Medical Conditions Aggravated by Exposure
No data available.

Emergency Personnel Protection
No data available.

B. Fire Fighting Information

Extinguishing Media
Co-ordinate fire-fighting measures to the fire surroundings; water spray, foam, dry extinguishing powder, carbon dioxide (CO2). Keep product and empty container away from heat and sources of ignition.

Specific Exposure Hazards
No data available.

Special Protective Equipment for Firefighters
Fight fire with normal precautions from a reasonable distance. Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions
Do not breathe dust; avoid dust formation.

Environmental Precautions
Keep away from drains, surface and ground water.

Steps to be Taken if Material is Released or Spilled
Stop leak if possible without risk. Take up mechanically. Clean contaminated surface.

D. Storage and Handling

General Handling
Wear personal protective equipment. Ensure adequate ventilation. Avoid contact with skin, eyes and clothing. Avoid ingestion and inhalation. Avoid dust formation.

Other Handling Precautions
Keep away from incompatible materials.
Incompatible materials: Strong oxidizing agents

Storage
Keep containers tightly closed in a dry, cool and well-ventilated place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
No data available. Bismuth oxide is not listed among Safe Work Australia Hazardous Chemicals. No exposure controls for bismuth oxide are presented on the ECHA site.[1]

Engineering Controls
Ensure adequate ventilation. Use process enclosures, local exhaust ventilation, or other engineering controls to manage airborne levels. If user operations generate dust, fume or mist, use ventilation and/or respiratory protection

Personal Protection Equipment
Respiratory Protection:
Effective dust mask. Use a dust respirator under conditions where exposure to the substance is apparent (e.g. generation of high concentration of dust (dust clouds), inadequate ventilation, development of respiratory tract irritation), and engineering controls are not feasible. Be sure to use an approved/certified respirator or equivalent.

Hand Protection:
Appropriate gloves; inspect before use.

Skin Protection:
Loved sleeved clothing, chemical resistant apron.

Eye protection:
Safety glasses with side-shields.

[1] Substance is known to be on the EEA market in nanomaterial form, as listed in the EUON Nanomaterials in the EU market list.

Other Precautions:
Regular hygiene: Avoid contact with skin, eyes and clothing. Wash hands before breaks and immediately after handling the product When using, do not eat, drink or smoke.

F. Transport Information

UN Number: Not regulated

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

AICS: 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.

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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.

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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.

BUTYL ALCOHOL (1-BUTANOL)

This dossier on butyl alcohol (1-butanol) presents the most critical studies pertinent to the risk assessment of 1-butanol 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; Kl).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Butan-1-ol

CAS RN: [redacted]

Molecular formula: C4H10O

Molecular weight: 74.123

Synonyms: 1-Butanol, 1-Butyl alcohol, 1-hydroxybutane, Butan-1-ol, butyl alcohol, Butyl hydroxide, Butylalcohol, CCS 203, ET5740PTB, Hemostyp, Methylolpropane, n-Butanol, n-Butyl alcohol, N300PTB, Nacol 4, PP100, Propylcarbinol

SMILES: CCCCO

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of 1-Butanol

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Clear, colorless liquid with an alcoholic odor	2	ECHA
Melting point	<-90°C	2	ECHA
Boiling point	119°C	2	ECHA
Density	0.81 g/cm^3 @ 20°C	2	ECHA
Vapor pressure	< 10 hPa @20°C	2	ECHA
Partition coefficient (log K_{ow})	1 @ 25°C	1	ECHA

Property	Value	Klimisch score	Reference
Water solubility	66 g/L @ 20°C	1	ECHA
Flash point	35°C	2	ECHA
Auto flammability	355°C	1	ECHA
Viscosity	2.947 mPa s @ 20°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

1-Butanol is readily biodegradable and not expected to bioaccumulate. No experimental data are available for adsorption/desorption; the estimated Koc value is 3.471 L/kg.

A calculated log Koc of 0.54 is available, suggesting a high mobility of 1-butanol in soil.

B. Biodegradation

1-Butanol is readily biodegradable. In a BOD test, degradation was 87% after 10 days and 92% after 20 day, meeting the 10-day window (ECHA) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for 1-butanol. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value from log K_{ow} of 1.0 is 10.01 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 3.471 L/kg.

D. Bioaccumulation

There are no bioaccumulation studies on 1-butanol. 1-Butanol is not expected to bioaccumulate based on a log K_{ow} of 1.0 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Butyl alcohol is slightly acutely toxic to experimental animals via the oral and dermal routes of exposure; a low acute toxicity was observed after inhalative exposure. The chemical is classified in Australia as respiratory system and skin irritant but is not

considered a skin sensitiser. Butyl alcohol is not expected to be genotoxic; although there are no data on the carcinogenicity of butyl alcohol, based on the lack of genotoxicity, it is not expected to be. Few studies have evaluated reproductive or developmental toxicity but the available studies do not indicate reproductive or developmental effects. Any developmental toxicity is expected to be secondary to maternal toxicity.

B. Acute Toxicity

Butyl alcohol is slightly acutely toxic to experimental animals via the oral and dermal routes of exposure; a low acute toxicity was observed after inhalative exposure.

Oral

The most sensitive LD50 value was provided by a study comparable to OECD TG 401 (Union Carbide Corporation 1967). Here, 60 -day-old female Harlan Wistar rats were dosed with butan-1 -ol at various dose levels per gavage. The acute LD50 value was 2.83 mL/kg bw in female rats, corresponding to 2290 mg/kg bw (calculated with a density of 0.81 g/mL). No further data were available.

A comparable LD50 level was observed in a study following the standard acute method with acceptable restrictions (Jenner et al.1967). In this study, 5 young adult Osborne-Mendel rats per sex were dosed with butan-1-ol at different, but unspecified doses. The rats were observed for 14 days and the LD50 values were calculated. After 14 d observation period, the LD50 was 2510 mg/kg bw in rats. Mortality occurred within 4 - 18 h after dosing, and depression and coma were reported as clinical signs. Weighing and performance of necropsy was not reported.

In another oral acute study, groups of 10 female rats were orally gavaged with 3160, 3980, 5000 or 6300 mg/kg and observed for 14 days after dosing. Here, 0, 3, 8 and 10 rats died at dose levels of 3160, 3980, 5000 or 6300 mg/kg, respectively. Deaths following oral doses occurred in many cases within 4 hours and in all but one instance within 24 hours. The LD50 was 4360 mg/kg/bw for female rats (Union Carbide Corporation 1951).

For other common test species oral LD50 values were reported with limited details: 2680 mg/kg bw for mice (Rumyanstev et al., 1979, Val. 4), 3500 mg/kg bw for rabbits (Munch, 1972; Munch and Schwarze, 1925, Val. 4), 1200 mg/kg bw for Golden hamsters (Dubina and Maksimov, 1976, Val. 4), and a minimum lethal dose of 1782 mg/kg bw for dogs (Von Oettingen, 1943, Val. 4). In the ECETOC JACC (2003) document also one publication with an oral LD50 in rats below 2000 mg/kg (790 mg/kg) is reported.

Dermal

The most reliable data were provided by a study comparable to OECD TG 402 (Union Carbide Corporation 1951). Here, butan-1 -ol was applied to the shaved skin of rabbits

for 24 hours under occlusive conditions. Four doses of 1.26 to 10 ml/kg were applied to groups of four male rabbits and a LD50 value of 4.24 ml/kg bw (corresponding to ca. 3434 mg/kg bw; calculated with a density of 0.81 g/mL) was determined after an observation period of 14 days. Three rabbits of the 5 mL/kg bw group and all rabbits of the 10 ml/kg bw group died; all deaths occurred on the day of application. Body weight gain during the observation period was highly variable in the sublethal dose groups and negative in the survivor of the 5 mL/kg bw group. No information regarding clinical signs or local effects was available. In the ECETOC JACC (2003) document further dermal LD50 values in rabbits of 7600, 5300 and 4200 mg/kg are reported.

Inhalation

In a study similar to OECD TG 403, 10 Sprague-Dawley rats per sex per dose were whole-body exposed to vapour atmospheres of butan-1-ol for 4 h and observed for 14 d. The LC0 is >17.76 mg/L; no mortality or clinical signs were observed at 17.76 mg/L; only slightly reduced body weight gain was observed. Therefore, the LD50 level is considered to be > 20 mg/L (BASF 1979).

In another study, which was similar to the inhalation hazard test of OECD TG 403, 12 Sprague-Dawley rats of both sexes were exposed to a vapour saturated butan-1-ol atmosphere for 7 h. None of the animals died (BASF 1980).

Additionally, in a further study comparable to OECD TG 403 no mortalities were observed after exposure to a substantially saturated vapour for 8 hours in male rats and after exposure to 8000 ppm (ca. 24 mg/L) for 4 h in female rats, respectively. Poor coordination or prostration was observed in both trials (Union Carbide Corporation 1951).

C. Irritation

Respiratory Irritation

The chemical is classified in Australia as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). The available data from observations in animals and humans support this classification.

Based on an inhalation study in mice, it was reported that 1268 ppm (3909 mg/ m^3) of the chemical was predicted to be intolerable in humans, 127 ppm (390.9 mg/ m^3) would be uncomfortable in humans and 13 ppm (40 mg/ m^3) was expected to have no effect on humans (OECD 2001).

Skin Irritation

The chemical is classified in Australia as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). The available data from observations in animals and humans support this classification.

Moderate irritation was reported in a 24 hour patch test (non-guideline study) where 405 or 500 mg of the chemical was applied to the skin of the rabbits. It was reported that these effects may be due to the chemical's defatting (chemical dissolving of dermal lipids from the skin) and drying characteristics (OECD 2001).

Another non-guideline study reported the chemical was a skin irritant in several Vienna white rabbits exposed to 0.5 mL of the chemical for five minutes, one hour or two hours under occlusive conditions. The animals were observed for eight days. The authors concluded that exposure for two hours under occlusive conditions resulted in higher Draize scores and observed superficial necrosis (death of tissue). However, there was no full thickness destruction of the skin (REACH).

Eye Irritation

The chemical is classified in Australia as hazardous with the risk phrase 'Risk of serious damage to the eyes' (Xi; R41) in HSIS (Safe Work Australia). The available data from observations in animals and humans support this classification.

The chemical was reported to be a severe eye irritant when tested according to OECD Test Guideline (TG) 405 using 0.1 mL of the chemical applied to three New Zealand white rabbits. Severe ocular lesions were present at the end of the seven-day observation period, indicating severe eye damage and irreversible effects on the eye (REACH).

The chemical was reported to be a severe eye irritant in rabbits in non-guideline studies where 1.62 or 20 mg of the chemical was applied into rabbit eyes over a 24 or 72 hour period (OECD 2001). An additional non-guideline study reported severe corneal irritation when 0.005 mL of the chemical was applied into rabbit eyes.

D. Sensitization

Based on available repeat dose dermal studies, the chemical is not expected to be a skin sensitiser. OECD (2001) reported that human studies and experience show that the chemical is not likely to be a skin sensitiser.

E. Repeated Dose Toxicity

Oral

A no observed adverse effect level (NOAEL) of 125 mg/kg bw/day and a lowest observed adverse effect level (LOAEL) of 500 mg/kg bw/day in male and female CD rats was reported based on results from a repeat dose oral study (Kl = 1) using the chemical (OECD 2001). Groups of male and female rats (30/sex/group) were administered the chemical via gavage at 0, 30, 125 or 500 mg/kg/day for 13 weeks. It was reported that ataxia (impaired muscle coordination) and hypoactivity were observed at the highest

dose during the final six weeks of the study. No treatment related effects were reported in the 30 and 125 mg/kg/ bw/day dose groups (OECD 2001).

Inhalation

In a non-guideline study, the chemical was applied to the skin of rabbits under occlusive conditions over a period of 21 days. Local effects were reported such as drying of the skin, cracking, wrinkling and exfoliation of the epidermis. However, no systemic toxicity was reported (REACH). In another non-guideline repeat dose dermal study on rabbits, 42 to 55 mL/kg of the chemical applied to the skin of rabbits over four consecutive days resulted in 100 % mortality. However, the same study reported that 30 applications of 20 mL/kg of the chemical over six weeks did not produce any deaths (OECD 2001).

Dermal

No data are available.

F. Genotoxicity

The chemical is not expected to be genotoxic.

The chemical tested negative in a number of tests for genotoxicity. These included several in vitro tests (OECD Guideline 473: mammalian chromosome aberration test on Chinese hamster lung fibroblasts V79; OECD Guideline 471: bacterial reverse mutation assay on *S. typhimurium* TA 98, TA 100, TA 98, TA 1535 and TA 1537; OECD Guideline 476: mammalian cell gene mutation test on Chinese hamster lung fibroblasts V79) and in vivo tests (OECD Guideline 474: mouse micronucleus) (OECD 2001, REACH).

In Vitro Studies

Table 2: *In vitro* Genotoxicity Studies on

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (S. typhimurium strain TA 98, TA 100, TA 98, TA 1535 and TA 1537)	-	-	2	Jung et al., 1992
Mammalian cell gene mutation (Chinese hamster lung fibroblasts (V79))	-	-	1	REACH

*+, positive; -, negative

In Vivo Studies

Fewer studies are available for in vivo testing but are also negative for genotoxicity. According to the results of a reliable mouse study conducted according to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) (KI =1), the single oral

administration of butan-1-ol did not lead to any increase in the number of polychromatic erythrocytes containing either small or large micronuclei. The rate of micronuclei was always in the same range as that of the negative control in all dose groups and at all sacrifice intervals. No inhibition of erythropoiesis determined from the ratio of polychromatic to normochromatic erythrocytes was detected.

G. Carcinogenicity

OECD (2001) reported that based on the number of negative mutagenicity and clastogenicity findings, the chemical is not expected to be a carcinogen. A weight of evidence study reported that the chemical is not expected to have carcinogenic potential as it does not contain structural components to support carcinogenicity (REACH, HSDB).

H. Reproductive and Developmental Toxicity

The chemical is not expected to be toxic to reproduction (OECD 2001). In a non-guideline study, male and female Sprague Dawley (SD) rats were exposed to the chemical via inhalation at 0, 3000 or 6000 ppm for seven hours/day. Female rats were exposed to the chemical throughout gestation, while males were exposed to the chemical for six weeks prior to mating. No harmful effects on fertility or pregnancy rate were reported at any of the dose levels. In another non-guideline study, no testicular toxicity (effect on testes weight or histopathology) was reported in SD male rats that were administered the chemical via oral intubation at 533 mg/kg bw/day over six days (OECD 2001).

Any developmental effects were only reported to be observed secondary to maternal toxicity, so the chemical is not expected to be a developmental toxin. OECD (2001) reported that the chemical showed mild foetotoxicity and developmental variations in offspring only at or near the maternally toxic and, in some cases, lethal dose of 8000 ppm. Offspring of female SD rats exposed via inhalation to 0, 3500, 6000 or 8000 ppm of the chemical on gestations days 1 to 19, reported a reduction of foetal weights at 6000 and 8000 ppm and a slight increase in skeletal malformations at 8000 ppm but not at the lower dosage levels. At a maternally toxic dose of 8000 ppm, decreased weight gain, food consumption and dam deaths were reported. The NOAEL for offspring and dams was 3500 ppm as there was a slight decrease in foetal weight at the 6000 ppm dose level.

In another 20 day study in male and female SD rats exposed to 0, 3000 or 6000 ppm of the chemical via inhalation, a small number of behavioural and neurochemical variations in offspring at 6000 ppm were reported. No maternal toxicity was reported throughout gestation for females or for six weeks prior to mating for males as a result of maternal or paternal exposure. However, the effects observed in offspring were not regarded as

biologically significant by the authors due to inconsistences between dose-response patterns.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for butyl alcohol 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 lowest NOAEL from these studies is 125 mg/kg-day based on CNS effects in rats from a 90-day oral gavage study (Kl = 1; REACH). The NOAEL of 125 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) = 3
UF_D (database uncertainty) = 1

Oral RfD = 125/(10 x 10 x 1 x 3 x 1) = 125/300 = 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 human and no animal cancer data are available. As such, the substance is not classifiable as to human carcinogenicity according to guidelines provided by the World Health Organization (WOE).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

1-Butanol is a flammable liquid.

1-Butanol does not exhibit the following physico-chemical properties:

- Explosivity
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The substance is exhibits a low order of acute and chronic aquatic toxicity as demonstrated by the information provided below.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on 1-butanol.

Table 3: Acute Aquatic Toxicity Studies on 1-Butanol.

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephelas promelas	96-hr LC_{50}	1,376	1	ECHA
Daphnia magna	48-hr EC_{50}	1,328	1	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	225	1	ECHA

Chronic Studies

The 21-d NOEC from a *Daphnia* reproduction test is 4.1 mg/L (ECHA) [Kl. score = 2].

96-hr EC_{10} to *Pseudokirchneriella subcapitata* is 134 mg/L (ECHA) [Kl. score = 1].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for 1-butanol 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 (1,376 mg/L), invertebrates (1,328 mg/L), and algae (225 mg/L). Results from chronic studies are available for invertebrates (4.1 mg/L) and algae (124 mg/L). On the basis that the data consists of short-term studies for three trophic levels and long-term studies for two trophic levels, an assessment factor of 50 has been applied to the lowest reported EC_{10} value of 4.1 mg/L for fish. The $PNEC_{water}$ is 0.08 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 $PNEC_{soil}$ is 0.004 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.07/1500) \times 1000 \times 0.08$
$= 0.004$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 3.471 \times 0.02$
$= 0.07$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for 1-butanol based on the molecular connectivity index (MCI) is 3.471 L/kg (EPA, 2019).
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).

1-Butanol is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Based on a measured log K_{ow} of 1.0, 1-butanol does not meet the screening criteria for bioaccumulation.

The lowest chronic EC_{10} or NOEC value for 1-butanol is >0.1 mg/L. The acute $E(L)C_{50}$ values are >1 mg/L. Thus, 1-butanol does not meet the criteria for toxicity.

The overall conclusion is that 1-butanol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable liquid Category 3
Acute toxicity Category 4
Specific target organ toxicity Category 3
Skin irritation Category 2
Eye damage Category 1

B. Labelling

Danger

C. Pictogram

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

A. First Aid

<u>Eye Contact</u>

Rinse continuously with water for several minutes. Remove contact lenses if present and easy to do so. Continue rinsing. Call physician or poison center.

Skin Contact
Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower.

Inhalation
Remove victim to fresh air and keep at rest in a position comfortable for breathing.

Ingestion
Call physician or poison center.

Notes to Physician
May cause drowsiness or dizziness

Irritating to eyes, respiratory system and skin. Central nervous system effects. Hearing impairment Treat symptomatically.

Medical Conditions Aggravated by Exposure
No data available

Emergency Personnel Protection
First-Aid Providers: Avoid exposure to blood or body fluids. Wear gloves and other necessary protective clothing. Dispose of contaminated clothing and equipment as bio-hazardous waste.

B. Fire Fighting Information

Extinguishing Media
Use foam, dry chemical, CO2 or water spray for extinction. Alcohol-resistant Foam; butanol is an alcohol. Do not use a solid (straight) water stream as it may scatter and spread fire.

Specific Exposure Hazards
Combustion products include carbon monoxide and carbon dioxide. Flammable. May be ignited by heat, sparks or flames. Material can burn with invisible flame. Vapor may travel considerable distance to source of ignition and flash back.
Vapors may form explosive mixtures with air. Most vapors are heavier than air. They will spread along the ground and collect in low or confined areas (sewers, basements, tanks). Container explosion may occur under fire conditions or when heated. Fire may produce irritating, corrosive and/or toxic gases.

Special Protective Equipment for Firefighters
Wear SCBA and fully encapsulating, gas-tight suit when handling these substances. Structural firefighter's uniform is NOT effective for these materials.

C. Accidental Release Measures

Personal Precautions
Ensure adequate ventilation. Keep people away from and upwind of spill/leak. Avoid contact with skin, eyes and clothing. Use personal protective equipment. Remove all sources of ignition. Pay attention to flashback. Take precautionary measures against static discharges. All equipment used when handling the product must be grounded. Use spark-proof tools and explosion-proof equipment. In case of large spill, water spray or vapor-suppressing foam may be used to reduce vapors, but may not prevent ignition in closed spaces.

Environmental Precautions
Prevent further leakage or spillage if safe to do so. Prevent product from entering drains. Prevent entry into waterways, sewers, basements or confined areas. In case of large spill, dike if needed. Dike far ahead of liquid spill for later disposal.

Steps to be Taken if Material is Released or Spilled
Stop leak if you can do it without risk. Absorb spill with inert material (e.g. vermiculite, dry sand or earth).
Use appropriate tools to put the spilled material in a suitable chemical waste disposal container. Use clean non-sparking tools to collect absorbed material.
Clean contaminated surface thoroughly.

D. Storage and Handling

General Handling
Wear personal protective equipment. Use only in well-ventilated areas. Avoid contact with skin, eyes and clothing.
Keep away from heat and sources of ignition. Do not breathe vapors or spray mist. Do not ingest. When using do not smoke. Handle in accordance with good industrial hygiene and safety practice.

Other Handling Precautions
Remove all sources of ignition. To avoid ignition of vapors by static electricity discharge, all metal parts of the equipment must be grounded. Keep away from incompatible materials.

Storage

Keep container tightly closed in a dry and well-ventilated place. Store at room temperature in the original container. Keep away from heat and sources of ignition. Store in a segregated and approved area. Store away from incompatible materials. Incompatible Materials: Oxidizing agents, Acids, Alkali Metals, Halogens, Aluminum, Caustics, isocyanates

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
The workplace exposure standard for butanol in Australia is 152 mg/m3 as an 8-hr TWA. No STEL is listed.

Engineering Controls
Ensure adequate ventilation. Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors and mist below their respective threshold limit value.

Personal Protection Equipment
Respiratory Protection:
Where ventilation is not adequate, respiratory protection may be required. Avoid breathing vapours or mists. Select and use respirators appropriately. When mists or vapours exceed the exposure standards then the use of the following is recommended: Approved respirator with organic vapour and dust/mist filters. Filter capacity and respirator type depends on exposure levels.

Hand Protection:
Use appropriate, impervious gloves. Inspect gloves before use.

Skin Protection:
Chemical resistant apron, long sleeved clothing

Eye protection:
Use face shield, chemical goggles or safety glasses with side shield protection as appropriate.

Other Precautions:
No additional notes available.

F. Transport Information

UN Number 1120
Hazard class 3

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

AICS: 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.

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HYDROCARBONS, C12-C15, N-ALKANES, ISOALKANES, CYCLICS, <2% AROMATICS

This dossier on hydrocarbons, C12-C15, n-alkanes, isoalkanes, cyclics, <2% aromatics (C12-C15 aliphatic hydrocarbons (<2% aromatics)) presents the most critical studies pertinent to the risk assessment of C12-C15 aliphatic hydrocarbons (<2% aromatics) 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 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: Hydrocarbons, C12-C15, n-alkanes, isoalkanes, cyclics, <2% aromatics

CAS RN: [redacted] [CAS No. [redacted] EC No. 920-107-4]

Historically, hydrocarbons, C12-C15, n-alkanes, isoalkanes, cyclics, <2%aromatics was included within the CAS RN [redacted] for distillates, (petroleum), hydrotreated, light. This CAS RN is broadly defined as "A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. It consists of hydrocarbons having carbon number predominantly in the range of C9 to C16 and boiling in the range of approximately 150°C to 290°C (302° to 554°F)." This CAS RN can include hydrocarbon streams and solvents that can vary widely in their compositions, processing, and classifications. The EU Hydrocarbon Solvents Producers Association (HSPA), for the purposes of REACH registrations, established more precise definitions for hydrocarbon solvents and established a new substance identification and naming convention.[1] Hydrocarbons, C12-C15, n-alkanes, isoalkanes, cyclics, < 2% aromatics would have the CAS RN [redacted] and EC. No. 920-107-4 and would be within the HSPA category for C9-C14 Aliphatics (≤2% aromatics).

Molecular formula: Not available (UVCB substance)

Molecular weight: Not available (UVCB substance)

Synonyms: Hydrocarbons, C12-C15, n-alkanes, isoalkanes, cyclics, <2% aromatics; distillates, petroleum, hydrotreated, light; C12-C15 aliphatic hydrocarbons (<2% aromatics)

SMILES: Not available (UVCB substance)

[1] https://www.reachcentrum.eu/Consortia%20Documents/P-I163/Other/20110401160024-HSPA_CAS_April__2011.pdf.

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of C12-C15 Aliphatic Hydrocarbons (<2% Aromatics)

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colorless to faint yellow with a slight odor.	2	ECHA
Melting point	-30°C	2	ECHA
Boiling point	233 to 266°C	2	ECHA
Density	0.79 to 0.85 g/cm^3 @ 15°C	2	ECHA
Vapor pressure	0.003 kPa @ 20°C (calculated)	2	ECHA
Partition coefficient (log K_{ow})	Not determined (UVCB substance)	-	-
Water solubility	Not determined (UVCB substance)	-	-
Flash point	102°C	2	ECHA
Auto flammability	>200°C	2	ECHA
Viscosity	3.56 mm^2/s @ 20°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

There are no biodegradation data on C11-C15 aliphatic hydrocarbons (<2% aromatics). However, a hydrocarbons, C11-14, n-alkanes, isoalkanes, cyclics (<2% aromatics) hydrocarbon fluid was shown to be readily biodegradable. The C12-C15 aliphatic hydrocarbons (<2% aromatics) are expected to highly absorb to sediment and soil. The C12-C15 aliphatic hydrocarbons (<2% aromatics) is expected to have constituents with the potential to bioaccumulate.

B. Biodegradation

No biodegradation data are available on C12-C15 aliphatic hydrocarbons (<2% aromatics).

In an OECD 301F test, degradation of hydrocarbons, C11-14, n-alkanes, isoalkanes, cyclics (<2% aromatics) hydrocarbon fluid was 69% after 28 days (ECHA) [Kl. score = 1]. The results indicate

that this substance is readily biodegradable even though it did not meet the 10-day window because the criterion does not apply to multi-component substance when assessing their ready biodegradability (ECHA) [Kl. score = 1].

C. Environmental Distribution

C12-C15 aliphatic hydrocarbons (<2% aromatics) and C9-C14 aliphatic hydrocarbons (≤2% aromatics) are UVCB substances. The standard tests to determine the K_{oc} are for single substances and not for UVCB substances. Therefore, a K_{oc} value for C12-C15 aliphatic hydrocarbons (<2% aromatics) was not determined.

The calculate K_{oc} values for linear aliphatic hydrocarbons dodecane (C12) and tetradecane (C14) are 110,000 and 759,000 L/kg, respectively, using SPARC v4.2 program in the Concawe Library of Petrorisk (ECHA). These values suggest that C12-C15 aliphatic hydrocarbons (<2% aromatics) will highly absorb to sediment and soil.

D. Bioaccumulation

C12-C15 aliphatic hydrocarbons (<2% aromatics) and C9-C14 aliphatic hydrocarbons (≤2% aromatics) are UVCB substances. The calculated BCF values for linear aliphatic hydrocarbons undecane (C11), dodecane (C12), and tetradecane (C14) are 337.8, 790.9, and 962.9 L/kg, respectively using the BCFWIN V2.16 model within EPISuite 3.12. The predicted BCFs for hydrocarbons are considered to be generally overly conservative because biotransformation is not quantitatively taken into account. For these linear aliphatic hydrocarbons, the values indicate that they are not expected to bioaccumulate. However, both C12-C15 aliphatic hydrocarbons (<2% aromatics) and C9-C14 aliphatic hydrocarbons (≤2% aromatics) contain branched and cyclic aliphatic hydrocarbons that are expected to have a greater potential to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of C9-C14 aliphatic hydrocarbons (≤2% aromatics) is low by the oral, dermal, and inhalation route. It is, however, an aspiration hazard. C9-C14 aliphatic hydrocarbons (≤2% aromatics) are neither skin nor eye irritants or a dermal sensitizer. Repeated inhalation exposure of rats to a C9-C14 aliphatic (≤2% aromatic) hydrocarbon fluid showed no target organ effects; oral exposures to very high doses of these hydrocarbons showed irritation to the gastrointestinal tract and effects in the liver that likely represent an adaptive response to the metabolism of the hydrocarbons and not a toxic response. C9-C14 aliphatic hydrocarbons (≤2% aromatics) are not genotoxic; nor do they exhibit and evidence of reproductive or developmental toxicity in rats.

B. Acute Toxicity

The oral LD_{50} in rats for C9-C14 aliphatic, ≤2% aromatic hydrocarbon fluids is >5,000 mg/kg (ECHA) [Kl. score = 2.

The 4-hour inhalation LC_{50} in rats for C9-C14 aliphatic, ≤2% aromatic hydrocarbon fluids is > 4,951 mg/m^4 (ECHA) [Kl. scores =1 and 2].

The dermal LD_{50} in rats for C9-C14 aliphatic, ≤2% aromatic hydrocarbon fluids is >5,000 mg/kg (ECHA) [Kl. score = 2].

C. Irritation

C9-C14 aliphatic, ≤2% aromatic hydrocarbon fluids are neither skin nor eye irritants (ECHA) [Kl. scores = 1 and 2].

D. Sensitization

C9-C14 aliphatics, <2% aromatic hydrocarbon fluids were not skin sensitizers when tested in guinea pig maximization tests (ECHA) [Kl. score = 2].

A C9-C14 aliphatic, <2% aromatic hydrocarbon fluid showed no indication of skin sensitization in a human repeated insult patch test (ECHA).

E. Repeated Dose Toxicity

Oral

Male and female rats were dosed by oral gavage with 0, 500, 2,500 or 5,000 mg/kg with a C9-C14 aliphatic, <2% aromatic hydrocarbon fluid 7 days/week for 13 weeks. Additional groups of animals were dosed with 0 or 5,000 mg/kg for 13 weeks, followed by a 4-week recovery period. There were dose-related changes in the hematology and serum chemistry parameters which were consistent with changes seen in the liver. Hepatocellular hypertrophy (liver cell enlargement) were seen in both males and females in all dose groups and were reversible. The liver effects were not considered to be an indication of toxicity but an adaptive response due to the metabolism of the hydrocarbons. There were also mucosal thickening and other signs of irritation to the stomach and anus, which appeared to be the direct result of high-dose intubation of a locally irritating material. All treatment-related effects were reversible within the 4-week recovery period. The NOAEL for systemic effects in this study is considered to be 5,000 mg/kg-day (ECHA) [Kl. score = 1].

Inhalation

Male and female rats were exposed by inhalation to 0, 2,600, 5,200, or 10,400 mg/m^3 of a C9-C14 aliphatic (<2% aromatic) hydrocarbon fluid, 6 hours/day, five days/week for 13 weeks. There was no mortality or effects in either the hematology or the serum chemistry parameters. The male rats at all dose levels had increased liver and kidney weights; male heart weights were also increased at 10,400 mg/m^3; and kidney weights were increased in the 10,400 mg/m^3 group. Kidney effects indicative of alpha-2u-globulin nephropathy was observed at all dose levels. There were no other effects that were considered to be treatment-related. The alpha-2u-nephropathy in the male rats was not considered to be relevant to humans; for the organ weight changes other than the male kidneys, there were no corresponding histopathologic changes. The NOAEL for this study is 10,400 mg/m^3, the highest exposure concentration tested (ECHA) [Kl. score = 1].

Dermal
No studies are available.

F. Genotoxicity

In Vitro Studies

The key *in vitro* genotoxicity studies on C9-C14 aliphatic hydrocarbons (≤2% aromatics) are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on C9-C14 Aliphatic Hydrocarbons (≤2% Aromatics)

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	1	ECHA
Mammalian cell gene mutation (Chinese hamster V 79 cells)	-	-	2	ECHA
Chromosomal aberration (human lymphocytes)	-	-	1	ECHA

*+, positive; -, negative

In Vivo Studies

In two separate studies involving two different C9-C14 aliphatic (<2% aromatic) hydrocarbon fluids, male and female CD-1 mice were given a single oral gavage dose at concentrations of 0, 1,250, 2,500, or 5,000 mg/kg. The frequency of micronucleated polychromatic erythrocytes was not significantly increased in the treated mice compared to that in the controls (ECHA) [Kl. score = 1].

In two separate dominant lethal studies involving two different C9-C14 aliphatic (<2% aromatic) hydrocarbon fluids, male rats were exposed for 6 hours/day for five consecutive days to exposure concentrations of 0, 300, or 900 ppm. There was no evidence of a mutagenic response in the treated rats (ECHA) [Kl. score = 2].

G. Carcinogenicity

No carcinogenicity studies are available on the C9-C14 aliphatic (<2% aromatic) hydrocarbon fluids.

H. Reproductive Toxicity

A C9-C14 aliphatic (<2% aromatic) hydrocarbon fluid was tested in a combined repeated dose toxicity study with a reproductive/developmental toxicity screening test (OECD 422). Male and female SD rats were given oral gavage doses of 0, 25, 150, or 1,000 mg/kg-day. There was no indication of reproductive toxicity at any dose level. The NOAEL for reproductive toxicity is 1,000 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 1].

A C9-C14 aliphatic (<2% aromatic) hydrocarbon fluid was tested in a reproductive/developmental toxicity screening test (OECD 421). Male and female SD rats given oral gavage doses of 0, 100, 300, or 1,000 mg/kg-day. There was no indication of reproductive toxicity or any effects on the endocrine system at any dose level. The NOAEL for reproductive toxicity is 1,000 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 1].

I. Developmental Toxicity

A C9-C14 aliphatic (<2% aromatic) hydrocarbon fluid was tested in a rat pre-natal developmental toxicity study. Pregnant female rats were exposed by inhalation to 0, 300 or 900 ppm for 6 hours/day during gestation days 6 to 15. There was no evidence of maternal or developmental toxicity at either exposure level. The NOAEL for this study is 900 ppm (ECHA) [Kl. score = 1].

Another C9-C14 aliphatic (<2% aromatic) hydrocarbon fluid was tested in a rat pre-natal developmental toxicity study. Pregnant female rats were exposed by inhalation to 0, 300 or 900 ppm for 6 hours/day during gestation days 6 to 15. There was no evidence of maternal or developmental toxicity at either exposure level. The NOAEL for this study is 900 ppm (ECHA) [Kl. score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for C12-C15 aliphatic hydrocarbons (<2% aromatics) 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>
A 13-week oral gavage study was conducted on a C9-C14 aliphatic (<2% aromatic) hydrocarbon fluid in rats. There were no adverse effects at 5,000 mg/kg-day, the highest dose tested. The NOAEL of 5,000 mg/kg-day will be used to derive the oral reference dose and the drinking water guidance value for C12-C15 aliphatic hydrocarbons (<2% aromatics).

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) = 3
UF_D (database uncertainty) = 1

Oral RfD = 5,000/(10 x 10 x 1 x 3 x 1) = 5,000/300 = 17 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 = (17 x 70 x 0.1)/2 = 60 mg/L

B. Cancer

No carcinogenicity studies are available on C9-C14 aliphatic (<2% aromatic) hydrocarbon fluids. Thus, a cancer reference value was not derived for C12-C15 aliphatic hydrocarbons (<2% aromatics).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

C12-C15 aliphatic hydrocarbons (<2% aromatics) do not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

C12-C15 aliphatic hydrocarbons (<2% aromatics) has a low acute toxicity concern to aquatic life.

B. Aquatic Toxicity

Acute Studies

There are no aquatic toxicity data on C12-C15 aliphatic hydrocarbons (<2% aromatics). Table 3 lists the results of acute aquatic toxicity studies conducted on a C11-C14 aliphatic hydrocarbon fluid (<2% aromatics).

Table 3: Acute Aquatic Toxicity Studies on C11-C14 Aliphatic Hydrocarbon Fluid (<2% Aromatics)*

Test Substance	Test Species	Endpoint	Results (mg/L) [WAF]	Kl. score
C11-C14, n-alkanes, isoalkanes, cyclics (<2% aromatics)	*Oncorhynchus mykiss*	96-h LL_{50}	>1,000	1
C11-C14, n-alkanes, isoalkanes, cyclics (<2% aromatics)	*Daphnia magna*	48-h LL_{50}	>1,000	1
C11-C14, n-alkanes, isoalkanes, cyclics (<2% aromatics)	*Pseudokirchnerella subcapitata*	72-h LL_{50} 72-hr NOELR	>1,000	1

*All studies used the water accommodated fractions (WAFs) of the test substance.

Chronic Studies

The value for NOELRs were estimated by QSAR model – Petrotox. This model combines a partitioning model used to calculate the aqueous concentration of hydrocarbon components with the Target Lipid Model used to calculate acute and chronic toxicity of non-polar narcotic chemicals. Petrotox computes toxicity based on the summation of the aqueous-phase concentrations of hydrocarbon block(s) that represent a hydrocarbon substance and membrane-water partition coefficients that describe the partitioning of the hydrocarbons between the water and organisms.

The 28-day NOELR (No-Observed-Effect-Loading-Rate) for hydrocarbons, C12-15, aliphatic hydrocarbons (<2% aromatics) in freshwater fish is estimated to be >1,000 mg/L based on growth (ECHA) [Kl. score = 2].

The 28-day NOELR (No-Observed-Effect-Loading-Rate) for hydrocarbons, C12-15, aliphatic hydrocarbons (<2% aromatics) in freshwater invertebrates is estimated to be >1,000 mg/L based on reproduction (ECHA) [Kl. score = 2].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for C12-C15 aliphatic hydrocarbons (<2% aromatics) follow the methodology:

PNEC water
Using the QSAR model PETRORISK v7.04, the estimated $PNEC_{water}$ value for C11-15-iso- is 0.001 mg/L (CONCAWE) [Kl. score = 2].

PNEC sediment
Using the QSAR model PETRORISK, v7.04 the estimated $PNEC_{sediment}$ value for C11-15-iso- range from 42 to 260 mg/kg soil wet weight (CONCAWE), depending on the composition of the hydrocarbon classes (n- or iso-paraffins and type of cyclic paraffins) (CONCAWE) [Kl. score = 2].

PNEC soil
Using the QSAR model PETRORISK v7.04, the estimated $PNEC_{sediment}$ value for C11-15-iso- is 17 to 100 mg/kg soil wet weight (CONCAWE), depending on the composition of the hydrocarbon classes (n- or iso-paraffins and type of cyclic paraffins) (CONCAWE) [Kl. score = 2].

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).

Hydrocarbons, C11-14, n-alkanes, isoalkanes, cyclics (<2% aromatics) hydrocarbon fluid was readily biodegradable. Thus, C12-C15 aliphatic hydrocarbons (<2% aromatics) is not expected to meet the screening criteria for persistence.

C12-C15 aliphatic hydrocarbons (<2% aromatics) is an UVCB substance that contains constituents that have the potential to bioaccumulate. Thus, C12-C15 aliphatic hydrocarbons (<2% aromatics) meets the screening criteria for bioaccumulation.

Hydrocarbons, C11-14, n-alkanes, isoalkanes, cyclics (<2% aromatics) hydrocarbon fluid did not exhibit acute toxicity to fish, invertebrates, or algae at WAF up to 1,000 mg/L. Thus, C12-C15 aliphatic hydrocarbons (<2% aromatics) is not expected to meet the screening criteria for toxicity.

The overall conclusion is that C12-C15 aliphatic hydrocarbons (<2% aromatics) is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Aspiration Toxicity Category 1

B. Labelling

Danger

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. If irritation occurs, get medical attention.

Skin Contact
Wash the contaminated area of with soap and water. Remove and isolate contaminated clothing. 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.

Ingestion
Do not induce vomiting. Get medical attention immediately.

Notes to Physician
If ingested, material may be aspirated into the lungs and may 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
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
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, vapors, or spray Avoid contact with skin, eye, and clothing.

Environmental Precautions
Prevent from entering sewers, waterways, or low areas.

Steps to be Taken if Material is Released or Spilled
Pick up with non-combustible 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
Avoid breathing vapor or aerosol. Keep away from open flames, hot surfaces and sources of ignition. Provide sufficient ventilation in work area.

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

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Workplace Australia has not established an occupational exposure standard for C12-C15 aliphatic hydrocarbons (<2% aromatics).

Engineering Controls
Use adequate ventilation to control air-borne concentrations.

Personal Protection Equipment
Respiratory Protection:
If workers are exposed to concentrations at a level that is not adequate to protect work health, they must use appropriate, certified respirators. The following type of respirator should be considered for this material: particulate, dust or mists. For high airborne concentrations, use an approved supplied-air respirator, operated in positive pressure mode.

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

C12-C15 aliphatic hydrocarbons (<2% aromatics) 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

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CHLOROUS ACID, SODIUM SALT

This dossier on chlorous acid, sodium salt presents the most critical studies pertinent to the risk assessment of chlorous acid, sodium salt 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 chlorite

CAS RN: [redacted]

Molecular formula: $ClHO_2.Na$

Molecular weight: 90.44

Synonyms: Chlorous acid, sodium salt; sodium chlorite

SMILES: [O-]Cl=O.[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Chlorous Acid, Sodium Salt

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White solid, slightly hydroscopic crystals or flakes. Aqueous solutions are colorless to greenish yellow with a slight chlorine-like odor	2	ECHA
Melting Point	180 – 200°C; decomposes at 200°C	2	ECHA
Density	2.432 g/mL	1	ECHA
Vapor Pressure	1.1×10^{-7} Pa @ 25°C	1	ECHA

Property	Value	Klimisch score	Reference
Partition Coefficient (log K_{ow})	<-2.7	1	ECHA
Water Solubility	Very soluble (572 g/L @ 20°C)	1	ECHA
Oxidizing Properties	25.6% aq. solution – not an oxidizing liquid	1	ECHA

Chlorous acid, sodium salt in its dry form is a strong oxidizer.

Chlorous acid, sodium salt readily dissociates in aqueous solutions to the sodium (Na^+) and chlorite (ClO_2^-) ion. The chlorite (ClO_2^-) ion is in equilibrium with chlorous acid ($HClO_2$) in water. The chemical reaction is as follows:

$ClO_2^- + H^+ \rightleftharpoons HClO_2$

At pH values found in environmental media or physiological fluids, the chlorite ion will be the predominant form (pK_a of chlorous acid is 1.94).

Under acidic conditions, chlorous acid ($HClO_2$) will predominate and will disintegrate to chlorine dioxide (ClO_2). Chlorine dioxide (ClO_2) will degrade further to chlorite (ClO_2^-), and, ultimately, the chloride ion (Cl^-) is formed. The proportion of each oxy-chlorine species depends in part on the pH of the solution.

III. ENVIRONMENTAL FATE PROPERTIES

Chlorous acid, sodium salt readily dissociates in aqueous solutions to the sodium (Na^+) and chlorite (ClO_2^-) ion. The chlorite ion will ultimately degrade to chloride ions. Both sodium and chloride ions are ubiquitous in the environment. Biodegradation is not applicable to sodium chlorite. Neither sodium chlorite nor its dissociated ions are expected to adsorb to soil or sediment, or bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Chlorous acid, sodium salt (sodium chlorite) in solution is moderately-to-highly toxic by the oral route, but has low acute toxicity by the dermal route. It is corrosive the skin and eyes. It is not a skin sensitizer. The critical effect seen in rodents given repeated oral administration of sodium chlorite is hemolytic anemia. Sodium chlorite was not

mutagenic in a bacterial reverse mutation (Ames) test; however, chlorine dioxide (which breaks down to chlorite) was mutagenic in the mouse lymphoma assay in the absence and presence of metabolic activation. *In vivo* genotoxicity studies on sodium chlorite were generally negative. No reproductive toxicity was seen in male or female rats given sodium chlorite in drinking water. There was, however, an effect on post-natal development in pups from the first generation; the effect was not seen in the pups from the second generation. There was no developmental toxicity in pregnant female rabbits given sodium chlorite in drinking water.

B. Acute Toxicity

The oral LD_{50} in rats is 284 mg/kg (ECHA) [Kl. score = 1]. The oral LD_{50} in rats of a 31% aqueous solution of chlorous acid, sodium salt is 390 mg/kg (ECHA) [Kl. score = 2).

There are no acute inhalation toxicity studies.

The dermal LD_{50} in rabbits is 134 mg/kg (ECHA) [Kl. score = 1]. The dermal LD_{50} in rabbits of a 31% aqueous solution of chlorous acid, sodium salt is >2,000 mg/kg (ECHA) [Kl. score = 2).

C. Irritation

Application of 0.5 mL of undiluted chlorous acid, sodium salt to the skin of rabbits for 4 hours under occlusive conditions was corrosive (ECHA) [Kl. score = 2]. Application of 0.5 mL of a 34.5% solution of chlorous acid, sodium salt to the skin of rabbits for four hours under semi-occlusive conditions was essentially non-irritating (ECHA) [Kl. score = 1].

Instillation of 0.1 mL of a 31% aqueous solution of chlorous acid, sodium salt to the eyes of rabbits was severely irritating (ECHA) [Kl. score = 2].

D. Sensitization

Chlorous acid, sodium salt was not considered to be a skin sensitizer when tested in a mouse local lymph node assay (ECHA). [Kl. score = 1]

E. Repeated Dose Toxicity

<u>Oral</u>
Male and female Crj:CD(SD) rats were dosed by oral gavage with 0, 10, 25, or 80 mg/kg chlorous acid, sodium salt for 13 weeks. Five animals died during the study: one in the 25 mg/kg group and five in the 80 mg/kg group subsequent to blood sampling. The deaths in the 80 mg/kg group were likely treatment-related; the animals were anemic and blood sampling may have exacerbated this problem, contributing to their death. Clinical signs were noted in the 25 and 80 mg/kg animals, the most notable being

salivation. Body weights and feed consumption were similar across all groups. Hematological effects were noted in the 80 mg/kg animals. The group mean erythrocyte count was significantly lower (both sexes). In males, hematocrit and hemoglobin levels were significantly lower, and methemoglobin levels and neutrophils counts were significantly higher than controls. The reticulocyte count was increased, but was not statistically significant. Two of the 80 mg/kg rats that prematurely died had marked changes in these hematological parameters. Morphological changes were also seen in the blood smears of three 80 mg/kg females: these were polychromasia, poikilocytosis, macrocytosis, and neutrophilia. Lymphocyte counts were significantly lower than controls in the 80 mg/kg males, and was likely due to the increased neutrophil count. Where the primary red blood cell parameters (mean erythrocyte count, hemoglobin, and hematocrit) were affected, there were also associated changes in mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration. In the 25 mg/kg animals (both sexes) and the 10 mg/kg males, statistical trends highlighted a dose-dependent downward trend for erythrocyte counts. Statistical significance was not confirmed by direct comparison with the control group, and group mean values were within background range. Urine volume was unusually high in four 80 mg/kg females, and urinary specific gravity was reduced. There were no histopathologic changes seen in the kidneys of these animals. Absolute and relative spleen weights were increased in the 80 mg/kg males. Absolute spleen weights were increased in the 10 and 80 mg/kg females; relative spleen weights were increased in the 25 and 80 mg/kg females. Relative adrenal weights were increased in the 80 mg/kg males. Absolute adrenal weights were increased in the 80 mg/kg females; relative adrenal weights were increased in the 25 and 80 mg/kg females. Histopathologic changes indicative of chronic irritation were seen in the stomachs of many of the 80 mg/kg animals and a few of the 25 mg/kg males. Extramedullary hematopoiesis was seen in the spleen of a few 80 mg/kg animals and one animal each in the lower two dose groups. The NOAEL for this study is 10 mg/kg-day (ECHA). [Kl. score = 1]

Male C/J and C57L/L mice were given in their drinking water 0, 0.75, 7.5, or 75 mg/L chlorous acid, sodium salt (0, 0.19, 1.9, or 19 mg/kg-day chlorite ion) for 30 days. There were slight signs of oxidative stress of red blood cells at the high-dose. Glucose-6-phosphate dehydrogenase (G6PD) activity and osmotic fragility were slightly increased. Erythrocytes with irregular shapes were also observed. It was suggested that the primary effect of chlorous acid, sodium salt was a disruption of the erythrocyte cell membrane. However, the glutathione level in the erythrocyte was not affected and there were no associated signs of hemolytic anemia, suggesting that the slight increase in G6PD activity acted as a sufficient compensatory mechanism to limit the oxidative stress. The NOAEL for this study is considered to be 7.5 mg/L chlorous acid, sodium salt or 1.9 mg/kg-day chlorite (Moore and Calabrese, 1980). [Kl. score = 2]

Male C57L/J mice were given chlorous acid, sodium salt in their drinking water for 30, 90, or 180 days. The doses were 0, 3, 15, or 75 mg/L expressed as chlorite ion. The average daily doses were estimated to be: 0, 0.74, 3.57, and 17.23 mg/kg-day for the

30-day period; 0, 0.64, 3.15, and 16.2 mg/kg-day for the 90-day period; and 0, 0.69, 3.71, and 17.11 mg/kg-day for the 180-day period. There were no significant changes in body weight gain, absolute or relative kidney weights, water consumption, or histopathologic changes in the kidney. The NOAELs for this study are: 17.23, 16.20, and 17.11 mg/kg-day for the 30-, 90-, and 180-day exposure periods, respectively (Connor et al., 1985). [Kl. score = 2]

Inhalation
No studies are available.

Dermal
No adequate studies are available.

F. Genotoxicity

In Vitro Studies

Table 2 lists the results of the *in vitro* genotoxicity studies on chlorous acid, sodium salt.

Table 2: *In vitro* Genotoxicity Studies on Chlorous Acid, Sodium Salt

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* TA97, TA102 strains)	-	-	4	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	+**	+**	2	ECHA

*+, positive; -, negative
**Test material: chlorine dioxide (chlorite is a breakdown product)

In Vivo Studies

Male and female CD-1 mice were given by oral gavage a single dose of 0, 0.2, 0.5, or 1 mg/day (0, 10, 25, or 59 mg/kg-day) chlorous acid, sodium salt. Chromosomal aberrations were not increased in bone marrow cells of treated mice compared to those in the controls (Meier et al., 1985; ECHA).

Male and female CD-1 mice were given by oral gavage 0, 0.2, 0.5, or 1 mg/day (0, 10, 25, or 59 mg/kg-day) chlorous acid, sodium salt for five consecutive days. There were no significant differences between treated and control mice in the frequency of micronuclei or chromosomal aberrations in bone marrow cells (Meier et al., 1985; ECHA).

Male ddY mice were given a single intraperitoneal injection of 0, 7.5, 15, 30, or 60 mg/kg chlorous acid, sodium salt. Micronucleated polychromatic erythrocytes were statistically significantly increased at all dose levels. The increase was dose-dependent, but the frequency of micronucleated polychromatic erythrocytes decreased at the highest dose level (Hiyashi et al., 1988; ECHA). [Kl. score = 2]

Male ddY mice were given a single intraperitoneal injection of 0 or 15 mg/kg chlorous acid, sodium salt for four consecutive days. The frequency of micronucleated polychromatic erythrocytes were similar between treated and control mice (Hiyashi et al., 1988; ECHA). [Kl. score = 2]

Male ddY mice were given a single oral dose of 0, 37.5, 75, 150, or 300 mg/kg chlorous acid, sodium salt. There was no significant increases in the frequency of micronucleated polychromatic erythrocytes in the bone marrow of the treated mice compared to the controls (Hiyashi et al., 1988; ECHA). [Kl. score = 2]

G. Carcinogenicity

No studies are available.

H. Reproductive Toxicity

A two-generation reproductive toxicity study has been conducted on chlorous acid, sodium salt. Male and female SD rats were given in their drinking water 0, 35, 70, or 300 ppm chlorous acid, sodium salt. The average daily intakes are: 0, 4, 8, and 30 mg/kg-day for males ; and 0, 5, 10, and 39 mg/kg-day for females. The average daily intakes for chlorite are: 0, 2.9, 6, and 22 mg/kg-day for males; and 0, 4, 7.5, and 29 mg/kg-day for females. During lactation, the drinking water levels were reduced 50% to 17.5, 35, and 150 ppm chlorous acid, sodium salt. Water consumption was reduced in all treated groups. Body weights and feed consumption were reduced in the 70 and 300 ppm groups. There was no evidence of reproductive toxicity at any dose level. In the 300 ppm group, pup weights were reduced at birth and on PND 11 (-14%) compared to the controls. There was a decrease in the percent of the 300 ppm F_{2a} pups with eyes open on PND15 compared to the control group; this effects was not observed for the F_1 or F_{2b} pups. There was a small, but statistically significant, increase in the average time to preputial separation for the 70 and 300 ppm F_1 pups and in the vaginal opening for the 300 ppm F_1 pups. Similar changes were not observed for the F_2-generation pups. All of the high-dose animals exhibited mild methemoglobinemia. Thyroid levels were unaffected by treatment. There was a small decrease in the amplitude of auditory startle responses in the 70 and 300 ppm pups on PND 25; the toxicological significance of this effect is questionable. The NOAEL for reproductive toxicity is 300 ppm chlorous acid, sodium salt, the highest dose tested. The NOAEL for developmental toxicity is 35 ppm (4 and 5 mg/kg-day chlorous acid, sodium salt for males and females, respectively)

based on the increase in the average time to preputial separation in the ≥70 ppm F_1 pups. The NOAELs for hematological effects is 70 ppm (8 and 10 mg/kg-day chlorous acid, sodium salt for males and female, respectively). The NOAEL for neurotoxicity is 300 ppm (30 and 39 mg/kg-day chlorous acid, sodium salt for males and females, respectively) (ECHA) [Kl. = 2].

I. Developmental Toxicity

Pregnant New Zealand White rabbits were given 0, 200, 600, or 1,200 mg/L (0, 12.2, 36.6, or 58.8 mg/kg-day) chlorous acid, sodium salt in their drinking water during GD 7 to PND 19. The animals in the mid- and high-dose groups showed reduced water consumption, along with reduced feed consumption, production of fecal pellets, and body weight gain. There was no evidence of embryotoxicity or teratogenicity at any dose level. The NOAELs for maternal and developmental toxicity are 12.2 and 58.8 mg/kg-day, respectively (ECHA). [Kl. score = 1]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for chlorous acid, sodium salt 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 lowest NOAEL values from key toxicity studies on chlorous acid, sodium salt are listed below in Table 3.

Table 3: Lowest NOAEL Values from Key Toxicity Studies on Chlorous Acid, Sodium Salt by the Oral Route

Species/sex	Study Duration	mg/kg-day	Endpoint	Reference
Male/female rats	13 weeks	10	Clinical signs, stomach irritation	ECHA
Male pups	2-generation reproductive	4	- average time to preputial separation	ECHA
Male parental rats	2-generation reproductive	8	Hematological effects	ECHA

Species/sex	Study Duration	mg/kg-day	Endpoint	Reference
Female pregnant rabbits	Developmental (GD 6 to PND 17)	12.2	¯ Body weight gain, feed consumption	ECHA

The lowest NOAEL is 4 mg/kg-day based on increased average time to preputial separation in F_2 male pups from a two-generation reproductive toxicity study (ECHA). The NOAEL of 4 mg/kg-day will be used for determining the oral Reference dose (RfD) and the drinking water guidance value.

Derivation of an Oral Reference Dose

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 = 4/(10 x 10 x 1 x 10 x 1) = 4/1000 = 0.004 mg/kg-day

Derivation of a 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 = (0.004 x 70 x 0.1)/2 = 0.014 mg/L

Australian Drinking Water Guidelines

The Australian drinking water guideline value for chlorite is 0.3 mg/L (ADWG, 2011).

The Australian drinking water guideline value for sodium is 180 mg/L based on aesthetics (ADWG, 2011).

B. Cancer

No carcinogenicity studies were found on chlorous acid, sodium salt. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Chlorous acid, sodium salt in solution does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing Potential

[It should be noted that chlorous acid, sodium salt as a solid is a strong oxidizer.]

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Chlorous acid, sodium salt has a high acute toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 4 lists the results of acute aquatic toxicity studies conducted on chlorous acid, sodium salt.

Table 4: Acute Aquatic Toxicity Studies on Chlorous Acid, Sodium Salt

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-h LC_{50}	149	2	ECHA
Daphnia magna	48-h EC_{50}	<1	2	ECHA

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Peudokirchneriella subcapitata	96-h EC_{50}	1	1	ECHA

Chronic Studies

No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for chlorous acid, sodium salt 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 (149 mg/L), invertebrates (<1 mg/L), and plants (1 mg/L). 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 EC_{50} value of 1 mg/L for algae. The $PNEC_{aquatic}$ is 0.001 mg/L.

PNEC sediment

No reliable experimental toxicity data on sediment organisms are available. Chlorous acid, sodium salt 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 chlorous acid, sodium salt. Therefore, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. Based on its properties, no adsorption of chlorous acid, sodium salt 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 chlorous acid, sodium salt is dominated by its water solubility. Sorption of chlorous acid, sodium salt should probably be regarded as a reversible situation, *i.e.*, the substance is not tightly nor permanently bound. K_{oc} and K_{ow} parameters do not readily apply to inorganics, such as chlorous acid, sodium salt. Therefore, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, chlorous acid, sodium salt 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).

Chlorous acid, sodium salt is an inorganic salt that dissociates completely in water to sodium (Na^+) and chlorite (ClO_2^-) ions. Chlorite will ultimately degrade to chloride (Cl^-) ions. Biodegradation is not applicable to these inorganic ions. For the purposes of this PBT assessment, the persistent criteria is not considered applicable to this inorganic salt.

As an inorganic compound, neither chlorous acid, sodium salt nor its dissociated ions are expected to accumulate. Thus, chlorous acid, sodium salt does not meet the criteria for bioaccumulation.

There are no chronic toxicity studies on chlorous acid, sodium salt. The acute $E(L)C_{50}$ values for chlorous acid, sodium salt are $\leq$1 mg/L in invertebrates and algae. Thus, chlorous acid, sodium salt meets the criteria for toxicity.

The overall conclusion is that chlorous acid, sodium salt is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification (Chlorous acid, sodium salt solutions)

Acute Toxicity Category 3 [Oral]
Skin Corrosive Category 1B
STOT RE Category 2 [Target organ: blood]
Aquatic Acute Category 1
Aquatic Chronic Category 3
AUH031: Contact with acids liberates toxic gas (non-GHS hazard statement)

B. Labelling

Danger

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
Remove and isolate contaminated clothing. Rinse skin immediately with water for at least 15 min. 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 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
Rinse mouth with water and then drink plenty of water. Get medical attention. Do not induce vomiting. Never give anything by mouth to an unconscious person.

Notes to Physician
Chlorine dioxide vapors are emitted when this product contacts acids or chlorine. If these vapors are inhaled, monitor patient closely for delayed development of pulmonary edema which may occur up to 48-72 hours post-inhalation Following ingestion, neutralization and use of activated charcoal is not indicated (OxyChem, 2015).

B. Fire Fighting Information

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

Specific Exposure Hazards
Dried material can ignite upon contact with combustibles. This product may represent an explosion hazard if it contacts acids, chlorine, or organic materials. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: chlorine and sodium oxides.

Special Protective Equipment for Firefighters
Structural firefighter's 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 fire area if it can be done without risk.

C. Accidental Release Measures

Personal Precautions
Ventilate enclosed areas. Do not walk through spilled material. Do not touch damaged containers or spilled material unless wearing appropriate protective clothing. Wear appropriate personal protective equipment, avoid direct contact. Do not breath mist, vapors, 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 Spilled
As an immediate precautionary measure, isolate spill or leak area for at least 50 meters in all directions. Keep unauthorized personnel away. Remove all sources of ignition. Absorb or cover with dry earth, sand, or other non-combustible material and transfer to containers. Dike to collect large liquid spills. Every attempt should be made to avoid mixing spilled material with other chemicals or debris when cleaning up. Dried material can ignite upon contact with combustibles. Dispose immediately.

D. Storage And Handling

General Handling
Do not get in eyes, on skin, or on clothing. Do not ingest or taste. Wear appropriate personal protective equipment, avoid direct contact. Do not breath mist, vapours, or spray. Use caution when combining with water. DO NOT add water to corrosive liquid, ALWAYS add corrosive liquid to water while stirring to prevent release of heat, steam, and fumes. This product becomes a fire hazard if allowed to dry. Remove and wash contaminated clothing to avoid fire.

Storage
Keep contain tightly closed. Store in a cool, dry, well-ventilated place. Keep from direct sunlight. Avoid exposure to sunlight or ultraviolet light. Keep separated from acids, reducing agents, combustible material, oxidizing agents, hypochlorite, organic solvents and compounds, garbage, dirt, organic materials, household products, chemicals, soap products, paint products, vinegar, oils, pine oil, dirty rags, sulfur-containing rubber, or any other foreign matter.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Workplace Australia has not established an occupational exposure standard for chlorous acid, sodium salt.

Engineering Controls
Good general ventilation should be used. Localized ventilation should be used where vapours, mist, or aerosols may be generated.

Personal Protection Equipment
Respiratory Protection:
Wear an approved acid gas respirator with dust/mist pre-filters if any exposure to dust of mist is possible.

Hand Protection:
Wear appropriate chemical-resistant gloves.

Skin Protection:
Wear protective clothing to minimize 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

Sodium chlorite (dry)
UN1496 (SODIUM CHLORITE)

Class: 5.1
Packing Group: II

Environmentally Hazardous Substance

Sodium chlorite (liquid)
UN1908 (CHLORITE SOLUTION)
Class: 8
Packing Group: II
Contains Sodium chlorite

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

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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

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CINNAMALDEHYDE

This dossier on cinnamaldehyde presents the most critical studies pertinent to the risk assessment of cinnamaldehyde in its use in coal seam or shale 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 3-phenylacryladehyde

CAS RN: [redacted]

Molecular formula: C_9H_8O

Molecular weight: 132.16 g/mol

Synonyms: Cinnamaldehyde; (2E)-3-phenylprop-2-enal; 3-phenylacrylaldehyde; cinnamal; (E)-cinnamaldehyde; 3-phenylpropenal; cinnamic aldehyde; phenylacrolein; cinnamylaldehyde; 3-phenyl-2-propenal; trans-cinnamaldehyde; (E)-3-phenylpropenal; (E)-3-phenyl-2-propenal; 3-phenylacrolein; 3-phenyl-2-propenaldehyde; 3-phenyl-2-propen-1-al; acrolein, 3-phenyl-; 2-propenal, 3-phenyl-; 2-propenal, 3-phenyl-, (2E)-

SMILES: C1=CC=C(C=C1)C=CC=O

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Cinnamaldehyde

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Light colorless clear liquid	1	ECHA
Melting point	-18°C @ 96.990 kPa	1	ECHA
Boiling point	>250°C @ 96.990 kPa	1	ECHA
Density	1,041 kg/m^3 @ 20°C and 96.75 kPa	1	ECHA
Vapor pressure	3.853 Pa @ 25°C	2	ECHA
Partition coefficient (log K_{ow})	2.107±0.0017 @ 25°C	1	ECHA
Water solubility	2.865 g/L @ 25°C	1	ECHA
Flash point	105°C @ 96.83 kPa	1	ECHA
Auto flammability	Not auto-flammable	1	ECHA
Viscosity	22.12 mPa s @ 20°C 18 mPa s @ 40°C	1	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Cinnamaldehyde is expected to biodegrade and not expected to bioaccumulate to any significant extent. It has a low potential to adsorb to soil or sediment.

B. Biodegradation

Cinnamaldehyde is readily biodegradable. In an OECD 301B test, degradation of cinnamaldehyde was 89% after 7 days, 94% after 14 days, and 100% after 28 days, indicating ready biodegradation (ECHA) [Kl. score = 2]. In an OECD 301D test, biodegradation was 24.98% after 5 days. The BOD_5 value was 0.635 mg O_2/mg (ECHA) [Kl. score = 1].

If a chemical is found to be inherently biodegradable or 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 cinnamaldehyde. Using KOCWIN in EPISUITE™ (EPA, 2018), the estimated K_{oc} value from log K_{ow} of 2.107 is 55.82 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 36.82 L/kg. Based on this estimated value, cinnamaldehyde is expected to have very high mobility in soil. If released to water, based on the K_{oc} value and its high water solubility, it is also not expected to adsorb to suspended solids and sediment.

D. Bioaccumulation

A bioaccumulation study in fish was conducted to estimate the bioconcentration factor (BCF) value for cinnamaldehyde. The BCF value was calculated using a log K_{ow} of 1.9 and a regression derived equation. The estimated BCF value for cinnamaldehyde was determined to be 8 which indicates that this chemical is non-bio accumulative in aquatic organisms (ECHA) [KI. score =2].

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Cinnamaldehyde is of relatively low acute toxicity by the oral, dermal, and inhalation routes of exposure. It is an irritant to skin and eyes and is considered a sensitizer per the guinea pig maximization test. Oral repeat dose studies suggest that cinnamaldehyde has relatively low toxicity. There are no studies on the inhalation routes of exposure. Dermal repeat studies suggest that cinnamaldehyde has low toxicity. Cinnamaldehyde was not mutagenic in *in vitro* and *in vivo* genotoxicity tests, and it is not carcinogenic. Cinnamaldehyde is a not a reproductive or developmental toxicant.

B. Metabolism

Male Fischer 344 rats were given doses of 5, 50, and 500 mg/kg bw/day of cinnamaldehyde by oral gavage for seven days. Cinnamaldehyde was rapidly absorbed within the body and distributed to the gastrointestinal tract, the kidneys, the liver, and a small amount distributed to fat. Benzoic acid is the major metabolic of cinnamaldehyde. After 24 hours more than 80% of cinnamaldehyde is excreted in the urine and a small amount (<7%) is excreted in the faeces (ECHA) [KI. score =2].

The metabolism of 2 and 250 mg/kg bw/day of cinnamaldehyde was evaluated using male and female CD-1 mice exposed via the intraperitoneal route of exposure for 72 hours. About 94% of the administered dose was recovered in the urine after 72 hours. Less than two percent of the administered dose was remained in the mice after 72 hours. The major urinary metabolites were hippuric acid, 3-hydroxy-3-phenylpropionic acid, benzoic acid, and benzyl glucuronide (ECHA) [KI. score = 2].

C. Acute Toxicity

The 14-day acute oral LD_{50} in male and female Osborne-Mendel rats administered 2220 mg/kg bw/day of cinnamaldehyde via oral gavage was determined to be 2,220 mg/kg bw/day (ECHA) [Kl. Score = 2].

An acute oral toxicity study was conducted using male and female guinea pigs given cinnamaldehyde by oral gavage. The LD_{50} was determined to be 3400 mg/kg bw/day (ECHA) [KI. score =2].

Inhalation

There are no acute inhalation studies are available for cinnamaldehyde. An acute inhalation LC_{50} was predicted for cinnamaldehyde using the QSAR toolbox. The 4-hour LC50 in male and female Wistar rats exposed to cinnamaldehyde was predicted to be 68.889 ppm (ECHA) [KI. score =2].

Dermal

An OECD Guideline (Acute Dermal Toxicity) study was conducted using male and female albino Wistar rats exposed to cinnamaldehyde using occlusive dressing for 14 days. The dermal LD_{50} was determined to be is >2,000 mg/kg bw/day (ECHA) [Kl. Score = 2].

D. Irritation

Skin

Application of 0.1 mL of cinnamaldehyde to the skin of New Zealand white rabbits for 4 hours under semi-occlusive conditions was considered slightly-to-moderate irritating. The primary dermal irritation index (PDII) for cinnamaldehyde after 24, 48, and 72 hours was determined to be 3.25. This data indicates that cinnamaldehyde was moderately severely irritating to the skin of New Zealand white rabbits(ECHA) [Kl. score = 2].

An OECD Guideline 439 (In Vitro Skin Irritation: Reconstructed Human Epidermis Test method) study was conducted using non-transformed keratinocytes in a human skin model. The man tissue viability for cinnamaldehyde, when compared to the control, was determined to be 4.1%. This data indicates that cinnamaldehyde is considered to be irritating to human skin (ECHA) [KI. score =1].

Cinnamaldehyde, at doses of 0.02, 0.1%, and 0.8% in ethanol, was applied to the skin (upper arm) of healthy humans over a six-week period Cinnamaldehyde was determined to be severely irritating to the skin based on results from a human patch test (ECHA)[KI. score =2].

Eye

Instillation of 0.1 mL cinnamaldehyde to the eyes of New Zealand rabbits for 24 hours was considering irritating. The mean of the 24-, 48-, and 72-hours scores were: 1.00 for corneal opacity,

0.00 for iridial lesions, 2.00 for conjunctival redness, and 1.22 for chemosis. All effects were resolved by Day 14 of the observation period (ECHA) [Kl. score = 1].

The ocular irritation potential of cinnamaldehyde was determined using an OECD 492 guideline (Reconstructed Human Cornea-like Epithelium RhCE test method for identifying chemicals not requiring classification and labelling for eye irritation or serious eye damage) study. The mean tissue viability of cinnamaldehyde was determined to be 4.1 %. Cinnamaldehyde was determined to be irritating to the human eye (ECHA) [KI. score =1].

Instillation of 8% of cinnamaldehyde to the human eye was determined to be irritating (ECHA)[KI. score =2].

E. Sensitisation

Cinnamaldehyde was considered a skin sensitizer when tested in a guinea pig maximization test (ECHA) [Kl. score = 2].

F. Repeated Dose Toxicity

Oral

Male and female F344 rats were given in their diet 0, 4,100, 8,200, 16,500, or 33,000 ppm cinnamaldehyde (microcapsulated) for three months in a study conducted by the National Toxicology Program. The average daily intake was 0, 275, 625, 1,300, and 4,000 mg/kg-day for males, and 0, 300, 570, 1,090, and 3,100 mg/kg bw/day-day for females. There was no mortality during the study. Mean body weights were reduced in the ≥16,500 ppm animals as a result of decreased feed consumption from unpalatability of the dosed feed. There was a non-significant increase in serum bile acid concentration at all dose levels suggesting an effect on the liver, but there were no corresponding histopathologic effects. An increase in lesions of the forestomach mucosa was seen in the ≥8,200 ppm animals and included squamous epithelial hyperplasia. There was also chronic active inflammation in the 33,000 ppm males and the ≥16,500 ppm females. The NOAEL was considered to be 4,100 ppm, which corresponds to 275 and 300 mg/kg bw/day in males and females, respectively (Hooth et al., 2004; as cited in ECHA) [Kl. score = 1].

Male and female rats were fed in their diet 0, 1,000, 2,100, or 4,100 ppm cinnamaldehyde for 12 weeks. The average daily intake was 0, 50, 100, or 200 mg/kg bw/day-day. There were no significantly differences between treated and control animals in urine sugar and albumin, blood haemoglobin levels, growth, food intake, or other physiological criteria. The NOAEL for this study is 4,100 ppm for males and females, which corresponds to 200 mg/kg bw/day (ECHA) [Kl. score = 2].

Male and female F344 rats were given in their diet 0, 1,000, 2,100, or 4,100 ppm cinnamaldehyde (microcapsulated) for two years in a study conducted by the National Toxicology Program. The average daily intake was 0, 50, 100, or 200 mg/kg bw/day. The survival of the 4,100 ppm males was greater than the controls. The mean body weights of the 4,100 ppm animals were generally less he controls throughout the study. Feed consumption of the ≥2,100 ppm males and the 4,100 ppm females was less than the controls at the beginning and end of the study. There were no non-neoplastic lesions that were considered to be treatment related. The NOAEL for this study is 4,100 ppm for males and females, which corresponds to 200 mg/kg bw/day (Hooth et al., 2004; as cited in ECHA) [Kl. score = 1].

Male and female B6C3F$_1$ mice were given in their diet 0, 1,000, 2,100, or 4,100 ppm cinnamaldehyde (microcapsulated) for two years in a study conducted by the National Toxicology Program. The average daily intake was 0, 125, 270, or 540 (males) and 570 (females) mg/kg bw/day. Mean body weights of the ≥2,100 ppm animals were generally less than the controls throughout the study. There were no non-neoplastic lesions that were considered to be treatment related. Incidences of minimal olfactory epithelial pigmentation was significantly increased in the 4,100 ppm males and the ≥2,100 ppm females. The NOAEL for this study is 1,000 ppm in males and females, which corresponds to 125 mg/kg bw/day, based on reduced body weights at 270 mg/kg bw/day (Hooth et al., 2004; as cited in ECHA) [Kl. score = 1].

An oral subacute toxicity was conducted using male and female B6C3F1 mice exposed 0,656, 1310,2620, 5250, or 10,500 mg/kg bw/day cinnamaldehyde for 14 days (2 weeks: 5 days/week for a total of 12 doses). There were no significant differences in body weight, liver weight, spleen weight, and kidney weight. There were no statistical differences in organ: body weight ratios between surviving treated mice and the control mice. All of the mice in the two highest dose groups, as well as the all the female mice and three male mice from the 2620 mg/kg bw/day dose group, died withing the first two days of dosing. There were no clinical signs or gross lesions observed in the surviving mice or the dead mice. Mild forestomach hyperplasia was observed in both sexes of mice exposed to cinnamaldehyde. Minimal kidney nephropathy was observed in the mice exposed to dose of more than 1310 mg/kg bw/day. A NOAEL of 656 mg/kg bw/day was established for this study. A LOAEL of 1,310 mg/kg bw/day was established in this study based on body weight, organ weight, and histopathological examinations (ECHA) [KI. score = 2].

Inhalation

There are no studies are available. As shown in Table 1, cinnamaldehyde has a low vapor pressure which suggests that the generation of inhalable vapours is low. Under normal conditions, human exposure to cinnamaldehyde by the inhalation route of exposure is highly unlikely.

Dermal

A dermal sub chronic dermal toxicity study was conducted using female Balb/c mice exposed to 25µl 25 percent (v/v) solution of cinnamaldehyde for 4-5 days. The NOAEL was determined to be 25µl (ECHA) [KI. score =2].

A dermal sub chronic dermal toxicity study was conducted using mice exposed to 750 mg/kg bw/day 3D (intermittent) of cinnamaldehyde. A LOAEL value of 750 mg/kg/3D was established for mice exposed to cinnamaldehyde for three days (ECHA) [KI. score =2].

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on cinnamaldehyde are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on cinnamaldehyde

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 Bacterial Reverse Mutation Assay (S. typhimurium TA 98, TA100, TA 102, TA 1535, TA1537)	-	-	1	ECHA

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
OECD Guideline 471 (*In Vitro* Mammalian Chromosome Aberration Test)	-	-	1	ECHA
OECD Guideline 476 (*In Vitro* Mammalian Cell Gene Mutation Test using the Hprt and xprt genes)	-	-	1	ECHA
Bacterial reverse mutation assay (Salmonella typhimurium TA97, TA98, TA100, TA1335, and TA1537)	-	-	2	ECHA
In vitro mammalian cell micronucleus test	-	-	2	ECHA

*+, positive; -, negative

In Vivo Studies

Male and female B6C3F$_1$ mice were administered in their feed 0, 4,100, 8,200, 16,500, or 33,000 ppm cinnamaldehyde (microcapsulated) for three months in a study conducted by the National Toxicology Program. The average daily intake was 650, 1,320, 2,550, and 5,475 mg/kg bw/day for males, and 0, 625, 1,380, 2,680, and 5,200 mg/kg bw/day for females. There were no increases in the frequency of micronucleated normochromatic erythrocytes in the peripheral blood in the treated animals compared to the controls (ECHA) [Kl. score = 2].

A mouse bone marrow micronucleus test was used to evaluate the genotoxic potential of cinnamaldehyde in ddY mice. Male mice were given oral doses of 0, 250, 313, and 500 mg/kg of cinnamaldehyde for 24 hours. Cinnamaldehyde did not induce any gene mutations in male ddY mice (ECHA) [Kl. score = 2].

H. Carcinogenicity

Male and female F344 rats were administered in their diet 0, 1,000, 2,100, or 4,100 ppm cinnamaldehyde (microcapsulated) for two years in a study conducted by the National Toxicology Program. The average daily intake was 0, 50, 100, or 200 mg/kg bw/day-day. The tumour incidences were similar between the treated and control animals. A NOAEL of 200 mg/kg bw/day (4100 ppm) was reported for this study (Hooth et al., 2004; as cited in ECHA) [Kl. score = 2].

Male and female B6C3F$_1$ mice were administered in their diet 0, 1,000, 2,100, or 4,100 ppm cinnamaldehyde (microcapsulated) for two years in a study by the National Toxicology Program. The average daily intake was 0, 125, 270, or 540 (males) and 570 (females) mg/kg bw/day-day. The tumour incidences were similar between the treated and control animals. The NOAEL was considered to be 4100 ppm (540 mg/kg bw/day for males and 570 mg/kg bw/day females (Hooth et al., 2004; as cited in ECHA) [Kl. score = 1].

An OECD Guideline 451 (Carcinogenicity study) was conducted in male and female Fischer 344 rats exposed to 0, 235, 470, 940, 1880, 3750 mg/kg bw/day of cinnamaldehyde by oral gavage for 16 days. There were no effects observed at the lowest dose level while all the animals in the two highest dose groups died within the first seven days of dosing. There was minimal to moderate forestomach hyperplasia observed in the males who received a dose of ≥470 mg/kg bw/day. A NOAEL of 235 mg/kg bw/day was reported in this study based on no occurrence of hyperplastic lesions or forestomach hyperplasia. There was clear evidence of distended gastrointestinal tracts in

animals who were given doses of 1880 or 3750 mg/kg bw/day as well as slightly decreased body weights in females of the 940 mg/kg bw/day dose group. The target organ toxicity value was reported to be 470 mg/kg bw/day (ECHA) [KI. score = 2].

I. Reproductive Toxicity

There are no adequate studies are available.

J. Developmental Toxicity

Pregnant female CD-1 mice were dosed by oral gavage with 0 or 1,200 mg/kg bw/day cinnamaldehyde on gestational days 6 to 13. The dams were allowed to deliver, and the pups were weaned up to postnatal day 3. There was no effect on maternal survival or body weight development and all 34 litters were viable. The number of liveborn per litter, the survival and birthweight of pups and their weight gain was not affected by treatment. The LOAEL for maternal and developmental toxicity is 1,200 mg/kg-day (ECHA) [Kl. score = 2].

An OECD Guideline 414 (Prenatal Developmental Toxicity) study was conducted in Wistar rats exposed to 0, 125, 250, 500 mg/kg bw/day of cinnamaldehyde by oral gavage from gestation day five to gestation day 19. The NOAEL for maternal systemic toxicity was reported to be 250 mg/kg bw/day. This effect level was based on mortality, clinical signs of toxicity, statistically/biologically significant decreased in body weight on gestation day 17 and gestation day 20. There were significant decreased in food intake on gestation day 8 and 11 and several gross/histopathology findings. The NOAEL for developmental toxicity was reported to be 250 mg/kg bw/day based on decreased fetal body weights observed in the 500 mg/kg bw/day (ECHA) [KI. score =1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for cinnamaldehyde 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>

A two-year oral repeat dose study was conducted by the national toxicology program in male and female F344 rats. The lowest NOAEL from this study was reported to be 4,100 ppm which corresponds to a dose level 200 mg/kg bw/day.
The NOAEL of 200 mg/kg bw/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 = 200/ (10 x 10 x 1 x 1 x 1) = 200/100 = 2 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, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (2x 70 x 0.1)/2 = 7 mg/L

B. Cancer

Cinnamaldehyde was not carcinogenic to rats or mice when given in the diet for two years. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Cinnamaldehyde does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Cinnamaldehyde has low chronic toxicity potential to aquatic organisms. Since cinnamaldehyde is readily biodegradable in water, it was reported to be non-toxic to aquatic fish, invertebrates, and algae at environmentally relevant concentrations.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies on cinnamaldehyde.

Table 2: Acute Aquatic Toxicity Studies on Cinnamaldehyde

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Danio rerio (Brachydanio rerio)	96-hr LC_{50}	4.3 (mortality)	1	ECHA
Danio rerio (Brachydanio rerio)	96-hr LC_{50}	2.35 (mortality)	1	ECHA

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Danio rerio (Brachydanio rerio)	96-hr LC_{50}	>3.9- <5.5 (mortality)	1	ECHA
Poecilia reticulata (Guppy fish)	96-hr LC_{50}	>3.5- <6.5	2	ECHA
Lepomis macrochirus (Bluegill fish)	96-hr LC_{50}	>20	2	ECHA
Daphnia magna	48-hr EC_{50}	3.21	2	ECHA
Daphnia magna	48-hr EC_{50}	3.86	2	ECHA
Daphnia magna	48-hr EC_{50}	11.5	2	ECHA
Desmodesmus subspicatus	72-hr EC_{50}	31.6	2	ECHA
Chlorella vulgaris	72-hr EC_{50}	16.09	2	ECHA

Since the test chemical is readily biodegradable in water, the chemical was considered to be non-toxic to aquatic fish, invertebrates and algae at environmentally relevant concentrations (ECHA).

Chronic Studies

In an OECD Guideline 211 (Daphnia magna reproduction test) study, the 21-day EC_{50} was reported to be 0.402 mg/L based on reproduction (ECHA) [KI. score =2].

Based on a prediction completed using ECOSAR version 1.11, a long-term toxicity value for fish was predicted for cinnamaldehyde. Based on effects observed in a flow through freshwater system in fish, the NOEC value for the substance was estimated to be 15.159 mg/L for fish for 28 days of exposure duration. (ECHA) [KI. score = 2].

C. Terrestrial Toxicity

In a short-term toxicity study to birds (avoidance [repellency] test), the 5-day LOEL value was 1% w/w for *Colinus virginianus* (Northern Bobwhite Quail). (ECHA) [KI. score = 2].

D. Calculation of PNEC

The PNEC calculations for cinnamaldehyde 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 (2.35 mg/L), *Daphnia* (3.21 mg/L), and algae (16.09 mg/L). Results from a chronic study in fish was reported to be 15.159 mg/L. On the basis that the data consists of short-term results from three trophic levels and chronic studies on one trophic levels, an assessment factor of 100 has been applied to the lowest reported NOEC of 15.159 mg/L for fish. The $PNEC_{water}$ is 0.152 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 0.179 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (1.51/1280) \times 1000 \times 0.152$
$= 0.179$ 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]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 1.47/1000 \times 2400]$
$=1.51\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 36.82 \times 0.04$
$=1.47$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for Cinnamaldehyde based on the molecular connectivity index (MCI) is 36.82 L/kg (EPA, 2019).
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 0.075 mg/kg soil dry weight.
The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.74/1500) \times 1000 \times 0.152$
$= 0.075$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 36.82 \times 0.02$
$= 0.74$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for cinnamaldehyde based on the molecular connectivity index (MCI) is 36.82 L/kg (EPA, 2019).
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, 2017).

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

Based on a measured log K_{ow} of 2.107± 0.0017, cinnamaldehyde does not meet the screening criteria for bioaccumulation.

The NOEC from a chronic fish study was>0.1 mg/L. The acute E(L)C_{50} values for cinnamaldehyde are >1 mg/L. Thus, cinnamaldehyde does not meet the criteria for toxicity.

The overall conclusion is that cinnamaldehyde is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H315-Skin Irritant Category 2
H319-Eye Irritant Category 2
H317-Skin Sensitizer Category 1
H312-Aquatic Acute Toxicity Category 2
H335-STOT SE3

B. Labelling

Warning!

According to the classification provided by companies to ECHA in REACH registrations this substance causes serious eye irritation, is harmful to aquatic life with long lasting effects, is harmful in contact with skin, causes skin irritation and may cause an allergic skin reaction.

C. Pictogram

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

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: 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.

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. (NTP, 1992)

Notes to Physician

Symptoms of exposure to this compound may include inflammation and erosion of gastrointestinal mucosa. The vapor or mist causes irritation of the eyes, mucous membranes and upper respiratory tract. ACUTE/CHRONIC HAZARDS: This chemical may be harmful by inhalation, ingestion or skin absorption. It may cause irritation of the skin, eyes, upper respiratory tract, and mucous membranes. When heated to decomposition it may emit toxic fumes of carbon monoxide and carbon dioxide.

Medical Conditions Aggravated by Exposure

Irritation properties of the substance may aggravate asthma and/or other respiratory conditions.

Emergency Personnel Protection

Personal protective equipment must be used in accordance with known hazards of the substance.

B. Fire Fighting Information

Extinguishing Media

This chemical is combustible. Fires involving this material can be controlled with a dry chemical, carbon dioxide or Halon extinguisher.

Specific Exposure Hazards

May ignite after a delay period in contact with NaOH.

Special Protective Equipment for Firefighters

Use respiratory protection equipment as deemed necessary by hazards associated with the substance.

C. Accidental Release Measures

Personal Precautions

Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove clothing immediately if substance gets inside. Then wash thoroughly and put on clean clothing.

Environmental Precautions

Do not release to discharge into open drains or waterways.

Steps to be Taken if Material is Released or Spilled

If you spill this chemical, FIRST REMOVE ALL SOURCES OF IGNITION. Then, use absorbent paper to pick up all liquid spill material. Contaminated clothing and absorbent paper should be sealed in a vapor-tight plastic bag for eventual disposal. Solvent wash all contaminated surfaces with 60-70% ethanol followed by washing with a soap and water solution. Do not re-enter the contaminated area until the Safety Officer (or other responsible person) has verified that the area has been properly cleaned.

Wastewater from contaminant suppression, cleaning of protective clothing/equipment, or contaminated sites should be contained and evaluated for subject chemical or decomposition product concentrations. Concentrations shall be lower than applicable environmental discharge or disposal criteria. Alternatively, pre-treatment and/or discharge to a POTW is acceptable only after review by the governing authority. Due consideration shall be given to remediation worker exposure (inhalation, dermal and ingestion) as well as fate during treatment, transfer and disposal.

Do not contaminate water by cleaning of equipment or disposal of wastes

D. Storage and Handling

General Handling

Do not use, pour, spill or store near heat or open flame.

Other Handling Precautions

Observe label precautions. Immediately change contaminated clothing. Apply preventive skin protection. Wash hands and face after working with substance.

Storage

STORAGE PRECAUTIONS: You should keep this material in a tightly closed container under an inert atmosphere and store it at refrigerated temperatures. (NTP, 1992)

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure limit for cinnamaldehyde.

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:
Where the neat test chemical is weighed and diluted, wear a NIOSH-approved half face respirator equipped with an organic vapor/acid gas cartridge (specific for organic vapors, HCl, acid gas and SO2) with a dust/mist filter. (NTP, 1992)

Hand Protection:
Chemical resistant gloves.

Skin Protection:
For agricultural use requirements, PPE required for early entry to treated areas that is permitted under applicable Worker Protection Standards and that involves contact with anything that has been treated, such as plants, soil, water, is: Coveralls, waterproof gloves, shoes plus socks.

Eye protection:
Protective eyewear shall be worn at all times.

Other Precautions:
None other specific precautions are stipulated.

F. Transport Information

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

UN 1993

Class: 3

Packaging Group: II

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

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CITRIC ACID

This dossier on citric acid presents the most critical studies pertinent to the risk assessment of citric 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 information presented in this dossier was obtained primarily from the OECD-SIDS documents on citric acid (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).

Based on an assessment of environmental hazards, NICNAS identified citric acid as a chemical of low concern to the environment (NICNAS, 2017). Chemicals of low concern are unlikely to have adverse environmental effects if they are released to the environment from coal seam gas operations. In addition, NICNAS has assessed citric acid in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to the environment.[1]

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-hydroxypropane-1,2,3-tricarboxylic acid

CAS RN: [redacted]

Molecular formula: $C_6H_8O_7$

Molecular weight: 192.122 g/mol

Synonyms: citric acid; 1,2,3-propanetricarboxylic acid, 2-hydroxy-; 2-hydroxy-1,2,3-propanetricarboxylic acid

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

Citric acid is a ubiquitous natural substance that is an intermediate in the basic physiological tricarboxylic acid (TCA) cycle in every eukaryote cell.

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of citric acid

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	White crystalline odorless solid	2	ECHA
Melting Point	153°C @ 101.3 kPa	2	ECHA
Boiling Point	Not available due to substance decomposition	2	ECHA
Density	1670 kg/m^3 @ 20° C (relative density)	2	ECHA
Vapor Pressure	2.21 × 10^{-6} Pa @ 25° C	2	ECHA

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

Property	Value	Klimisch Score	Reference
Partition Coefficient (log K_{ow})	-1.5 to -1.8 (temperature not indicated)	2	ECHA
Water Solubility	592 g/L @ 20°C (very soluble)	2	ECHA
Flash Point	345°C @ 101.3 kPa	4	ECHA
Flammability	Not flammable	2	ECHA
Auto flammability	1010°C	4	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Citric acid is readily biodegradable. It is not expected to bioaccumulate. Due to its high-water solubility, citric acid is unlikely to adsorb to soil or sediment.

B. Biodegradation

Citric acid can be considered readily biodegradable based on the results of the ready and inherent aerobic biodegradation studies listed in Table 2. If a chemical is found to be readily biodegradable, it is categorized as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

Table 2: Biodegradation studies on citric acid (OECD 2001a, b)

Test System	Results*	Notes	Klimisch Score
Modified Sturm	97% (CO_2 evolution); 100% (DOC removal)	Readily biodegradable; exposure period not stated	2
Closed Bottle Test	BOD_{30}/COD Ratio = 90%	Readily biodegradable	2
BOD_5/COD Ratio	BOD_5 = 526 mg; COD = 728 mg; BOD_5/COD Ratio = 0.72	Readily biodegradable; concentration of test substance and activated sludge not stated	2
BOD_1/ThOD Ratio	BOD_1/ThOD Ratio = 13%	-	2
BOD_{20}/ThOD Ratio	BOD_{20}/COD Ratio = 98%	Readily biodegradable; initial test substance concentration 720 mg/L	2
Zahn-Wallen Test	85%, 1 day (DOC removal)	Inherently biodegradable	2
Zahn-Wallen Test	98%, 7 days (DOC removal)	Inherently biodegradable	
Coupled Units Test	93% (COD removal)	Ultimately biodegradable; exposure period not stated.	2

C. Environmental Distribution

No experimental data are available for citric acid. Using KOCWIN program in EPISuite™ (USEPA, 2016), the estimated K_{oc} value from the K_{ow} value of -1.08 is 0.3617 L/kg.

Based on this K_{oc} value, citric acid is not expected to adsorb to soil if released and has a high mobility. If citric acid is released to water, it is not expected to adsorb to suspended soils or sediment based on its K_{oc} value and rapid hydrolysis.

D. Bioaccumulation

The log K_{ow} for citric acid is -1.5 to -1.8. Thus, citric acid is not expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Citric acid exhibits low toxicity by the oral and dermal routes. It is an eye irritant, but slightly to non-irritating to the skin. No adequate studies were found to evaluate the sensitization potential of citric acid. Minimal toxicity and no carcinogenic effects were observed in rats given oral doses of citric acid for up to two years. Citric acid was not mutagenic to bacteria, but *in vitro* studies using human lymphocytes showed genotoxic effects. *In vivo* genotoxicity studies were negative. There were no reproductive or developmental effects in rats given oral doses of citric acid.

B. Acute Toxicity

Oral

The acute oral LD_{50} in male and female Füllinsdorf albino (SPF) mice exposed to 0,3,4.2, 6, 8.5 and 13 g/kg bw of citric acid via oral gavage was reported to be 5,400 mg/kg bw/day (ECHA) [KI.score=2].

The acute oral LD_{50} in male ICR-JCL male rats was reported to be 11,700 mg/kg (ECHA) [KI.score=2].

The acute oral LD_{50} values in SD-JCL male mice are 5,400 and 5,790 mg/kg (ECHA) [KI.score= 2].

Inhalation

There are no reliable studies available.

Dermal

The acute dermal LD_{50} value in rats is >2,000 mg/kg (ECHA) [KI.score=1].

C. Irritation

Skin

Application of 0.5 g citric acid powder to the skin of New Zealand white rabbits for 4 hours under semi-occlusive conditions was slightly irritating. The mean of the 24, 48 and 72-hour scores were 0.3 for erythema and 0.0 for oedema (ECHA) [KI.score=1].

Application of citric acid powder to the intact skin of New Zealand white rabbits for 4 hours under semi-occlusive conditions was reported to be non-irritating based on a primary dermal irritation index (PDII) score of 0.33/2 (ECHA) [KI.score=1].

Application of a 30% solution of citric acid to the intact skin of New Zealand white rabbits was found reported to slightly irritating to rabbits with intact (abraded skin) and non-irritating to rabbits with non-abraded skin based on a primary dermal irritation index (PDII) scores of 0.8/8 and 0/8 respectively (ECHA) [KI.score=2].

Application of a 50% aqueous solution of citric acid to New Zealand white rabbits for 4 hours under occlusive conditions was reported to be non-irritating (ECHA) [KI.score=2].

Eye

Instillation of a 30% aqueous solution of citric acid into the eyes of New Zealand white rabbits produced well defined to moderate conjunctival irritation that did not fully resolve after the 14-day observation period (ECHA) [KI.score=1]. Given the fact that the 30% solution effects would have been allowed to dissipate for 21 days, it likely that the test substance would not be considered irritating to the eyes (ECHA).

Instillation of a 10% solution of citric acid into the eyes of New Zealand white rabbits was associated with weak to moderate conjunctival effects, which resolved after 7 days (ECHA) [Kl.score=1].

Respiratory

In a study preliminary to the evaluation of antitussive agents, citric acid was chosen as most consistent in the cough response elicited as measured by the mean number of coughs produced with five inhalations in human volunteers (ECHA). 10% citric acid gave the highest number of positive reactors.

In a study to develop a method for the use of citric acid in testing antitussive medicines with human volunteers, a training period was used to determine the concentration of citric acid solution able to produce three to six coughs after one inhalation (ECHA). There were three test periods one hour apart. 5 inhalations were administered at 3-minute intervals in each test period. The number of coughs was counted after each inhalation. Each subject was given a placebo tablet after the first test period but was informed that they could receive either a placebo or an anti-tussive tablet.

The total number of coughs after each inspiration over the three test periods was compared among subjects and between test periods and inspirations. Statistical variance and F-values were analysed.

The concentration of citric acid producing between three and six coughs after a single inhalation was found to vary from 5% to 25%. Adaptation to the citric acid aerosol occurred during the initial training period, but further adaptation during the test period was low, except between the first and second inhalation.

Some reduction in response between the first and second test periods might be attributable to a placebo reaction. It was concluded that the administration of citric acid to induce coughing using the method described would be useful in evaluating antitussive medicines, providing that a double-blind trial using a placebo was used.

A study was conducted to evaluate the effect of inspiratory flow rate on the cough response in humans to citric acid (ECHA). It was considered by the authors that the cough response to citric acid is produced mainly by irritation of the larynx and trachea. Variations in the inspiratory flow rate might lead to changes in deposition of the drug, and consequently in the cough threshold. The effect of inspiratory flow rate was studied in 11 healthy non-smoking volunteers aged 23 to 29 years

(9 male, 2 female). The citric acid was administered by inhalation of a nebulized solution via apparatus which limited and measured the inspiratory flow rate to 50, 100 and 150 l/minute of increasing concentrations of citric acid.

The test was finished when a cough was produced after each inhalation at one concentration (cough threshold) or the maximum concentration was reached. Each concentration was given at three different flow rates. The exposures were repeated on 3 days at least 48 hours apart.

The mean cough threshold was determined to be 21 (±9-54) mg/l at an inspiratory flow rate of 50 l/min and 43 (±13-141) mg/l at 150 l/minute. It was concluded that inspiratory flow rate should be controlled when cough challenges with citric acid are performed.

Inhalation of citric acid was shown to cause cough and bronchoconstriction in the guinea pig. The bronchoconstriction seems to involve cholinergic and capsaicin sensitive neurons (ECHA).

Citric acid was seen to elicit a cough response in the guinea pig (ECHA) in a study in which the time-response relationship observed with citric acid showed a maximum response around 5 to 10 minutes of exposure for isolated coughs and a fade in response as the exposure continued.

D. Sensitisation

In a skin prick test, with very limited provided details, it was reported that citric acid, caused positive results in 3 of 91 patients whereof one of the patients also reacted to benzoic and propionic acids (ECHA) [KI.score=4].

In a skin sensitisation, study with limited details, citric acid was concluded to not be a skin irritant or a sensitizer when tested to human volunteers (ECHA) [KI.score=4]. At induction, patches of 4% citric acid in a cuticle cream were applied onto the skin of 56 human volunteers, under a semi-occlusive dressing, three times a week for three weeks. At challenge, 4% citric acid in a cuticle cream was applied dermally to 56 human volunteers two weeks after the last induction (ECHA) [KI.score=4].

E. Repeated Dose Toxicity

<u>Oral</u>

Male and female rats were administered 2000, 4000, 8000 and 16000 mg/kg bw/day of citric acid via oral gavage daily for five successive days. A NOAEL of 4000 mg/kg bw/day was established for both male and female rats based on overall clinical signs, mortality, and body weight. A LOAEL of 8000 mg/kg bw/day was established for male and female rats based on clinical signs, increased mortality and body weight gain. A 10-day LD_{50} value of 55560 ± 0.44 mg/kg bw/day was also reported in rats (gender not specified) (ECHA) [KI.score=2].

Mice were administered 1000, 2000, 4000 and 8000 mg/kg bw/day of citric acid via oral gavage daily for ten successive days. A NOAEL of 1000 mg/kg bw/day was established based on clinical signs, mortality, and body weight. A LOAEL of 2000 mg/kg bw/day was established based on clinical signs, increased mortality and body weight gain (ECHA) [KI.score=2].

Male rats were given 0, 1.2, 2.4 or 4.8% citric acid in their feed for 6 weeks. The daily intakes were reported to be 1,150, 2,260 or 4,670 mg/kg-day. The high-dose animals had mild blood and urine parameter changes and slight degeneration of the thymus gland and spleen. The NOAEL is 2.4% in the diet or 2,260 mg/kg-day (OECD, 2001a,b) [KI.score=4]

Rats were given 3% or 5% citric acid in their diet for two years. The estimated daily intakes were 1,200 and 2,000 mg/kg/day, respectively. A slight decrease in growth was reported in the 2% group, but no tissue abnormalities in the major organs. The NOAEL is 1,200 mg/kg/day (OECD, 2001a,b). [Kl.score=4]

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In vitro Studies

Table 2 presents the results of the *in vitro* genotoxicity studies on citric acid.

Table 2: *In vitro* genotoxicity studies on citric acid

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
In vitro mammalian cell micronucleus test (lymphocytes: peripheral human)	-	+	2	ECHA
Bacterial Reverse Mutation Assay (S. typhimurium TA 1535, TA 100, TA 98, TA 1537, TA 92, and TA 94)	-	-	2	ECHA
Comet assay (human lymphocytes)	+	NA	2	ECHA
Chromosome aberration test (human peripheral lymphocytes)	+	NA	2	ECHA

*+, positive; -, negative; NA, not applicable

Citric acid was not mutagenic in bacterial reverse mutation assays with strains of *S. typhimurium* or *E. coli* with and without metabolic activation (OECD, 2001a,b; ECHA) [Kl.score=2].

Peripheral human lymphocytes were treated with 50 to 3,000 µg/ml citric acid. A statistically significant dose-dependent increase in the micronuclei was observed. In another set of studies by the same laboratory, there was a statistically significant and dose-related increase in the number of cells with aberrations, including sister chromatid unions. The study authors reported that the pH of the medium was unchanged (ECHA) [Kl.score=2].

In vivo Studies

Citric acid was reported to be non-mutagenic in a rodent dominant lethal assay when male Sprague-Dawley rats were given either a single oral dose of citric acid (1.2, 12.0 or 120 mg/kg) or a single oral dose on five consecutive days (300, 500 or 3,500 mg/kg) (OECD 2001a,b; as reported in ECHA) [Kl.score=2].

There were no treatment related increases in cells with chromosomal aberrations in observed in the bone marrow of male Sprague-Dawley rats given either a single oral dose of citric acid (1.2, 12.0 or 120 mg/kg) or a single oral dose on five consecutive days (300, 500, 3000 or 3,500 mg/kg) (ECHA) [KI.score=2].

G. Carcinogenicity

Oral

There was no evidence of carcinogenicity in rats given 3% or 5% citric acid in feed (1,200 or 2,000 mg/kg/day, respectively) for two years (OECD, 2001a,b) [KI.score=4].

In a rat feeding study, animals dosed with 5% citric acid in the diet did not show an excess of tumors in comparison with control animals when tested over a period of 2 years (Horn et al., 1957, as reported in ECHA). However, there was limited evidence that high doses of citrate salts increased the incidence of tumors produced by co-administration of known bladder carcinogens (Inouea et al., 1988; Ono et al., 1992; de Camargo et al., 1991; Fukushima et al.,1986; Behnke et al., 1964; as reported in ECHA). Where citric acid or citrate salts were administered alone during these studies, no dose-related tumors were noted (ECHA).

H. Reproductive Toxicity

In a non-standard repeat dose dietary study (duration and frequency not specified), 5% citric acid in feed did not affect either the number of young born to mice or rats or their subsequent survival up to the point of weaning (ECHA) [KI.score=4].

In a reproductive toxicity study, 1.2% w/w citric acid was administered in feed given daily to male and female rats over a period of 90 weeks and it was reported that citric acid did not give rise to any reproductive effects (ECHA).

The no adverse effect level (NOAEL) for reproductive toxicity in rats has been reported as 2500 mg/kg/bw/day (Kim et al., 2013, citing Citric acid SIDS initial assessment report [OECD SIDS, 2001]; as cited in ECHA).

I. Developmental Toxicity

Hamsters were administered citric acid via oral gavage daily from gestation day 0 to gestation day 10 resulted in a NOAEL of > 272 mg/kg bw/day based on teratogenicity (ECHA) [KI.score=2].

Wistar rats were exposed to citric acid by oral gavage from gestation day 6 to gestation day 15. A NOAEL of >295 was established for this study based on teratogenicity (ECHA) [KI.score=2].

Albino CD-1 mice were exposed to citric acid by oral gavage from gestation day 6 to gestation day 15. A NOAEL of >241 mg/kg bw/day was established for this study based on teratogenicity (ECHA) [KI.score=2].

Pregnant female rats were dosed by oral gavage with 0, 2.95, 13.7, 63.6 or 295 mg/kg citric acid on GD 6-15. No maternal or developmental effects were noted. The NOAEL for maternal and developmental toxicity is 295 mg/kg-day, the highest dose tested (OECD, 2001a,b; ECHA) [KI.score= 2].

Pregnant female rats were dosed by oral gavage with 0, 2.41, 11.2, 52 or 241 mg/kg citric acid on GD 6-15. No maternal or developmental effects were noted. The NOAEL for maternal and developmental toxicity is 241 mg/kg-day, the highest dose tested (OECD, 2001a,b; ECHA) [KI.score=2].

Pregnant female rabbits were dosed by oral gavage with 0, 4.25, 19.75, 91.70 or 425 mg/kg citric acid on GD 6-18. No maternal or developmental effects were noted. The NOAEL for maternal and developmental toxicity is >425 mg/kg-day, the highest dose tested (OECD, 2001a,b; as cited in ECHA) [KI.score=2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for citric 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).

A. Non-Cancer

In a two-year dietary study, the only effect seen in rats fed either 3 or 5% citric acid (approx. 1,200 or 2,000 mg/kg/day) was a slight decrease in growth in the 5% dose group. In the absence of statistical analysis of the body weight gain data, a conservative approach was taken, and the 5% dose group was considered an LOAEL. The NOAEL of 3% citric acid in the diet (1,200 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 / ($UF_A \times UF_H \times UF_L \times UF_{Sub} \times UF_D$)

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 = 1,200/(10 × 10 × 1 × 1 × 1) = 1,200/100 = <u>12 mg/kg/day</u>

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 = (12 × 70 × 0.1)/2 = 42 mg/L

B. Cancer

Citric acid was not carcinogenic to rats in a chronic dietary study. Thus, no cancer reference value was derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

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

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Citric acid is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

The 48-hour LC_{50} values in *Leuciscus idus melanotus* (golden orfe) from two separate laboratories were 440 mg/L and 760 mg/L (ECHA) [Kl.score=2]. The 96-hour LC_{50} in *Lepomis macrochirus* (fathead minnow) is >100 mg/L (ECHA) [Kl.score=2).

The 24-hour EC_{50} in *Daphnia* is 85 mg/L in un-neutralized test solution and 1,535 mg/L in a neutralized solution (OECD, 2001a,b; as cited in ECHA) [Kl.score=2].

The 8-day toxicity threshold value (EC_0) of 640 mg/L and a NOEC of 425 mg/L was determined for citric acid in Scenedesmus quadricauda (ECHA; OECD, 2001a,b) [Kl. score=2].

Chronic Studies

Citric acid is essential in the Krebs cycle (or TCA cycle), which in turn is an essential chemical cycle that takes place in all living organisms to generate energy, via the generation of adenosine triphosphate (ATP). This means that citric acid is naturally present inside all living organisms, and it is very unlikely that it will be found in the environment at concentrations high enough to exert hazards to organisms (ECHA). Short-term aquatic toxicity data indicate that citric acid is of low toxicity. Further, the substance is readily biodegradable, has a log K_{ow} <3 and is highly soluble. Therefore, it is very unlikely to persist in the environment long enough to cause long-term effects. As a result, the completion of chronic studies was not required, and no studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for citric acid 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 (440 mg/L) and *Daphnia* (1,535 mg/L, neutralized). On the basis that the data consist of short-term results from two trophic levels, an assessment factor of 1,000 has been applied to the lowest reported effect concentration of 440 mg/L for fish. The $PNEC_{water}$ is 0.44 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 0.277 mg/kg wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.807/1280) \times 1000 \times 0.44$
$= 0.277$ 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]

$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{soilid}]$
$= 0.8 + [0.2 \times 0.014/1000 \times 2400]$
$= 0.807\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).

BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$
$= 0.3617 \times 0.04$
$= 0.014$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for citric acid is estimated to be 0.3617 L/kg.
F_{oc} = fraction of organic carbon suspended 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 0.002 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.007/1500) \times 1000 \times 0.44$
$= 0.002$ 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]

$Kp_{soil} = K_{oc} \times f_{oc}$

$= 0.3617 \times 0.02$

$= 0.007\ m^3/m^3$

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for citric acid is estimated to be 0.3617 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).

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

The log K_{ow} values for citric acid are -1.5 to -1.8. Thus, citric acid does not meet the screening criteria for bioaccumulation.

There are no chronic aquatic toxicity studies on citric acid. The acute $E(L)C_{50}$ values for citric acid are >1 mg/L in fish and invertebrates. Thus, it does not meet the screening criteria for toxicity.

The overall conclusion is that citric acid is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

The information in this section is for a citric acid solution.

A. Classification

H315: Causes skin irritation
H319: Causes serious eye irritation
H335: May cause respiratory irritation
Eye irritation-category 2A
Skin irritation-category 2
Specific target organ toxicity (single exposure)- category 3

B. Labelling

Warning

C. Pictogram

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

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. Firefighting 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 Spilt

Pick up with absorbent material. Dispose of contaminated material as prescribed.

D. Storage and Handling

General Handling

No special measures necessarily provided product is used correctly.

Other Handling Precautions

Avoid eye and skin contact.

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 citric acid.

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

Citric 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

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1-PROPANAMINIUM, 3-AMINO-N-(CARBOXYMETHYL)-N,N,-DIMETHYL-N-COCO ACYL DERIVS., HYDROXIDES, INNER SALTS
[COCOAMIDOPROPYL BETAINE]

This dossier on 1-propanaminium, 2-amino-N-(carboxymethyl)-N,N-dimethyl-N-cocoalkyl [cocoamidopropyl betaine] presents the most critical studies pertinent to the risk assessment of cocoamidopropyl betaine 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 alkylamidopropyl betaines, which includes cocoamidopropyl betaine (OECD, 2006; OECD, 2007), 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): 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-,N-coco acyl derivs., hydroxides, inner salts

CAS RN: [redacted]

Molecular formula (mean)* [1]: $C_{12.8}H_{39.8}N_2O_3$ [OECD, 2007]

Molecular weight (mean)* [1]: ca. 355 g/mol [OECD, 2007]

Synonyms: 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-,N-coco acyl derivs., hydroxides, inner salts; 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl,N-coco acyl derivs., hydroxides, inner salts; 1-propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-,N-coco acyl derivs., inner salts; cocoamidopropyl betaine; cocoamido propyl betaine; cocoamidopropylbetaine; N-cocamidopropyl-dimethylglycine; coco amide propylbetaine; acetobetain, dimethyl-C12-18-acylamidopropyl-; (N-cocoamidopropyl)-N,N-dimethylglycin, hydroxide, inner salts

SMILES: O=C(NCCCN(CC(=O)O)(C)C)CCCCCCCCCCC for C12 fatty acid

[1] *The calculation of the molecular formula and weight is based on the typical alkyl chain length distribution:
C8: 7% (Caprylamidopropyl betaine)
C10: 6% (Capramidopropyl betaine)
C12: 51% (Lauramidopropyl betaine)
C14: 18% (Tetradecylamidopropyl betaine, Myristamidopropyl betaine)
C16: 8% (Palmitamidopropyl betaine)
C18: 10% (Stearamidopropyl betaine)

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Cocoamidopropyl Betaine

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid	2	ECHA
Melting point	283°C (calculated for C12 fatty acid; QSAR)	2	OECD, 2007; ECHA
Boiling point	651°C for C12 fatty acid (calculated; QSAR)	2	OECD, 2007; ECHA
Density	1.05 – 1.07 g/cm^3	2	OECD, 2007
Vapor pressure	0 PA @ 25°C (calculated; QSAR)	2	OECD, 2007
Partition coefficient (log K_{ow})	-1.28 to -3.63 @ 25°C*	4	OECD, 2007
Water solubility	1.62-8,769 mg/L @ 25°C (calc.) ≥10 g/L @ 25°C (aq. soln, measured)	2	OECD, 2007
Flash point	>230°C	4	HERA, 2005
Auto flammability	Not auto-flammable	1	OECD, 2007

*log Kow (C8) = -1.28; log Kow (C10) = -0.30; log Kow (C12) = 0.69; log Kow (C14) = 1.67; log Kow (C16) = 2.65; log Kow (C18) = 3.63.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Cocamidopropyl betaine is readily biodegradable; has a low potential to bioaccumulation; and is expected to have low-to-moderate adsorption to soil and sediment.

B. Biodegradation

Cocamidopropyl betaine is readily biodegradable. In an OECD 301 D test, degradation was 84% after 30 days (ECHA) [Kl. score = 2]. In an OECD 301 E test, degradation was 90% and 100% after 14 and 28 days, respectively (ECHA) [Kl. score = 2]. In an OECD 301 B test, degradation was 84% an 99% after 7 and 28 days, respectively (ECHA) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption

No experimental studies are available on cocamidopropyl betaine. Using KOCWIN v2.00, the K_{oc} value calculated by the MCI method for cocamidopropyl betaine with a C12 fatty acid side chain is 648 L/kg (ECHA) [Kl. score = 2].

D. Bioaccumulation

No experimental studies are available on cocamidopropyl betaine. Using the QSAR model BCFBAF v3.01, the bioaccumulation factor (BCF) of cocamidopropyl betaine with a C12 fatty acid chain was estimated to be 70.8 L/kg (ECHA). Thus, the bioaccumulation potential of cocamidopropyl betaine is low (ECHA) [Kl. score = 2].

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of cocamidopropyl betaine is low-to-moderate by the oral and dermal routes. An aqueous solution of 30% cocamidopropyl betaine is not irritating to the skin. The potential for eye irritation is dependent on the concentration of cocamidopropyl betaine: a 5-10% solution is slight-to-moderately irritating, while a 30% solution is severely irritating. Cocamidopropyl betaine has shown some skin sensitizing responses in both guinea pigs and humans; the response is thought to be due to impurities. Repeated dose toxicity studies in rats by the oral route have shown that cocamidopropyl betaine is irritating to the gastrointestinal tract, with no indication of any systemic effects up to 300 mg/kg-day. It is not genotoxic; and there was no indication of developmental toxicity in rats given cocamidopropyl betaine by the oral route.

B. Acute Toxicity

The oral LD_{50} values for cocoamidopropyl betaine are >1,500 mg/kg [Kl. scores = 1].

No acute inhalation studies are available on cocoamidopropyl betaine.

The dermal LD_{50} value in rats for cocoamidopropyl betaine is >600 mg/kg (OECD, 2007) [Kl. score = 1].

C. Irritation

Application of 0.5 g. of a 30-35% aqueous solution of cocoamidopropyl betaine to the skin of rabbits under semi-occlusive conditions were not irritating (OECD, 2007) [Kl. scores = 1].

There are several eye irritation studies conducted on cocamidopropyl betaine in rabbits. A 5-10% solution of cocamidopropyl betaine produced mild to moderate irritation to the eyes of rabbits, which were reversible; solutions containing 15% were irritating to highly irritating; and a 30% aqueous solution was irritating with irreversible damage (OECD, 2006; OECD, 2007 [Kl. scores = 1 and 2].

D. Sensitization

Two independent guinea pig maximization tests have been conducted on cocoamidopropyl betaine (OECD, 2006). There was no sensitization response in one test [Kl. score = 2], and the second test gave ambiguous results [Kl. score = 2]. The purity of the cocoamidopropyl betaine was not reported.

The sensitizing potential of cocoamidopropyl betaine in humans is low. Commercial cocoamidopropyl betaine may, however, contain impurities identified as sensitizers (amidoamine and/or 3-dimethylaminopropylamine) which may explain positive results in human patch tests. There is no evidence for a photosensitizing potential. In a guinea pig adjuvant study with less stringent test conditions, cocoamidopropyl betaine was not a skin sensitizer (OECD, 2006) [Kl. score = 2]. A modified Draize sensitization test with guinea pigs also showed no sensitization response with cocoamidopropyl betaine (OECD, 2006; OECD, 2007) [Kl. score = 2].

A few cases of sensitization in humans have been reported from the use of personal cleansing products containing cocoamidopropyl betaine. It is thought that these cases may have been due to impurities of cocoamidopropyl betaine, such as amidoamine and DMPA, that could be present in the formulations (OECD, 2006). Nonetheless, cocamidopropyl betaine can be considered to be a potentially weak skin sensitizer.

E. Repeated Dose Toxicity

Oral

Male and female SD rats were dosed by oral gavage with 0, 250, 500 or 1,000 mg/kg of a 30% aqueous solution of cocoamidopropyl betaine, 5 days/week for 28 days. The only treatment-related findings were forestomach lesions at the highest dose level, probably as a result of the irritant effect of the test substance. The NOAEL for systemic toxicity in this study is 1,000 mg/kg-day, which corresponds to 300 mg cocoamidopropyl betaine/kg-day (OECD, 2006; OECD, 2007) [Kl. score = 2].

Male and female SD rats were dosed by oral gavage with 0, 250, 500 or 1,000 mg/kg of a 30% aqueous solution of cocoamidopropyl betaine, 5 days/week for 90 days. The only treatment-related findings were forestomach lesions at the 500 and 1,000 mg/kg dose levels, probably as a result of the irritant effect of the test substance. The NOAEL for systemic toxicity in this study is 1,000 mg/kg- day, which corresponds to 300 mg cocoamidopropyl betaine/kg-day (OECD, 2006; OECD, 2007) [Kl. score = 2].

Inhalation

No studies are available.

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The results from in vitro genotoxicity studies on cocoamidopropyl betaine are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Cocoamidopropyl Betaine

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	OECD, 2007
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	OECD, 2007
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	OECD, 2007
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	-	4	OECD, 2007

*+, positive; -, negative

In Vivo Studies

Male and female OF1 mice were given intraperitoneal injections of 0, 20, or 200 mg/kg of a 27% solution of cocoamidopropyl betaine on two consecutive days. The frequency of micronucleated erythrocytes were similar in the bone marrow cells of the treated mice compared to that in the control mice (OECD, 2006; OECD, 2007) [Kl. score = 2].

G. Carcinogenicity

No studies are available.

H. Reproductive Toxicity

No studies are available.

I. Developmental Toxicity

Pregnant female CD rats were dosed by oral gavage with 0, 330, 990, or 3,300 mg/kg of a 28.9% aqueous solution of cocoamidopropyl betaine on GD 5 to 19. The dams in the ≥990 mg/kg dose groups had reduced body weights and stomach ulcers. Embryotoxic effects (increased numbers of resorptions, decreased number of viable fetuses, decreased fetal body weight) were observed only in the 3,300 mg/kg dose group. The NOAEL for maternal toxicity was 330 mg/kg-day (corresponding to 95 mg cocoamidopropyl betaine/kg-day). The NOAEL for developmental toxicity was 990 mg/kg-day, which corresponds to 286 mg cocoamidopropyl betaine/kg-day (OECD, 2006; OECD, 2007) [Kl. score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for cocamidopropyl betaine 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

In a 90-day rat oral study, there were no treatment-related effects associated with systemic toxicity at 300 mg/kg-day cocoamidopropyl betaine, the highest dose tested. The NOAEL of 300 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) = 3
UF_D (database uncertainty) = 1

Oral RfD = 300/(10 x 10 x 1 x 3 x 1) = 300/300 = 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, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (1 x 70 x 0.1)/2 = 3.5 mg/L

B. Cancer

There are no carcinogenicity studies on cocoamidopropyl betaine. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Cocoamidopropyl betaine does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The acute and chronic toxicity of cocamidopropyl betaine is of moderate concern to aquatic life.

B. Aquatic Toxicity

Acute Studies

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

Table 3: Acute Aquatic Toxicity Studies on Cocamidopropyl Betaine

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Danio rerio	96-hr LC_{50}	2	2	ECHA
Daphnia magna	48-hr EC_{50}	6.4	2	ECHA
Desmodesmus subspicatus	72-hr EC_{50}	48 (growth)	4	ECHA

Chronic Studies

The 28-day NOEC for cocamidopropyl betaine in *Oncorhynchus mykiss* is 0.16 mg/L (ECHA) [Kl. score = 4].

The 21-day NOEC for cocamidopropyl betaine in a Daphnia reproduction test is 0.9 mg/L (ECHA) [Kl. score = 2].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for cocamidopropyl betaine 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 (2 mg/L), invertebrates (6.4 mg/L), and algae (48 mg/L). The NOEC values from chronic studies are available for fish (0.16 mg/L) and invertebrates (0.9 mg/L). On the basis that the data consists of acute studies from three trophic levels and chronic studies from two trophic levels, an assessment factor of 50 has been applied to the lowest reported NOEC value of 0.16 mg/L for fish. The $PNEC_{aquatic}$ is 0.0032 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 0.033 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (13.24/1280) \times 1000 \times 0.0032$
$= 0.033$

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]

$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 25.92/1000 \times 2400]$
$= 13.24$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$
$= 648 \times 0.04$
$= 25.92$

Where:
K_{oc} = organic carbon normalized distribution coefficient (L/kg). The K_{oc} for cocamidopropyl betaine with a C12 fatty acid side chain calculated from KOCWIN v2.0 using the MCI method is 648 L/kg (ECHA).
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 0.028 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (12.96/1500) \times 1000 \times 0.0032$
$= 0.028$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 648 \times 0.02$
$= 12.96$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for cocamidopropyl betaine with a C12 fatty acid side chain calculated from KOCWIN v2.0 using the MCI method is 648 L/kg (ECHA)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).

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

Based on calculate BCF values of 70.8 L/kg, cocamidopropyl betaine does not meet the screening criteria for bioaccumulation.

The chronic toxicity data on cocamidopropyl betaine is >0.1 mg/L. The acute $E(L)C_{50}$ values for cocamidopropyl betaine in fish, invertebrates, and algae are >1 mg/L. Thus, cocamidopropyl betaine does not meet the screening criteria for toxicity.

The overall conclusion is that cocamidopropyl betaine is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

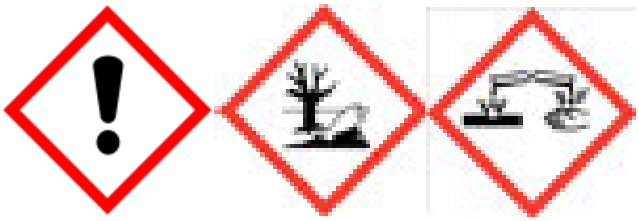
A. Classification

Skin Irritant Category 2
Eye Irritant Category 2
Skin Sensitizer Category 1
Aquatic Chronic Toxicity Category 3

B. Labelling

Warning
According to the classification provided by companies to ECHA in REACH registrations this substance causes serious eye irritation, is harmful to aquatic life with long lasting effects, causes skin irritation and may cause an allergic skin reaction.

C. Pictogram



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

A. First Aid

Eye Contact
Rinse immediately with plenty of running water. If easy to do, remove contact lenses. Get medical attention if symptoms persist.

Skin Contact
Wash with soap and water. Get medical attention if symptoms occur.

Inhalation
Treat symptomatically. Move to fresh air. Get medical attention if symptoms persist.

Ingestion
Rinse mouth with water. If material has been swallowed, give small quantities of water to drink. Do not induce vomiting. Never give anything by mouth to an unconscious person. Get medical attention if symptoms occur.

B. Fire Fighting Information

Extinguishing Media
Water spray, dry chemical, alcohol-resistant foam, carbon dioxide. Do not use water jet as an extinguisher, as this will spread the fire.

Specific Exposure Hazards
Fine dust clouds may form explosive mixtures with air. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include: carbon dioxide, carbon monoxide, nitrogen 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
Keep unnecessary personnel away. Keep people away from an upwind of spill or leak. Keep out of low areas. Wear appropriate personal protective equipment. Do not touch damaged containers or spilled material unless wearing appropriate protective clothing. Ensure adequate ventilation.

Environmental Precautions
Prevent entry into waterways, sewers, basements or confined 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. Large spills: dike the spilled material.

D. Storage and Handling

General Handling
Avoid contact with eyes. Provide adequate ventilation. Wear appropriate personal protective equipment. Observe good industrial hygiene practices.

Other Handling Precautions
Wash hands thoroughly after handling.

Storage
Store in original tightly closed container. Store away from incompatible materials (strong oxidizing agents, peroxides, phenol).

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Workplace Australia has not established an occupational exposure standard for cocamidopropyl betaine.

Engineering Controls
Ensure adequate ventilation, especially in confined areas.

Personal Protection Equipment
Respiratory Protection:
In case of insufficient ventilation, wear suitable respiratory equipment.

Hand Protection:
For prolonged or repeated skin contact use suitable protective gloves.

Skin Protection:
Wear suitable protective clothing.

Eye protection:
Wear safety glasses with side shields (or goggles).

Other Precautions:
Handle in accordance with good industrial hygiene and safety practice. Eyewash fountains and safety showers must be easily accessible. Routinely wash work clothing and protective equipment to remove contaminants.

F. Transport Information

Cocamidopropyl betaine 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.

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ACRYLAMIDE/SODIUM ACRYLATE COPOLYMER

This dossier on acrylamide/sodium acrylate copolymer presents the most critical studies pertinent to the risk assessment of acrylamide/sodium acrylate copolymer 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: 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.

IV. HUMAN HEALTH HAZARD ASSESSMENT

No studies are available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

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[1]."

[1] https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-i-human-health-assessments#cas-A_[redacted]

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.

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 vapors. 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 oxidizing 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.

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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.

CROTONALDEHYDE

This dossier on crotonaldehyde presents the most critical studies pertinent to the risk assessment of crotonaldehyde 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): (2E)-but-2-enal

CAS RN: [redacted]

Molecular formula: C4H6O

Molecular weight: 70.091

Synonyms: Crotonaldehyde, Crotoinic aldehyde, β-Methacrolein, β-Methyl acrolein, 2-butenal, Propylene aldehyde

SMILES: C/C=C/C=O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Crotonaldehyde

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Water-white to straw-colored liquid with a pungent odor.	2	ECHA
Melting point	-76°C	2	ECHA
Boiling point	102.2°C	2	ECHA
Density	0.852 g/cm^3 @ 20°C	2	ECHA
Vapor pressure	40 hPA @ 25°C	2	ECHA
Partition coefficient (log K_{ow})	0.6 (QSAR)	2	EPA, 2019
Water solubility	181 g/L @ 20°C	2	ECHA

Property	Value	Klimisch score	Reference
Flash point	13°C	2	ECHA
Auto flammability	165°C	1	ECHA
Flammability	Highly flammable	-	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

"In two supporting studies on inherent biodegradability, an inherent biodegradability could be shown. However, it is stated in both reports that the elimination could also be related to volatility of the substance and not only to biodegradation. Only in one study, it could be shown by BOD-determination that the test substance was in fact biodegraded." (ECHA)

"Distribution modelling suggests an environmental distribution of crotonaldehyde mainly in soil and water with a low potential of adsorption to soil particles and a medium potential of reaching the air via volatilization from the water surface." (ECHA)

"The substance crotonaldehyde was predicted to have a soil sorption coefficient (Koc) of 10.66 L/kg, corresponding to a log Koc of 1.0277." (ECHA)

"Based on the modelled data it can be shown that the main parts of crotonaldehyde are distributed in soil and water. Only a small part can be found in the air, whereas the distribution in the sediment is negligible." (ECHA)

B. Biodegradation

Crotonaldehyde is readily biodegradable but fails the 10-day window.

In an EPA OTS 796.3200 ready biodegradability:closed bottle test, degradation was 32% after 5 days, 45% after 15 days, and 55% after 28 days (ECHA) [Kl. score = 2].

In an inherent biodegradation test (DIN 38 412 part 25, early draft), degradation was 78% after 5 days, 83% after 10 days, and 94% after 15 days. The COD was 2,060 mg O_2/g test material; the BOD_5 was 320 mgO_2/ g test material; and the BOD_5*100/COD was 15.5% (ECHA) [Kl. score = 2].

In an OECD 301 C (MITI-I) test, degradation was >80% with or without adjustment of the pH to 7.0 at Day 1 of culturing (ECHA) [Kl. score = 2].

In an OECD 301 E test, degradation was 22% after 7 days, 24% after 21 days, and 30% after 28 days (ECHA) [Kl. score = 2].

In an OECD 302 test, degradation was 90% after 19 days. However, similar values were seen in the abiotic control, probably due to the volatilization of the test material (ECHA) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for crotonaldehyde. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value from log K_{ow} of 0.6 is 10.66 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 1.793 L/kg.

D. Bioaccumulation

There are no bioaccumulation studies on crotonaldehyde. Crotonaldehyde is not expected to bioaccumulate based on a log K_{ow} of 0.6 (EPA, 2019).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Crotonaldehyde is an acutely toxic compound by oral, dermal and inhalation routes of exposure; it readily penetrates skin and may induce systemic toxicity. Inhalation may induce neurotoxicity. The substance is considered an irritant and/or corrosive to the respiratory tract, skin and eyes. Crotonaldehyde is considered very toxic to the respiratory tract, and the damage caused in one study was found to be non-reversible.

The following sections detail the available and relevant literature on the toxicity of crotonaldehyde. The information described below was obtained from NICNAS IMAP if available and the ECHA database. Please refer to those information sources for the studies referenced therein.

B. Acute Toxicity

Oral

The chemicals are classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia).

Based on a limited number of test results, the chemical has high acute oral toxicity in rats and mice. The median lethal dose (LD50) is 174–300 mg/kg bw in rats and 104–240 mg/kg bw in mice (CICAD, 2008; SCOEL, 2013; MAK, 2012). In an acute oral toxicity fixed

dose study (conducted similarly to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 420), male and female Sprague Dawley (SD) rats (5 animals/group) were administered the chemical by gavage at doses of 64.5, 107.5, 180, 300 and 500 mg/kg bw and observed for 14 days. Within 24 hours post-treatment, there were 27 out of 50 mortalities, including all animals in the 300 and 500 mg/kg bw groups and 7/10 deaths in the 180 mg/kg bw group. Observed sublethal effects for the surviving animals included lethargy, salivation, changes in motor activity and lacrimation. The LD50 was determined to be 174 mg/kg bw (REACH).

Dermal

The chemica is classified as hazardous with the risk phrase 'Toxic in contact with skin' (T; R24) in HSIS (Safe Work Australia). The available data (rabbit: LD50 128–380 mg/kg bw; guinea pig: 26 mg/kg bw) support this classification (CICAD, 2008; NIOSH, 1979). Reported signs of toxicity include local effects such as necrosis, oedema, erythema and congestion of capillaries, as well as damage to internal organs (REACH). The low LD50 values in two different animal species indicate that the chemical readily penetrates the skin and may induce systemic toxicity.

Inhalation

The chemical is classified as hazardous with the risk phrase 'Very toxic by inhalation' (T+; R26) in HSIS (Safe Work Australia). The available data (median lethal concentration for 4 hours (LC50) 69–120 ppm, equivalent to 0.19–0.34 mg/litre/4h) support this classification (SCOEL, 2013; REACH). Reported signs of toxicity include irritation and neurotoxicity. Examination of the deceased animals revealed haemorrhagic rhinitis, proliferative lesions in the bronchioles, pulmonary congestion and pulmonary oedema as well as haemorrhages of the lung, liver, heart and kidneys (SCOEL, 2013).

C. Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). In a non-guideline study, sensory irritation was quantified by measuring respiratory rate depression upon exposure of B6C3F1 mice to the chemical. The animals were sealed in an airtight vessel and exposed to 5 different concentrations for 10 minutes. The dose resulting in a 50% decrease in respiratory rate (RD50) was determined to be 4.88 ppm. Little or no recovery was reported (REACH).

The substance was also demonstrated to elict neurogenic inflammatory responses in airways of guinea pigs (Andre et al. 2008).

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). Several available study reports suggest that the chemicals

may be corrosive. However, the older studies on which this was based contained methodological deficiencies and were not conducted according to OECD test guidelines. An EU harmonised classification concluded that the chemical was a skin irritant after consideration of the available data. In the absence of further reliable information, amendment of the existing classification is not warranted.

In a non-guideline study, 0.5 mL of undiluted 2-crotonaldehyde was applied to the abraded and non-abraded skin of rabbits under occlusive conditions. The test substance was allowed to remain on the skin for 4 hours, then signs of irritation or corrosivity were recorded at 4, 24 and 72 hours after exposure and scored on a graded scale of 0–4. The chemical was classified as corrosive to rabbit skin, with maximum scoring attained. No description of the severity and type of skin effects are reported (REACH).

In another non-guideline study, undiluted chemical on intact rabbit skin for 15 minutes produced severe erythema and oedema after 5–9 hours. Hyperaemia appeared immediately after the skin came into contact with the chemical. After 2–3 days desquamation began, the skin became covered with serous crusts and regions of ulceration were seen. Symptoms on the exposed areas persisted for 12–15 days, then gradually healed towards the end of the observation period (2 months). After 15–17 days, partial detachment of necrotised regions of the ear or complete detachment of its distal portion were observed (ECHA). The study results indicated that the chemical was corrosive to rabbit skin.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) in HSIS (Safe Work Australia). The available data support this classification.

In an eye irritation study, the chemical was found to cause serious damage to rabbit eyes with volumes of 0.001–0.5 mL of undiluted crotonaldehyde applied to the cornea. After 24 hours, the observed eye irritation was described as being equal to that of acetic anhydride, which is corrosive. No reversibility data were reported (REACH).

D. Sensitization

The chemical was not demonstrated to be sensitising in a dose-dependent contact hypersensitivity test in female B6C3F1 mice. The concentrations of the substance crotonaldehyderanged from 0.3 % to 3.0 % in a solution of acetone in olive oil (4:1) for sensitisation and 10 % for the challenge. The mice received 20 µL of the chemical directly on prepared skin for 5 consecutive days. The chemical 2,4-Dinitrofluorobenzene (0.5 % dose) was used as a positive control (REACH; NTP, 1989).

E. Repeated Dose Toxicity

Oral
The chemical is classified as hazardous with the risk phrase 'Danger of serious damage to health by prolonged exposure if swallowed' (Xn; R48/22) in HSIS (Safe Work Australia). While the data are limited, the available data support this classification.

In a 14-day repeated dose oral toxicity study, groups of male and female SD albino rats were administered the chemical in feed at doses of 0, 22, 44, 88 and 175 mg/kg bw/day. No mortality was observed during the study and no evidence of treatment-related toxicity was observed in any of the parameters examined (REACH).

In a 90-day study, rats and mice (10 animals/sex/group) were gavaged with the chemical in doses of 0, 2.5, 5, 10, 20 and 40 mg/kg bw/day for 5 days/week for 13 weeks (REACH; SCOEL, 2013). There were dose-related increases in mortality and in inflammation of the nasal cavity in rats (but not in mice) at doses of 5 mg/kg bw/day and above, with a no observable adverse effect level (NOAEL) of 2.5 mg/kg bw/day established. Lesions of the forestomach were produced in rats at doses of 10 mg/kg bw/day and above (dose-related) and in mice of the highest dose group. However, these data were only presented in a journal abstract and no other details were provided.

In a chronic study, 23–27 male rats were exposed for 113 weeks to the chemical in the drinking water at concentrations of 0, 0.6 and 6 mmol/L (equivalent to 0, 7.3 and 53.9 mg/kg bw/day). The higher dose resulted in reduced body weight gain, while survival was not affected. Nearly half of the high-dose animals had moderate to severe non-neoplastic liver lesions (fatty metamorphosis, focal necrosis, fibrosis and cholestasis) and all the remaining animals (high and low dose) developed liver cell foci (Chung et al, 1986; SCOEL, 2013).

Dermal
Reliable animal studies on the effects of repeated dermal exposure were not available (SCOEL, 2013).

Inhalation
Reliable animal studies are not available (SCOEL, 2013; CICAD, 2008).

In a non-guideline study, rats were continuously exposed to 1.2 mg/m3 of crotonaldehyde for 3 months. Changes in motor activity and blood haemoglobin levels were observed. However, as no pathology or histology studies were undertaken, the data were insufficient to judge the applicability of these results (REACH).

F. Genotoxicity

In Vitro Studies
The substance crotonaldehyde has been found to bind to DNA and induce DNA-protein cross-links in vitro via Michael addition. In a non-guideline study, DNA adducts were

observed in calf thymus DNA treated with 1.0 mM solution of the chemical, either directly or with metabolic activation. The adducts that formed were identified as cyclic 1,N2-propanodeoxyguanosine (REACH). Adducts were also formed in CHO cells (REACH). 'Both the 1- and N2 positions of guanine are involved in base-pairing, hence the presence of the cyclic adduct may lead to mutations' (IARC, 1995).

In an Ames test conducted similarly to OECD TG 471, the substance crotonaldehyde was tested at 0.05–0.4 µL per plate for point mutations against Salmonella typhimurium strains TA 98, 100, 1535, 1537 and 1538 with or without S9 metabolic activation. The chemical had no mutagenic activity in any of the strains tested using the plate incorporation method. However, when a preincubation method was employed, it was mutagenic in S. typhimurium strain TA 100 with and without metabolic activation (REACH; IARC, 1995).

In another Ames test, crotonaldehyde was tested in *S. typhimurium* strains TA 102 and 104 with and without metabolic activation at concentrations of 0.075–1.4 µmol per plate. Using the preincubation method, the chemical was positive for mutagenicity in TA 104 without metabolic activation and negative in TA 102 (REACH; IARC, 1995).

In a non-guideline intrasanguineous mouse host-mediated assay, crotonaldehyde was administered orally (gavage) to CD-1 mice (0.009–0.094 mg/kg bw) during simultaneous intravenous injection of S. typhimurium TA 100. The chemical was found to be mutagenic, with a three-fold increase in revertants of TA 100 recovered from mouse blood compared to the control, at a dose of 0.032 mg/kg bw (REACH; CICAD, 2008; MAK, 2012).

In a sister chromatid exchange assay in mammalian cells conducted similarly to OECD TG 479, crotonaldehyde was tested in Chinese hamster ovary (CHO) cells. The results were positive from 0.5 µg/mL and above without activation (dose range tested: 0.16–1.6 µg/mL), and positive from 1.6 µg/mL with S9 metabolic activation (dose range tested: 1.6–160 µg/mL) (REACH). Positive results were also observed in other sister chromatid exchange studies carried out on human blood lymphocytes and lymphoblastoid Namalva cells (REACH).

In a mammalian chromosome aberration assay conducted similarly to OECD TG 473, crotonaldehyde was tested in CHO cells with positive results from 1.6 µg/mL onwards without metabolic activation (dose range tested: 0.5–5 µg/mL) and positive at the highest dose tested (16 µg/mL) with S9 metabolic activation (dose range tested: 1.6–16 µg/mL) (REACH). In another chromosome aberration study in human blood lymphocytes and lymphoblastoid Namalva cells (dose range tested: 5–250 µM), increased micronuclei were observed from 200 µM and above for lymphocytes, and from 100 µM and above for Namalva cells (REACH).

In a SOS-Chromotest, DNA repair functions were induced in Escherichia coli PQ37 using ethanol as a solvent instead of dimethyl sulfoxide (DMSO). A weak SOS result was obtained using the S. typhimurium strain TA1535/pSK1002 without metabolic activation (IARC, 1995; SCOEL, 2013; CICAD, 2008).

The substance crotonaldehyde has been tested for mutagenic activity in several other in vitro assays, including DNA damage and repair assays in mammalian and bacterial cells. Positive results were obtained in primary rat epithelial cells (stomach and colon). However, in a test conducted similarly to OECD TG 482, no unscheduled DNA synthesis was observed in a single DNA repair test in rat hepatocytes (REACH).

In Vivo Studies

In a study conducted similarly to OECD TG 475, chromosomal aberrations were observed in mouse bone marrow cells after 12 hours when the animals were administered a single dose of the chemical (8, 16, 32, or 200 µL/kg bw) by i.p. injection (REACH).

In a non-guideline study, crotonaldehyde was found to covalently bind to DNA and form cyclic DNA adducts in the dermis of Sencar mouse skin after topical application of the chemical (total dose 1.4 mmol, 98 mg) five times per week for three weeks (IARC, 1995; MAK, 2012). No background adducts were found in the skin of untreated mice. Systemic availability of the chemical was demonstrated by increased numbers of DNA adducts in the liver, lung and kidneys of rats after administration of crotonaldehyde at high doses via gavage (IARC, 1995; MAK, 2012).

In a study conducted similarly to OECD TG 477, sex-linked recessive lethal mutations and reciprocal translocations were induced in D. melanogaster injected with a single dose of crotonaldehyde at 3500 ppm (IARC, 1995; REACH). In another study, crotonaldehyde (4000 ppm) was administered to D. melanogaster via oral feeding, although the chemical was not found to be mutagenic after three days.

In a study conducted similarly to OECD TG 483, crotonaldehyde induced chromosomal damage in the spermatogonia of mice after oral administration in drinking-water or by i.p. injection. Special meiotic anomalies, such as degenerated cell nuclei, multispindle cells, polyploids and sperm anomalies were observed. However, no positive and negative controls were reported, rendering this study inadequate for the evaluation of germ cell mutagenicity (IARC, 1995; MAK, 2012; REACH). In another study conducted similarly to OECD TG 478, dominant lethal frequencies increased with dose (8, 16 or 32 µL/kg bw) in a mouse study following i.p. administration (REACH).

G. Carcinogenicity

The International Agency for Research on Cancer (IARC) has classified the chemical as 'Not classifiable as to its carcinogenicity to humans' (Group 3) (IARC, 1995) based on inadequate evidence for carcinogenicity in humans and animals.

In a single, non-guideline study, the trans isomer (E-crotonaldehyde, CAS No. [redacted] was administered to male Fischer 344 (F344) rats (23–27 animals/group) in drinking water at 0, 0.6 or 6.0 mM (equivalent to 0, 7.3 and 53.9 mg/kg bw/day) for 113 weeks (Chung et al., 1986). There were statistically significant increases in the incidence of hepatocellular neoplasms (including neoplastic nodules and hepatocellular carcinomas) in the low dose group. The incidences were 0/23, 9/27 and 1/23 in the control, low- and high-dose groups, respectively. The incidences of hepatocellular carcinomas alone were 0/23, 2/27 and 0/23, respectively. The incidences of enzyme-altered liver foci, which are considered precursors of neoplasms, were 1/23, 23/27 and 13/23 in the control, low- and high-dose groups, respectively. The increased incidences in both the low- and high-dose groups were statistically significant relative to controls. The lower incidence of neoplastic and preneoplastic lesions at the higher dose compared with the higher dose was not explained. However, the study was only carried out on a single sex and only using two doses. In addition, the incidence of tumours did not appear to be dose-related (IARC; Chung et al., 1986).

H. Reproductive and Developmental Toxicity

In a one-generation reproductive toxicity study, no reproductive effects were seen at the doses tested. The available information does not meet the criteria for hazard classification in regards to reproductive toxicity.

In a one-generation reproductive toxicity study carried out similarly to OECD TG 415, male and female F344 rats were treated with the chemical (0, 2.5, 5 and 10 mg/kg bw/day) by gavage daily until sacrifice. Males were dosed for 61 days prior to breeding, and females were dosed 31 days prior to breeding. There were no notable clinical observations with regards to gonadal function, mating behaviour or fertility in either male or female rats. A NOAEL of 10 mg/kg bw/day for both sexes was established for reproductive effects (REACH).

In another study, a single i.p. injection of crotonaldehyde (0, 8, 16 or 32 µL/kg bw, corresponding to 0, 6.8, 13.7 and 27.2 µg/kg bw) was administered to male Swiss albino mice. A statistically significant increase in the percentage of abnormal sperm heads was recorded at 16 and 32 µL/kg bw at 3 weeks, and at only the highest dose at 5 weeks. However, there were methodological deficiencies in this study, and the route of exposure is not appropriate for humans (REACH).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for crotonaldehyde 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 lowest NOAEL from these studies is 2.5 mg/kg-day based on reduced body weights, increased nasal tumors, histopathological findings in rats from 9-day oral gavage study (Kl = 2). The NOAEL of 2.5 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) = 3
UF_D (database uncertainty) = 1

Oral RfD = 2.5/(10 x 10 x 1 x 3 x 1) = 2.5/300 = 0.008 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 = (0.008 x 70 x 0.1)/2 = 0.03 mg/L

B. Cancer

Crotonaldehyde is not carcinogenic, so no cancer reference value was developed.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Crotonaldehyde is a flammable liquid.

Crotonaldehyde does not exhibit the following physico-chemical properties:
· Explosivity
· Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The substance exhibits a relatively high degree of acute and chronic aquatic toxicity as discussed below.

B. Aquatic Toxicity

Acute Studies

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

Table 2: Acute Aquatic Toxicity Studies on Crotonaldehyde

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-hr LC_{50}	0.65	1	ECHA
Pimephales promelas	96-hr LC_{50}	0.84	1	ECHA
Lepomis macrochirus	96-hr LC_{50}	3.0	2	ECHA
Daphnia magna	48-hr EC_{50}	2	1	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50} 96-hr EC_{50}	0.597 <0.881	1	ECHA

Chronic Studies

The 41-d NOEC to *Oryzias latipes* in an OECD 210 fish early life stage toxicity test is 0.0247 mg/L (ECHA) [Kl. score = 1].

The 96-hr EC_{10} to *Pseudokirschneriella subcapitata* is <0.385 mg/L based on growth rate (ECHA) [Kl. score = 1].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for crotonaldehdye 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 (0.65 mg/L), invertebrates (50 mg/L), and algae (0.597 mg/L). Results from chronic studies are available for fish (0.0247 mg/L) and algae (<0.385 mg/L). 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 NOEC or EC_{10} value of 0.0247 mg/L for fish. The $PNEC_{water}$ is 0.0005 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 $PNEC_{soil}$ is 0.00007 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.21/1500) \times 1000 \times 0.0005$
$= 0.00007$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 10.66 \times 0.02$
$= 0.21$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for crotonaldehyde based on the log K_{ow} is 10.66 L/kg (EPA, 2018).
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).

Crotonaldehyde is readily biodegradable but failing the 10-day window; thus, it does not meet the screening criteria for persistence.

Based on an estimated log K_{ow} of 0.6, crotonaldehyde does not meet the screening criteria for bioaccumulation.

The lowest chronic NOEC or EC_{10} value for crotonaldehyde is <0.1 mg/L. The acute $E(L)C_{50}$ values are <1 mg/L for fish and algae. Thus, crotonaldehyde meets the screening criteria for toxicity.

The overall conclusion is that crotonaldehyde is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute toxicity – category 1
Acute toxicity – category 3
Skin irritation – category 2
Eye damage – category 1
Germ cell mutagenicity – category 1B
Specific target organ toxicity (single exposure) – category 3
Specific target organ toxicity (repeated exposure) – category 2
Flammable liquid – category 2
Hazardous to the aquatic environment (acute) – category 1

B. Labelling

Danger

C. Pictogram

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

A. First Aid

Eye Contact
Rinse cautiously with water for at least 15 minutes. Remove contact lenses, if present and easy to do. Continue rinsing. Immediately call a poison center or doctor/physician.

Skin Contact
Immediately call a poison center or doctor/physician. Wash contaminated clothing before reuse. If skin irritation occurs: Get medical advice/attention. Take off immediately all contaminated clothing. Rinse skin with soap and water/shower.

Inhalation
Remove victim to fresh air and keep at rest in a position comfortable for breathing. Immediately call a poison center or doctor/physician.

Ingestion
Immediately call a poison center or doctor/physician. Rinse mouth. If swallowed give 1-2 glasses of water to drink immediately

Notes to Physician Vapours may cause irritation to the eyes, respiratory system and the skin. Treatment: Treat symptomatically. In case of lung irritation first treatment with dexametason aerosol (spray). If ingested, irrigate the stomach.

Medical Conditions Aggravated by Exposure
Respiratory disorder

Emergency Personnel Protection
No data available.

B. Fire Fighting Information

Extinguishing Media
Foam, Dry chemical, carbon dioxide (CO2)
Do not use a solid water stream as it may scatter and spread fire.

Note: Cool containers / tanks with water spray. Dike and collect water used to fight fire.

Specific Exposure Hazards
Under conditions giving incomplete combustion, hazardous gases produced may consist of carbon monoxide, carbon dioxide (CO2). Combustion gases of organic materials must in principle be graded as inhalation poisons

Special Protective Equipment for Firefighters
Self-contained breathing apparatus

C. Accidental Release Measures

Personal Precautions
Avoid contact with the skin and the eyes. Keep away from heat and sources of ignition. Provide adequate ventilation

Environmental Precautions
Prevent further leakage or spillage. Do not discharge into the drains/surface waters/groundwater. Product is very toxic to aquatic life with long lasting effects

Steps to be Taken if Material is Released or Spilled
Soak up with inert absorbent material. Do not use rags, paper towels or combustible materials to clean up a spill, because spontaneous combustion can occur. Keep in suitable, closed containers for disposal. Dispose of in accordance with local regulations

D. Storage and Handling

General Handling
Advice on safe handling: vapors may form explosive mixtures with air. The pressure in sealed containers can increase under the influence of heat. Refill and handle product only in closed system. Provide sufficient air exchange and/or exhaust in work rooms. Protection - fire and explosion: : Keep away from sources of ignition - No smoking. Vapours are heavier than air and may spread along floors. Take necessary action to avoid static electricity discharge. Ground and bond containers when transferring material.

Other Handling Precautions
In case of fire, emergency cooling with water spray should be available.

Storage
The product will oxidize in air and release heat. Oxidization creates acids and peroxides, that may lead to corrosive damages in storage and handling equipment. Technical measures/Storage conditions: Keep tightly closed in a dry, cool and well-ventilated place. Handle and open container with care. May need to store under nitrogen. Incompatible products: Keep away from: acids, bases, amines, oxygen, oxidizing agents, reducing agents.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
The workplace exposure standard for crotonaldehyde in Australia is 2 ppm (5.7 mg/m3) as an 8-hr TWA. No STEL is available.

Engineering Controls
General or dilution ventilation is frequently insufficient as the sole means of controlling employee exposure. Local ventilation is usually preferred. Explosion-proof equipment (for example fans, switches, and grounded ducts) should be used in mechanical ventilation systems.

Personal Protection Equipment
Respiratory Protection:
Respirator or full mask in accordance with guidance - or self-contained breathing apparatus

Hand Protection:
Chemical-resistant gloves. Suitable material: butyl-rubber Type: Butoject (Company KCL) or comparable; or refer to glove manufacturer's recommendation.

Skin Protection:
Impervious clothing

Eye protection:
Wear appropriate protective eyeglasses or tightly fitting chemical safety goggles. In addition to goggles, wear a face shield if there is a reasonable chance for splash to the face.

Other Precautions:
General advice: Avoid contact with skin and eyes. Do not breathe vapors or spray mist. Use only in an area equipped with a safety shower. Make sure eye wash fountain is available. Hygiene measures: When using, do not eat, drink or smoke. Take off all contaminated clothing immediately. Wash hands before breaks and immediately after handling the product.

F. Transport Information

UN Number 1143
Hazard class 6.1

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

AICS: Listed

XIII. REFERENCES

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

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DIETHANOLAMINE

This dossier on diethanolamine (DEA) presents the most critical studies pertinent to the risk assessment of diethanolamine 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): 2,2'-iminodiethanol

CAS RN: [redacted]

Molecular formula: $C_4H_{11}NO_2$

Molecular weight: 105.14

Synonyms: Diethanolamine; 2,2'-iminodiethanol; 2,2'-dihydroxydiethylamine; 2-[(2-hydroxyethyl)amino]ethanol; bis(2-hydroxyethyl)amine; DEA; di(2-hydroxyethyl)amine; ethanol, 2,2'-iminobis-(9Cl); ethanol, 2,2'iminodi-(8Cl)

SMILES: C(CO)NCCO

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Diethanolamine

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Crystals (prisms) or syrupy liquid (>82°F)	2	ECHA
Melting Point	27°C	1	ECHA
Boiling Point	268.9°C (decomposition occurs ≥200°C)	1	ECHA
Density	1.095.3 kg/m^3	2	ECHA
Vapor Pressure	1 hPa @ 108°C (measured); 0 hPa at 25°C	2	ECHA

Property	Value	Klimisch score	Reference
Partition Coefficient (log K_{ow})	-2.46 @ 25°C	2	ECHA
Water Solubility	Miscible	2	ECHA
Flash Point	176°C @ 1,013 hPa	2	ECHA
Auto flammability	375°C @ 1,013 hPa	1	ECHA
Flammable	Not flammable	1	ECHA
Viscosity	390.9 mPa s @ 30°C; 102.7 mPa s @ 50°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Diethanolamine is readily biodegradable. It is not expected to bioaccumulate, and it has low potential to adsorb to soil.

B. Biodegradation

Diethanolamine is readily biodegradable. In an OECD 301F test, there was 50% degradation after 7 days, 80% after 14 days, and 93% after 28 days (OECD 2007; ECHA) [Kl. score = 1]. In a "Ready" Biodegradability – Dissolved Organic Carbon (DOC) Die-Away test, there was 86% degradation after 7 days and 96% degradation after 10 days (ECHA) [Kl. score = 2]. In modified OECD 301E screening tests using river or pond water, there was 93% and 97% degradation (measured as DOC removal) after 28 days (OECD 2007; ECHA) [Kl. score = 2].

C. Environmental Distribution

<u>Distribution Modeling</u>

No experimental data are available for diethanolamine. The K_{oc} for diethanolamine (as the charged molecule) was calculated to be 10 at pH values between 5 and 8 (Franco and Trapp, 2008; Franco et al., 2009; ECHA). [Kl. score = 2]

D. Bioaccumulation

There are no bioaccumulation studies on diethanolamine. The BCF was estimated to be 2.3 based on calculations from OASIS Catalogic v.5.11.15 [BCF base-line model v.0208] (Dimitrov et al., 2005; ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Diethanolamine exhibits moderate acute toxicity by the oral route, but low acute toxicity by the inhalation and dermal routes. It is a skin irritant and a severe eye irritant. Diethanolamine is not a skin sensitizer. Repeated oral exposure to rats (in drinking water) resulted in anemia, kidney toxicity, demyelinization of the brain/spinal cord, and damage to the testes in males, which included adverse effects on the sperm. Repeated oral exposure to mice (in drinking water) resulted in adverse effects to the kidney, liver, and heart. Repeated dermal exposure to rats and mice resulted in systemic toxicity, which included kidney toxicity, anemia (rats only), and liver toxicity (mice only). Rats exposed nose-only to an aerosol of diethanolamine developed anemia, adaptive liver and kidney effects, damage to the male reproductive organs, and upper respiratory tract irritation. There was no evidence of neurotoxicity. In short-term oral studies, rats and mice exposed to diethanolamine showed some immune-modulating effects at dose levels that resulted in overt signs of systemic toxicity. Diethanolamine was not genotoxic in a variety of *in vitro* and *in vivo* genotoxicity tests. Diethanolamine was not carcinogenic to rats in a two-year NTP dermal bioassay; but, in mice, there was an increased incidence of liver tumors in males and females and kidney tumors in males. Studies by the oral and dermal routes showed testicular damage in male rats, but no adverse effects in female reproductive organs. Developmental toxicity, coincident with maternal toxicity, occurred in rats when exposures by the oral, dermal, or inhalation routes. There was no developmental toxicity in rabbits even at doses that caused maternal toxicity.

B. Pharmacokinetics/Metabolism

Following oral administration of [^{14}C]-diethanolamine, 57% of the dose was absorbed (Matthews et al., 1997). Absorption was lower through the skin than from oral administration. Diethanolamine may also facilitate its own absorption in rats, as 3% and 16% of the dermally applied doses (in 95% ethanol) of 2 and 27 mg/kg, respectively, were absorbed through the skin in a 48-hour period. Dermal absorption of diethanolamine is higher in the mouse than the rat: absorption was 25 to 60% from dermal doses of 8 to 80 mg/kg (Matthews et al., 1997).

The distribution of diethanolamine is similar across all routes of exposure (Matthews et al., 1997; Mendrala et al., 2001). The highest concentrations were found in the liver and

kidney. The half-life of diethanolamine from tissues is about 6-7 days (Mendrala et al., 2001).

Following an oral dose of [^{14}C]diethanolamine to male F344 rats, the livers showed levels of un-metabolized diethanolamine, N-methyl-diethanolamine, N,N-dimethyl-diethanolamine, and phosphates of diethanolamine. In addition, the organic extract of the liver had radioactivity co-eluting with phosphatidyl ethanolamine and phosphatidyl choline. When the organic extract was digested with sphingomyelinase, 30% of the phospholipids were identified as ceramides and the remaining 70% as phosphoglycerides. Incubation of human liver slices with [^{14}C]-diethanolamine showed similar incorporation of diethanolamine into ceramides, followed by methylation (Matthews et al., 1995).

Diethanolamine is excreted primarily in urine as the parent compound (25-36%), with lesser amounts of O-phosphorylated and N-methylated metabolites (Matthews et al., 1997).

C. Acute Toxicity

The oral LD_{50} value for male and female rats combined was determined to be 1,600 mg/kg (ECHA) [Kl. score = 2]. The oral LD_{50} in female Wistar rats is 1,820 mg/kg (ECHA) [Kl. score = 2].

There were no deaths in rats following an 8-hour inhalation exposure to an atmosphere enriched with diethanolamine vapor. The technically highest attainable concentration is 1.9 mg/m^3 or 0.44 ppm (ECHA) [Kl. score = 2]. There were no deaths in rats following an 8-hour exposure to 0.2 mg/L diethanolamine vapor (ECHA) [Kl. score = 2].

There are no reliable acute dermal toxicity studies on diethanolamine.

D. Irritation

Application of 2 mL of diethanolamine to the skin of rabbits for 20 hours was irritating. The mean of the 24, 48, and 72 hours scores were 2.00 for erythema and 1.33 for edema (ECHA) [Kl. score = 2].

Instillation of diethanolamine into the eyes of rabbits was irritating. The mean of the 24, 48, and 72 hour scores were 1.67 for corneal opacity; 0.00 for iridial lesions; 1.50 for conjunctival redness; and 0.83 for chemosis. Corneal lesions still persisted in one of two animals at the end of the 8-day observation period (ECHA) [Kl. score = 2]. Instillation of 100 mg diethanolamine into the eyes of rabbits produced a mean irritation score based on Kay and Calandra of 50.75, indicating severe irritation (ECHA) [Kl. score = 2].

E. Sensitization

Diethanolamine was not considered a skin sensitizer in a guinea pig maximisation test (ECHA). [Kl. score = 1]

F. Repeated Dose Toxicity

Oral

Male and female F344 rats were given diethanolamine in their drinking water for 13 weeks at concentrations of 0, 320, 630, 1,250, 2,500, or 5,000 ppm for males; and 0, 160, 320, 630, 1,250, or 2,500 ppm for females. The average daily intakes were estimated to be: 0, 25, 48, 97, 2,202, or 436 mg/kg-day for males; and 0, 14, 32, 57, 124, or 242 mg/kg-day for females. In the top dose group, 2/10 males died during the study. Weight gain was reduced in the ≥630 ppm males and the ≥320 ppm females. Decreased water consumption among the higher dose groups may have contributed in part to the decreased body weight gain. Clinical signs of toxicity included tremors, emaciation, abnormal posture, and rough hair coat in the two highest dose groups. A dose-dependent microcytic, normochromic anemia was seen in all dose groups for both sexes. Hematologic effects included decreases in erythrocyte and reticulocyte counts, hemoglobin concentration, hematocrit, MCV, and MCH. MCV was reduced in rats at all dose levels. Hematologic effects were not associated with microscopic changes in the femoral bone marrow. Relative kidney weights were increased in a dose-dependent manner in the ≥320 ppm males and ≥160 ppm females, accompanied by increases in the incidence and/or severity of nephropathy, renal tubular cell necrosis, or tubular mineralization. Nephropathy consisted of tubules lined by epithelial cells with more basophilic staining of the cytoplasm and a higher nuclear/cytoplasmic ratio; occasionally, thickened basement membranes were seen around these tubules. This lesion was present to a minimal degree in controls, particularly in male rats, but was increased in incidence and severity in the 5,000 ppm males and in most of the groups of treated females. Increased nephropathy was considered a regenerative change and was supported by the observation of tubular necrosis at the higher dose groups. Relative liver weights were increased in the ≥630 ppm males and ≥320 ppm females, with no corresponding histopathological changes in the liver. There was, however, mild to moderate increases in serum levels of total bile acids in the ≥160 ppm females and in the ≥630 ppm males. Decreases in testis and epididymis weights (≥1,250 ppm) were associated microscopically with degeneration of seminiferous epithelium and with hypospermia (≥2,500 ppm). Testicular degeneration was diagnosed in all high-dose males and in 3/10 of the 2,500 ppm males. Intraluminal cellular debris and reduced numbers of sperm cells were present in the epididymis. These findings correlated with decreases in sperm motility and sperm count per gram caudal tissue. There was also atrophy of the seminal vesicle and prostate glands in the higher dose group males. In females, the estrous cycle length was similar across all groups. Minimal to mild demyelination of the brain and spinal cord was noted in the ≥2,500 ppm males and the ≥1,250 ppm females; there were no neurological clinical signs that could be attributed

to these lesions. Cytoplasmic vacuolization of the zona glomerulosa of the adrenal cortex was seen in the 5,000 ppm males and in the ≥1,250 ppm females. This was a minimal change consisting of small clear vacuoles in the cytoplasm of these cells and may have been related to increased mineralocorticoid production secondary to kidney damage and/or dehydration. The most sensitive endpoints were the microcytic anemia in both sexes and kidney effects in females (weight, nephrotoxicity) and males (weights). The LOAELs are 320 ppm (25 mg/kg-day) for males and 160 ppm (14 mg/kg-day) for females (NTP 1992; Melnick et al., 1994a). [Kl. score = 1]

Male and female B6C3F1 mice were given diethanolamine in their drinking water at concentrations of 0, 630, 1,250, 2,500, 5,000 or 10,000 ppm for 13 weeks. The average daily intakes were estimated to be: 0, 104, 178, 442, 807, or 1,674 mg/kg-day for males; and 0, 142, 347, 884, 1,154, or 1,128 mg/kg-day for females. All of the ≥5,000 ppm animals and 3/10 of the 2,500 ppm females died during the study. Body weight gains were lower in the 2,500 ppm males and in the 1,250 and 2,500 ppm females. Animals that survived to the end of the study had similar water consumption compared to the controls. Clinical signs in the animals that died early in the 2,500 ppm group were tremors, ruffled fur, emaciated appearance, abnormal posture, and hypoactivity. There was no significant gross findings at necropsy in the mice that died early or survived to study termination. Absolute and relative liver weights were increased in a dose-dependent manner in male and female mice and was associated with increases in serum alanine aminotransferase and sorbital hydrogenase activities and, in addition, microscopic changes diagnosed as hepatocellular cytologic alteration and necrosis. Cytologic alteration consisted of multiple hepatocyte changes including hypertrophy with increased eosinophilia and disruption of hepatic cords. These lesions were observed in mice that died early and those that survived to the end of the study. There was also increased nuclear pleomorphism and the frequent presence of large, multinucleated hepatocytes. These “giant” cells often contained 10 or more nuclei. Hepatocyte necrosis was randomly distributed and involved single cells or small foci. Absolute and relative kidney weights were increased in males and were associated with a dose-dependent increase in the incidence of nephropathy among those mice that survived to the end of the study. Nephropathy was minimal; there were renal tubules lined by basophilic cells with high nuclear/cytoplasmic ratio. This was considered to be a regenerative response, although active tubular necrosis was observed only in a few early-death mice at ≥5,000 ppm. Increased heart weight was seen in the 2,500 ppm females, and relative heart weight was seen in the 2,500 ppm males and the 1,250 and 2,500 ppm females. There was also minimal-to-marked degeneration and necrosis of cardiac myocytes in both sexes exposed to ≥2,500 ppm. Myocardial degeneration was generally more severe in mice that died early than in those that survived to study termination. The most sensitive endpoint was the increase in liver weights with corresponding histopathological changes. The LOAEL was 630 ppm (104 and 142 mg/kg-day in males and females, respectively) (NTP, 1992; Melnick *et al.*, 1992b). [Kl. score = 1]

Inhalation

Male and female Wistar rats were exposed nose-only to 0, 15, 150, or 450 mg/m^3 diethanolamine aerosol, 6 hours/day, 5 days/week for 90 days. The MMAD values were 1.1 – 1.9 µm, 1.0 µm, and 0.6 – 0.9 µm for the 15, 150, and 450 mg/m^3 exposure groups, respectively. The percent aerosol ranged among the exposure groups, from 92 to 95%. There were no deaths during the study. The 400 mg/m^3 males had slightly decreased body weights. The neurotoxicity endpoints (functional observation battery, sensorimotor test/reflexes, and motor activity) and ophthalmoscopy examination showed no treatment-related effects. At 400 mg/m^3, there was a significant decrease in red blood cells, hemoglobin, hematocrit, and mean corpuscular volume in both sexes. A marginal increase in anisocytosis was seen in the 400 mg/m^3 males; and no treatment-related effects were seen in white or differential blood counts. ALP serum activity was increase in the ≥150 mg/m^3 animals, and reduced ALT in the ≥150 mg/m^3 males. Blood chemistry changes included increased calcium, total protein, albumin, globulin in the ≥150 mg/m^3 females; and increased total protein and albumin in the ≥150 mg/m^3 males as a trend. Absolute and relative liver and kidney weights were increased in the ≥150 mg/m^3 animals. Histopathologic examination showed diffuse testicular atrophy accompanied by oligozoospermia in the epididymides, and slight prostate atrophy in the some of the 400 mg/m^3 males. There was also minimal or slight tubular hyperplasia of the kidney in some females as well as intratubular lithiasis in increased number (also in the 400 mg/m^3 males). There was also indications of local irritation of the respiratory tract. The larynx appeared to be the most sensitive area where some epithelia damage was observed at all concentrations. Focal inflammation at the tracheal bifurcation occurred in the ≥150 mg/m^3 animals. No treatment-related effects were seen in the neuropathologic examination. The NOAEC for systemic toxicity is 15 mg/m^3. The LOAEC for localized effects (irritation) is 15 mg/m^3; a NOAEC was not established (Garner et al., 2008). [Kl. score = 1]

Male and female Wistar rats were exposed nose-only to 0, 1.5, 3, or 8 mg/m^3 diethanolamine aerosol, 6 hours/day, 5 days/week for 90 days. Additional group of female rats were exposed for 90 days followed by a 3-month recovery period. The MMAD values were 0.6 µm, 0.6 µm, and 0.7 µm for the 1.5, 3, and 8 mg/m^3 exposure groups, respectively. At 8 mg/m^3, the animals showed upper respiratory tract irritation in the form of squamous metaplasia of the laryngeal epithelium at the base of the epiglottis; this was accompanied by some inflammatory cell infiltration. These effects were reversible following the 3-month recovery period. The NOAEC for localized effects (irritation) is 3 mg/m^3 (ECHA). [Kl. score = 1]

Dermal

Male and female F344 rats were given daily dermal applications of 0, 32, 63, 125, 250, or 500 mg/kg diethanolamine, 5 days/week for 13 weeks. The animals that died during the study are as follows: one 500 mg/kg male during week 9 and 2 500 mg/kg females

that were killed in a moribund condition during week 10. Final mean body weights were lower in the ≥250 mg/kg male and the ≥125 mg/kg females. The primary clinical signs of toxicity in the ≥125 mg/kg animals were irritation and crusting of the skin at the application site. In all dosed groups, there was a moderate, poorly regenerative, microcytic, normochromic anemia in both sexes. Red blood cell variables were decreased in the ≥32 mg/kg dose groups. There were no histologic changes in the femoral bone marrow in any dose group. Serum biochemical changes in males were increased UN and albumin in the 63 and 250 mg/kg groups, respectively, and mild increases in ALT in the ≥125 mg/kg animals. In females, UN, albumin, and total protein increased in the ≥32 mg/kg groups (≥63 mg/kg for total protein), and total bile acids increased in the ≥250 mg/kg groups. A mild increase was seen in ALT in the 500 mg/kg females. The kidney was a target organ. Absolute and relative kidney weights in male and female rats; these were associated with increased severity or increased incidences of nephropathy, renal tubular cell necrosis, or tubular mineralization. The incidence and severity of nephropathy was increased in a dose-dependent manner at the lower dose levels in females, but there was no clear treatment effect on this lesion in males. Tubular necrosis was observed in the ≥250 mg/kg females, but no active necrosis was found in the corresponding male groups. Tubular mineralization, consistent with previous necrosis, was present in the 500 mg/kg males, as well as being increased in incidence and severity in most treated female groups. The absolute and relative liver weights were increased in a dose-dependent manner in both sexes; there were no corresponding histopathologic changes even though there were some mild serum biochemical changes. There were no adverse effects on the testes or epididymides; sperm morphology and vaginal cytology was unaffected by treatment. The skin lesions were dose-related in incidence and severity, and consisted of ulcers, chronic active inflammation, acanthosis, and hyperkeratosis. Demyelination in the medulla oblongata was observed in the 500 mg/kg animals, and in seven 250 mg/kg females; the lesions were characterized by intramyelinic vacuoles arranged symmetrically around the medial medulla oblongata in the region of the tectospinal tract. The lesions were minimal in severity and there was no spinal cord involvement. The LOAEL for this study is 32 mg/kg-day; a NOAEL was not established (NTP, 1992; Melnick et al., 1994a). [Kl. score = 1]

Male and female B6C3F$_1$ mice were given daily dermal applications of 0, 80, 160, 320, 630, and 1,250 mg/kg diethanolamine, 5 days/week for 13 weeks. At 1,250 mg/kg, there were early deaths and reduced body weight gain. Skin lesions were seen in the ≥80 mg/kg groups, there was acanthosis at 80 mg/kg and with a dose-dependent increased incidence up to ulcerations, inflammation, and hyperkeratosis at the higher levels. Liver weights were increased in a dose-dependent manner in the ≥32 mg/kg groups and were associated with morphological alterations in the liver in the ≥32 mg/kg groups. Kidney weights were increased in a dose-dependent manner in the ≥32 mg/kg groups with an increased incidence of tubular necrosis only in the 1,250 mg/kg group. There was also degeneration in the heart and cytologic alterations in the salivary gland

in the 1,250 mg/kg group only. The LOAEL for this study is 80 mg/kg-day; a NOAEL was not established (NTP, 1992;Melnick et al., 1994b) [Kl. score = 1]

G. Genotoxicity

In Vitro Studies

Table 2 presents the results of the *in vitro* genotoxicity studies on diethanolamine.

Table 2: *In vitro* Genotoxicity Studies on Diethanolamine

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	2	Dean et al. (1985)
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	Haworth et al. (1983)
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	-	2	Myhr et al. (1986)
Chromosomal aberration (rat liver cells RL1 and RL4)	-	NA	2	Dean et al. (1985)
Chromosomal aberrations (CHO cells)	-	-	2	Loveday et al. (1989)
Sister chromatid exchange (CHO cells)	-	-	2	Loveday et al. (1989)

*+, positive; -, negative; NA, not applicable

In vivo Studies

Male and female B6C3F_1 mice were given daily dermal applications of 0, 80, 160, 320, 630, or 1,250 mg/kg diethanolamine for 13 weeks. There was no induction of micronuclei in the peripheral blood erythrocytes at any dose level (NTP, 1992; Witt et al., 2000) [Kl. score = 1].

H. Carcinogenicity

Oral
No studies are available.

Inhalation
No studies are available.

Dermal
Male and female F344/N rats were given dermal application of diethanolamine for 104 weeks. For males, the doses were 0, 16, 32 or 64 mg/kg-day; and for females, the doses were 0, 8, 16 or 32 mg/kg-day. There was no difference in survival rates between treated and control animals. Mean body weights were lower in the 64 mg/kg-day males from week 8 to 89 and in the 32 mg/kg-day females from week 97 compared to the control animals. The incidences of tumors was not increased in the treated groups compared to the controls. (NTP, 1999). [Kl. score = 1]

Male and female $B6C3F_1$ mice were given dermal applications of 0, 40, 80 or 160 mg/kg-day diethanolamine by dermal application for 104 weeks. There was reduced survival in the treated female mice (88, 66, 66, and 46% for the 0, 40, 80 and 160 mg/kg-day groups, respectively). This was attributed to liver tumors. No differences were seen in survival rates in the treated male mice compared to the controls. Mean body weights in the 80 and 160 mg/kg-day males were lower than those in the control animals after week 88. Mean body weights in the treated female mice were lower than those of the controls from week 73 (40 and 80 mg/kg-day) and week 53 (160 mg/kg-day).

The incidence of hepatocellular adenomas and of hepatocellular adenomas and carcinomas (combined) were significantly increased in all male and female dose groups, while the incidences of hepatoblastoma was increased in the mid- and high-dose groups. In the female mice, the incidences of hepatocellular neoplasms were significantly higher in all dosed groups compared to the control. Non-neoplastic lesions were seen only in the liver of all male and female dose groups and consisted of cytoplasmic alteration, characterized by mild to moderate enlargement of centrilobular hepatocytes, and syncytial alteration, characterized by scattered hepatocytes with three or more small nuclei.

The incidence of renal tubule adenomas was also increased in males with a positive trend, but the incidences of carcinoma and hyperplasia did not follow this pattern. A step section evaluation found additional adenomas and hyperplasias in all treated male groups. The combined analysis of single and step sections indicated a dose-related increase in the incidence of renal hyperplasia and renal tubule adenoma or carcinoma (combined), and increase in the incidences of renal tubule adenoma in male mice (NTP, 1999). [Kl. score = 1]

Mode-of-Action for Mouse Liver Tumors in DEA-exposed Mice
Effects of DEA on choline homeostasis

Dietary choline deficiency or deprivation induces liver tumors in rodents (Newberne *et al.*, 1982). In contrast, dietary supplementation of choline with or without methionine reduces the incidence of liver tumors in carcinogen-treated mice (Fullerton *et al.* 1990; Newberne *et al.*, 1990). DEA is structurally similar to ethanolamine and choline, important endogenous precursors for normal membrane structure and function. Choline is also oxidized to betaine, an essential methyl group donor in 1-carbon metabolism. The mechanisms by which choline deficiency is thought to be carcinogenic include enhanced cell proliferation, altered methylation status, and altered signal transduction (Rogers, 1995; Zeisel, 1996; Zeisel and Blustjazn, 1994). The development of intracellular choline deficiency as the mode of action by which DEA cause the mouse liver tumors observed in the NTP bioassay is supported by the following experimental evidence:

1. $B6C3F_1$ mice dosed dermally with 160 mg/kg DEA, 5 days/week for 2 weeks showed a marked decrease in choline metabolites and S-adenosylmethionine (SAM) levels in their livers similar to animals kept on a choline-devoid diet, indicating the development of choline deficiency. These effects were reversed following a 2-week recovery period (Lehman-MeKeeman *et al.*, 2002). A significant reduction in the hepatic levels of choline metabolites, including choline, phosphocholine, and glycerophospho-choline, and SAM levels was also reported by Stott *et al.* (2000) with $B6C3F_1$ mice dosed in a similar regimen with DEA via dermal and/or oral routes.

2. $B6C3F_1$ mice have a much lower ability than C57Bl/6 mice to maintain nascent methylation capacity, a characteristic that is believed to contribute to a higher spontaneous liver tumor incidence in $B6C3F_1$ mice (Counts *et al.*, 1996). In a study by Lehman-McKeeman *et al.*, (2002), choline deficiency, as evidenced by changes in phosphocholine concentrations, was produced in both strains of mice. However, unlike the $B6C3F_1$ mouse, DEA did not alter SAM concentrations in the C57Bl/6 strain.

3. DEA is incorporated into rat liver phospholipids (Barbee and Hartung, 1979; Mathews *et al.*, 1995) and can alter the biosynthesis of hepatic phosphatidylethanolamine and phosphatidylcholine (PC). In cultured cells, DEA inhibited cellular uptake of choline, decreased PC synthesis, and became incorporated into phospholipid fractions. These *in vitro* effects were prevented by culturing cells in the presence of excess choline (Lehman-McKeeman and Gamsky, 1999).

4. DEA caused morphological transformation in Syrian hamster embryo (SHE) cell transformation assay. However, this response was prevented when SHE cells were cultured in a medium containing excess choline (Lehman-McKeeman and Gamsky, 2000).

5. DNA synthesis was increased in mouse and rat, but not human, hepatocytes incubated with DEA. Incubation of mouse and rat, but not human, hepatocytes in medium containing reduced choline increased DNA synthesis. Mouse and rat

hepatocytes incubated in medium with excess choline reduced DEA-induced DNA synthesis to control levels or below (Kamendulis and Klaunig, 2005).

6. DNA hypomethylation in GC-rich promotor regions observed in primary mouse hepatocytes which have been treated with DEA are similar to those caused by choline-deficient medium (Bachman *et al.*, 2005).

In situ formation of N-nitrosodiethanolamine

DEA is a secondary amine and may react with a nitrosating agent under certain conditions to form N-nitrosodiethanolamine. This nitrosoamine has been shown to be mutagenic *in vitro* and cause liver tumors in rats and doses of 2 mg/kg-day and higher (ECETOC, 1990). Rats given high, often toxic, oral bolus doses of DEA and nitrite have shown or inferred to produce N-nitrosodiethanolamine (Preussman *et al.*, 1981; Yamamoto *et al.*, 1995). Studies by Stott *et al.* (2000) showed, however, that mimicking the dosing conditions in the NTP study (160 mg/kg DEA dermally) and drinking water supplemented with 170 ppm sodium nitrite to favor nitrosation did not result in N-nitrosodiethanolamine formation in the gastric contents, blood or urine of mice. The findings of Stott *et al.* (2000) suggest that the mouse liver tumors observed in the NTP bioassay were unlikely due to *in situ* nitrosamine formation.

Relevance to Humans

There are marked species differences in susceptibility to choline deficiency, with rats and mice being far more susceptible than other species including humans (Zeisel and Blusztajn, 1994). Rats and mice have a higher dietary choline requirement than humans in large part because rodents oxidize choline more rapidly than humans (Sidransky and Farber 1960). DEA was carcinogenic in mice, but not in rats, in the NTP dermal carcinogenicity studies. The fact that DEA was not carcinogenic to rats, a species highly susceptible to choline deficiency, should be an important consideration in the overall evaluation of human cancer risk. DEA is less readily absorbed across rat skin than mouse skin, and the resulting blood and tissue concentrations of DEA are at least three-times lower in rats than in mice at similar dosages (Mathews *et al.*, 1997). Lehman-McKeeman *et al.*, (2002) determined the NOAEL for DEA-induced choline deficiency in mice (based on phosphocholine concentrations) to be 10 mg/kg-day. Thus, there is a critical concentration of DEA that must be reached in order to affect choline homeostatis. In the rats, the lack of a carcinogenic response suggests that it is unlikely that exposure to DEA reached this concentration or that rats are not as susceptible as mice to the effects of DEA on hepatic choline metabolism. Overall, the results suggest that the hepatocarcinogenic effects of DEA in mice are not predictive of similar susceptibility in other laboratory animals or humans. As noted by ECHA, “mechanistic research specifically on DEA indicates that, to the extent DEA can potentially induce tumours in mice, it does so by a mechanism that is not relevant to humans. Therefore, based on the available data, DEA is not considered carcinogenic for humans.”

I. Reproductive Toxicity

No specific reproductive toxicity studies have been conducted on diethanolamine by any route of exposure.

In the NTP 13-week drinking water study, F344 rats were given 0, 160 (females only), 320, 630, 1,250, 2,500 or 5,000 ppm (males only) diethanolamine. All high-dose males and 3/10 of the 2,500 ppm males showed testicular degeneration; male rats in the higher dose groups also had atrophy of the seminal vesicles and prostate glands. Testis and epididymal weights in the ≥1,250 ppm males were decreased and were associated microscopically with degeneration of seminiferous epithelium, as well as hypospermia and reduced sperm motility in the ≥2,500 ppm males. The NOAEL for reproductive effects in males was 630 ppm (corresponding to 48 mg/kg-day). There were no effects noted in the female reproductive organs (NTP 1992; Melnick *et al.* 1994b).

In a 90-day inhalation study, some of the male Wistar rats exposed whole-body to 400 mg/m^3 showed diffuse testicular atrophy accompanied by oligozoospermia in the epididymides, and slight prostate atrophy (ECHA).

J. Developmental Toxicity

Oral

A Chernoff-Kavlok screen was conducted on diethanolamine. Initially, four female CD-1 mice were given by oral gavage 0, 200, 380, 720, 1,370, 2,605, and 2,605 mg/kg diethanolamine during GD 6-15; a subsequent study was conducted which consisted of dosing 50 female CD-1 mice with 450 mg/kg during GD 6-15. Mortality was seen at ≥720 mg/kg, with 100% mortality in the ≥1,370 mg/kg groups. Dams dosed with ≥200 mg/kg showed clinical signs of intoxication. There was no mortality in the 450 mg/kg dams; nor was there any effect on litter size and pup birth weight, but the number of viable litters, the percent of pup survival, and pup weight gain were reduced (York *et al.* 1988). Kl. score = 2]

Female SD rats were dosed by oral gavage with 0, 50, 125, 200, 250, or 300 mg/kg diethanolamine from GD 6-19. All dams in the 300 mg/kg group had to be killed early due to excessive toxicity. At 200 and 250 mg/kg, the dams exhibited either morbidity or died. Water intake was affected early in the gestation period in the 125 and 250 mg/kg dams; it was comparable to controls after GD 12. Reduced maternal body weight and weight change, as well as food intake, were seen in the ≥200 mg/kg dose groups. The ≥125 mg/kg dams had increased absolute kidney weights on postnatal day (PND) 21. There were no maternal effects in the 50 mg/kg dams. There was postimplantation deaths at ≥200 mg/kg on PND 0 and increased early postnatal mortality (PND 0-4) in the ≥125 mg/kg dose groups. Pup body weight was reduced at ≥200 mg/kg, with females affected more than males. Pup body weight gain was predominantly reduced during the early postnatal period. There were statistically significant differences at the end of the

lactational period, which were flawed by the low number of animals. The NOAEL for maternal and postnatal developmental (screening) toxicity was 50 mg/kg-day (Price *et al.* 2005). [Kl. score = 2]

Inhalation

Pregnant female Wistar rats were exposed by inhalation to 0, 10, 50, or 200 mg/m^3 diethanolamine 6 hours/day on GD 6 to 15. Maternal toxicity was seen at 200 mg/m^3; there were vaginal hemorrhages in 8/21 pregnant rats on GD 14. There was also a markedly increased number of fetuses with skeletal variations (mainly cervical ribs) in the 200 mg/m^3 exposed group. The NOAEC for maternal and developmental toxicity is 200 mg/m^3 (ECHA). [Kl. score = 1]

Dermal

Pregnant female SD rats were given dermal applications of 0, 150, 500, or 1,500 mg/kg diethanolamine from GD 6 to 15. There was a dosing discrepancy and mid-dose was adjusted from 500 to 380 mg/kg. There was moderate skin irritation in the 380 mg/kg group, and severe skin irritation in the 1,500 mg/kg group. Body weight gain was lower in the 1,500 mg/kg group, and absolute and relative kidney weights were increased in the ≥380 mg/kg group All treated groups exhibited hematological effects that included anemia, abnormal red cell morphology (poikilocytosis, anisocytosis, polychromasia), and decreased platelet count. The 1,500 mg/kg group also had increased lymphocytes and total leukocytes. There were no treatment-related effects on body weight or incidences of malformations/abnormalities. In the 1,500 mg/kg litters, there were increased incidences of six skeletal variations involving the axial skeleton and distal appendages. The skeletal variations included poor ossification in the parietal bones; cervical centrum #5 and thoracic centrum #10; lack of ossification in all proximal hindlimb phalanges and some forelimb metacarpals; and callused ribs. The NOAELs for maternal and developmental toxicity are 150 and 380 mg/kg-day (Marty et al., 1999). [Kl. score = 2]

Pregnant female New Zealand rabbits were given dermal applications of 0, 35, 100, or 350 mg/kg diethanolamine on GD 6 to 18. At 350 mg/kg, maternal toxicity consisted of marked skin irritation, reduced feed consumption, and color changes in the kidneys. There were no hematologic changes. Body weight gain was reduced in the 100 mg/kg group. There was no evidence of developmental toxicity at any dose level. The NOAELs for maternal and developmental toxicity are 35 and 350 mg/kg-day (Marty et al., 1999). [Kl. score = 2]

K. Immunotoxicity

Female F344 rats were given oral gavage doses of 0, 50, 100, or 200 mg/kg diethanolamine for 14 days. Body weights and/or body weight changes were significantly decreased in the ≥100 mg/kg dose groups; liver and kidney weights were increased in a dose-dependent manner. A dose-dependent increase in urea nitrogen

was seen in all dose groups. Erythrocytes, hematocrit, hemoglobin and reticulocytes were dose-dependently decreased. The reticulocytes were the most sensitive erythroid parameter, which was decreased at all dose levels. Besides an increase in the proliferative response to allogenic cells (MLR), several immune functional assays were decreased including the natural killer cell response and the cytotoxicity of resident macrophages. Conversely, the cytotoxicity of peptone-elicited macrophages was increased. The LOAEL was 50 mg/kg-day based on a significant decrease in reticulocyte number and increase in urea nitrogen (Munson *et al.* 1992a). [Kl. score = 2]

Female B6C3F_1 mice were given oral gavage doses of 0, 100, 300, or 600 mg/kg diethanolamine for 14 days. There was no effect of body weights. The liver weights were increased and red blood cell count parameter were dose-dependently decreased at all dose levels. Diethanolamine treatment increased the number of B-cells, decreased the number of CD4+CD8- (18%) T-cell subsets. A dose-dependent decrease in the antibody-forming cell response to sheep erythrocytes at the high-dose was seen, as well as a decrease in the cytotoxic T-cell response at the highest effector/target ratio. The cytotoxicity of resident macrophages was decreased, but the cytotoxicity of resident macrophages stimulated with gamma interferon was not affected nor the cytotoxicity of peptone-elicited macrophages with or without stimulation. Among the three host resistance studies, a decrease in host resistance was observed to *Streptococcus pneumonia* and in the B16F10 melanoma tumor model. The LOAEL for this study was considered to be 100 mg/kg-day based on significantly reduced cytotoxic T lymphocytes (CTL) activity, an increase in tumor burden following challenge with the B16F10 melanoma tumor and a clear decrease in red blood cell parameter at the lowest dose (Munson *et al.* 1992b). [Kl. score = 2]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for diethanolamine 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

In a 13-week study conducted by the National Toxicology Program, F344 rats were given diethanolamine in their drinking water for 13 weeks. The doses were 0, 25, 48, 97, 2,202, or 436 mg/kg-day for males; and 0, 14, 32, 57, 124, or 242 mg/kg-day for females. The most sensitive endpoints were the microcytic anemia in both sexes and kidney effects in females (weight, nephrotoxicity) and males (weight). The LOAELs were 25 and 14 mg/kg-day) for males and females, respectively (NTP 1992; Melnick et al., 1994a).

In a 13-week study conducted by the National Toxicology Program, B6C3F_1 mice were given diethanolamine in their drinking water for 13 weeks. The doses were 0, 104, 178, 442, 807, or 1,674 mg/kg-day for males; and 0, 142, 347, 884, 1,154, or 1,128 mg/kg-day for females. The most sensitive endpoint was the increase in liver weights with the corresponding histopathological changes. The LOAELs were 104 and 142 mg/kg-day in males and females, respectively (NTP, 1992; Melnick *et al.*, 1992b).

The lowest NOAEL of 14 mg/kg-day from the rat 13-week drinking water study 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) = 10
UF_{Sub} (subchronic to chronic) = 10
UF_D (database uncertainty) = 1

[maximum UF = 3,000]

Oral RfD = 14/3,000 = <u>0.005 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 = (0.005 x 70 x 0.1)/2 = <u>0.02 mg/L</u>

B. Cancer

Diethanolamine was not carcinogenic to rats in the two-year NTP dermal bioassay; but, in the mice, there was an increased incidence of liver tumors in males and females and kidney tumors in males (NTP, 1999). As discussed above, the mouse liver tumors from DEA exposure are unlikely to be predictive of the carcinogenic risk to humans based on choline deficiency as a mechanism of carcinogenesis. No mode-of-action has been proposed for the kidney tumors in male mice.

NICNAS conducted a human health tier III assessment on diethanolamine (NICNAS). Regarding the classification for carcinogenicity, NICNAS concluded that "[t]he data on the mode of action are insufficient to conclude that diethanolamine-induced tumours in mice are relevant for humans and, therefore, based on the available information, diethanolamine is not classified for carcinogenicity."

Thus, a cancer reference value for diethanolamine was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Diethanolamine does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Diethanolamine exhibits moderate acute toxicity to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

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

Table 3: Acute Aquatic Toxicity Studies on Diethanolamine

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-h LC_{50}	460	2	ECHA
Pimephales promelas	96-h LC_{50}	1,460*	2	Mayes et al. (1983)

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-h LC_{50}	1,664	2	ECHA
Lepomis macrochirus	48-h LC_{50}	1,850	2	Turnbull et al. (1954)
Carassius auratus	24-h LC_{50}	>5,000 (neutralised) 800 (non-neutralised)	2	Bridlé et al. (1979)
Ceriodaphnia dubia	48-h EC_{50}	30.1 (24°C) 89.9 (20°C)	2	Cowgill et al. (1985)
Daphnia magna	48-h EC_{50}	55	2	LeBlanc (1980)
Daphnia magna	48-h EC_{50}	171	2	Zurita et al. (2005)
Pseudokirchneriella subcapitata	72-h EC_{50} (growth rate)	9.5 (Test 1) 19 (Test 2)	2	ECHA
Desmodesmus subspicatus	72-h EC_{50}	14.9 (growth rate) 6.2 (biomass)	2	ECHA
Desmodesmus subspicatus	72-h EC_{50}	107.3 (growth rate) 74.5 (biomass)	2	ECHA
Chorella vulgaris	72-h EC_{50}	778 (growth rate)	2	ECHA

*Geometric mean of 96-h LC_{50} values of fry, juvenile, and subadult fish. Not neutralized.

Chronic Studies

Table 4 lists the results of chronic aquatic toxicity studies on diethanolamine.

Table 4: Chronic Aquatic Toxicity Studies on Diethanolamine

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Daphnia magna	EC_{10} NOEC	1.05 0.76	1	ECHA
Pseudokirchneriella subcapitata	EC_{10} (growth rate)	1.4 (Test 1) 1.1 (Test 2)	2	ECHA
Desmodesmus subspicatus	EC_{10} (neutralized)	2.4 (growth rate) 2.0 (biomass)	2	ECHA
Desmodesmus subspicatus	EC_{10} (non-neutralized)	85.7 (growth rate) 41.3 (biomass)	2	ECHA
Pseudokirchneriella subcapitata	7-d NOEC	10	2	ECHA

C. Terrestrial Toxicity

In an earthworm (*Eisenia Andrei, Eisenia fetida*, or *Lumbricus terrestris*) study, the 35-day LC_{50} was 4,141 mg/kg soil dry weight (mortality); the 63-day EC_{50} was 776 mg/kg soil dry weight (reproduction); and the 63-day EC_{25} was 171 mg/kg soil dry weight (reproduction) (ECHA). [Kl. score = 2]

In a springtails (*Folsomia candida*) study, the 28-day LC_{50} was 8,301 mg/kg soil dry weight (mortality); the 28-day EC_{50} was 4,205 mg/kg soil dry weight (reproduction); and the 28-day EC_{25} was 2,102 mg/kg soil dry weight (reproduction) (ECHA). [Kl. score = 2]

D. Calculation of PNEC

The PNEC calculations for diethanolamine 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 (460 mg/L), *Daphnia* (30.1 mg/L), and algae (9.5 mg/L). Results from chronic studies are also available for two trophic levels, with the lowest EC_{10} value being 1.1 mg/L for *Daphnia* and algae. On the basis that the data consists of short-term results from three trophic levels and long-term results from three trophic levels, an

assessment factor of 50 has been applied to the lowest reported EC_{10} of 1.1 mg/L for algae. The $PNEC_{water}$ is 0.02 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 0.016 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.99/1280) \times 1000 \times 0.02$
$= 0.016$

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]

$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.4/1000 \times 2400]$
$= 0.99$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$
$= 10 \times 0.04$
$= 0.4$

Where:
K_{oc} = organic carbon normalized distribution coefficient (L/kg). The K_{oc} for diethanolamine (as the charged molecule) was calculated to be 10 L/kg.
F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

Experimental results are available for chronic toxicity on two trophic levels. Although $E(L)C_{50}$ values are available from these studies, there are no EC_{10} or NOEC values. Therefore, the PNECsoil was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.027 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.2/1500) \times 1000 \times 0.02$
$= 0.027$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 10 \times 0.02$
$= 0.2$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for diethanolamine (as the charged molecule) was calculated to be 10 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).

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

The estimated BCF value for diethanolamine calculated from a QSAR model is 2.3; thus, it does not meet the criteria for bioaccumulation.

The EC_{10} or NOEC values from the chronic aquatic toxicity studies on diethanolamine are >0.1 mg/L. Thus, diethanolamine does not meet the screening criteria for toxicity. In a mouse dermal carcinogenicity study, there was an increased incidence of liver tumors in males and females and kidney tumors in males. However, both ECHA and NICNAS has concluded that "[t]he data on the mode of action are insufficient to conclude that diethanolamine-induced tumours in mice are relevant for humans and, therefore, based on the available information, diethanolamine is not classified for carcinogenicity." Thus, diethanolamine does not meet the criteria for toxicity.

Therefore, diethanolamine is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Acute Toxicity Category 4 [Oral]
Skin Irritant Category 2
Eye Damage Category 1
STOT RE Category 2 [Target organs: liver, blood, kidney]

[Aquatic Acute Category 2]

B. Labelling

Danger

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
Remove contaminated clothing. Wash thoroughly with soap and water.

Inhalation
If inhaled, remove from area to fresh air. Give artificial respiration if victim is not breathing. Get medical attention.

Ingestion
Rinse mouth with water and then drink plenty 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
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: nitrogen oxides, carbon monoxide, carbon dioxide.

Special Protective Equipment for Firefighters
Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions
Use appropriate protective equipment. Handle in accordance with good industrial hygiene and safety practice. 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
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 diethanolamine.

Engineering Controls
Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection:
Use respiratory protection in case of vapor or aerosol release.

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

Diethanolamine 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.

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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.

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DISODIUM OCTABORATE TETRAHYDRATE

This dossier on disodium octaborate tetrahydrate presents the most critical studies pertinent to the risk assessment of disodium octaborate tetrahydrate 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): [Disodium octaborate]: disodium;(9,11-dioxido-5-oxoboranyloxy-2,4,6,8,10,12,13-heptaoxa-1,3,5,7,9,11-hexaborabicyclo[5.5.1]tridecan-3-yl)oxy-oxovorane

CAS RN: [redacted] (anhydrous form)

Molecular formula: $Na_2B_8O_{13}$

Molecular weight: 340.45 g/mol

Synonyms: Disodium octaborate tetrahydrate; disodium octaborate

SMILES: (disodium octaborate): B(=O)OB1OB2OB(OB(OB(O2)OB(O1)OB=O)[O-])[O-].[Na+].[Na]

Chemical Name (IUPAC): [Disodium octaborate]: disodium;(9,11-dioxido-5-oxoboranyloxy-2,4,6,8,10,12,13-heptaoxa-1,3,5,7,9,11-hexaborabicyclo[5.5.1]tridecan-3-yl)oxy-oxovorane

CAS RN: [redacted] (hydrated form)

Molecular formula: $Na_2B_8O_{13}\bullet 4H_2O$

Molecular weight: 412.4 g/mol

Synonyms: Disodium octaborate tetrahydrate; disodium octaborate

SMILES: (disodium octaborate): B(=O)OB1OB2OB(OB(OB(O2)OB(O1)OB=O)[O-])[O-].[Na+].[Na+]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of disodium octaborate tetrahydrate*

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	White, colourless, odourless, crystalline powder*	1	ECHA
Melting Point	>1,000°C @ 101.3 kPa	1	ECHA
Boiling Point	Study not relevant because the substance is a solid that melts >300°C	-	ECHA

Property	Value	Klimisch Score	Reference
Density	1874 kg/m^3 (temperature not indicated)	1	ECHA
Vapour Pressure	9.9×10^{-17} Pa @ 25°C	1	ECHA
Partition Coefficient (log K_{ow})	Not applicable because this substance is inorganic	-	ECHA
Water Solubility	223.65 g/L @ 20°C	1	ECHA
Flash Point	Not applicable because this substance is inorganic	2	ECHA
Auto flammability	Not a self-heating substance	1	ECHA
Viscosity	Not applicable because the substance is a solid	-	ECHA
Henry's Law Constant	Not available	2	ECHA

* CAS RN: [redacted] (anhydrous form).

Boron is almost exclusively found in the environment in the form of boron-oxygen 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, the chemicals in this group will dissociate and/or hydrolyse to release boron as boric acid [B(OH) (also formulated as H BO)] and/or borate anions (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 disodium octaborate tetrahydrate to B-equivalents is 0.2096.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Disodium octaborate tetrahydrate as a natural element is not degradable. It 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

Chemicals in this group 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 to9.0) (NICNAS, 2019).

C. Biodegradation

Degradation is not applicable to inorganic borates, such as disodium octaborate tetrahydrate. 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 disodium octaborate tetrahydrate 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) [Kl.score=2]. The chemistry of boron in soils and aquatic systems is simplified by the absence of oxidation- reduction reactions or volatilization. Redox processes can mobilize 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, disodium octaborate tetrahydrate is 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”. A BCF of <0.1 was reported in Chinook salmon fed boron-supplemented diets for 60 to 90 days (Hamilton & Wiedmeyer, 1990).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Disodium octaborate tetrahydrate exhibits low acute toxicity by the oral and dermal routes. It is not a skin or eye irritant, or a skin sensitizer. Toxicity studies on boric acid, borax (disodium tetraborate decahydrate), and boron oxide have been used to read-across to disodium octaborate tetrahydrate. This is justified because, in aqueous media at physiological pH, all of these inorganic borate compounds will predominantly exist as un-dissociated boric acid. The developing fetus 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 fetal body weight; and malformations and variations. Repeated inhalation exposure to 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. Acute Toxicity

The oral LD_{50} of disodium octaborate tetrahydrate in rats is 2,550 mg/kg (ECHA) [Kl.score=1]. The oral LD_{50} of boric acid in rats is 3,450 mg/kg (ECHA) [Kl.score=1]. The oral LD_{50} of anhydrous boric acid in rats is >2,500 mg/kg [Kl.score=1].

There are no acute inhalation studies on disodium octaborate tetrahydrate. 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) [Kl.score=1]. In another study, the 4-hour inhalation LC_{50} value for boric acid in rats was >2.03 mg/L (ECHA) [Kl.score=1]. The 4-hour inhalation LC_{50} value for disodium tetraborate pentahydrate in rats is >2.04 mg/L (ECHA) [Kl.score=1].

The dermal LD_{50} of disodium octaborate tetrahydrate in rabbits is >2,000 mg/kg (ECHA) [Kl.score=1]. The dermal LD_{50} of boric acid in rabbits is >2,000 mg/kg (ECHA) [Kl.score=1]. The dermal LD_{50} of sodium tetraborate pentahydrate in rabbits is >2,000 mg/kg (ECHA) [Kl.score=1].

C. Irritation

Application of 0.5 g of disodium octaborate tetrahydrate to the skin of rabbits for 4 hours under occlusive conditions was not irritating. The mean of the 24-, 48-, and 72-hour scores were 0.22 for erythema and 0.00 for edema (ECHA) [Kl.score=1].

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 edema (ECHA) [Kl.score=1]. Application of 0.5 g of sodium tetraborate pentahydrate to the skin of rabbits for 4 hours under occlusive conditions was not irritating. The mean erythema and edema scores were 0.00 (ECHA) [Kl.score=2].

Disodium octaborate tetrahydrate was not considered to be an eye irritant when 0.053 or 0.049 g was instilled into the eyes of rabbits (ECHA) [Kl.score=1]. Instillation of 0.08 mL boric acid into the eyes of rabbits was slightly irritating. The mean of 24-, 48-, and 72-hour scores were 0.22 for corneal opacity, 0.22 for iridial lesions, 2.8 for conjunctival redness, and 1.89 for chemosis (ECHA) [Kl.score=1].

D. Sensitisation

Disodium octaborate tetrahydrate was not a skin sensitizer to guinea pigs in a Buehler test (ECHA) [Kl.score=1].

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

E. 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 (EPA, 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) [Kl.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 (EPA, 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 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 of 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) [Kl.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 (EPA, 2004). There was mortality (8/10 males; 6/10, females) in the 20,000 ppm, 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 hematopoiesis 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) [Kl.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 (EPA, 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 of 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) [Kl.score=2].

Male and female B6C3F_1 mice were given 0, 2,500 or 5,000 ppm boric acid in their feed for 103 weeks (NTP, 1987). These dose levels were equivalent to 0, 275 or 550 mg/kg-day boric acid or 0, 48 or 96 mg B/kg-day (EPA, 2004). There was reduced survival in the male mice, which was significantly different from the controls in the 2,500 ppm mice after week 63 and in the 5,000 ppm mice after week 84. The survival rates by the end of the study were 82, 60 and 44% in the 0, 2,500, and 5,000 ppm males, respectively, and 66, 66 and 74% in the 0, 2,500, and 5,000 ppm females, respectively. Mean body weights were 10-17% lower in the 5,000 ppm animals after 32 (males) or 52 (females) weeks compared to the controls There was testicular atrophy and interstitial cell hyperplasia in the testes of the 5,000 ppm males. A dose-related increase in the incidences of splenic lymphoid depletion in male mice was also observed. NTP considered this lesion to be associated with stress and debilitation, and it is reflected in the increased mortality in these groups of male mice. The NOAEL for this study is <2500 ppm (NTP, 1987) [Kl.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 localized effects (irritation) is 175 mg/m^3 (ECHA) [Kl.score=2].

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

There are no *in vitro* genotoxicity studies on disodium octaborate tetrahydrate. The *in vitro* genotoxicity studies on boric acid are presented in Table 2.

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 disodium octaborate tetrahydrate.

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) [Kl.score=1].

G. Carcinogenicity

Oral

No studies have been conducted on disodium octaborate tetrahydrate.

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; EPA, 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].

Inhalation

No studies are available.

Dermal

No studies are available.

H. Reproductive Toxicity

A three-generation reproductive toxicity study was conducted in albino rats (strain not specified) 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, 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 most 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 albino rats (strain not specified) with disodium tetraborate decahydrate. 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, 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. Estrous 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].

I. Developmental Toxicity

Oral

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 fetal 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 0, 0.025, 0.005, 0.075, 0.1 or 0.2% boric acid in their feed 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, fetal 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 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 0, 0.1, 0.2 or 0.4% boric acid in their diet 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. Fetal body weights were reduced in the ≥0.2% groups, and there were increased incidences of resorptions and malformed fetuses 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) [Kl.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 fetuses was increased (73% versus 0%), and live litter size was reduced (2.3 fetuses versus 8.8). Thus, there were only 14 live fetuses (6 live litters) available for evaluation in the 250 mg/kg group. The percentage malformed fetuses/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) [Kl.score=1].

Inhalation

No studies are available.

Dermal

No studies are available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for disodium octaborate tetrahydrate 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 developing fetus and the testes are the two most sensitive targets of boron toxicity in multiple species (EPA, 2004; ECHA, 2010). 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 (EPA, 2004). The developmental effects from boron exposure include high prenatal mortality; reduced fetal body weight; and malformations and variations (EPA, 2004).

The U.S. Environmental Protection Agency (U.S. EPA) derived an Oral Reference Dose (RfD) for boron of 0.2 mg B/kg-day (U.S. EPA 2004) based on developmental effects in rats from two studies (Price *et al.* 1996a; Heindel *et al.* 1992).

The RfD was derived using the benchmark dose (BMD) method ($BMDL_{05}$ from Allen *et al.* 1996) using a data derived uncertainty factor of 66. Decreased fetal body weight ($BMDL_{50}$ = 59 mg boric acid/kg-day or 10.3 mg B/kg-day) was considered by Allen *et al.* (1996) as the most suitable endpoint for developing a point of departure, because the benchmark doses calculated for the other endpoints (incidence of total malformations, enlarged lateral ventricles in the brain, shortening of rib XIII, and variations of the first lumbar rib) were higher.

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) = 10.42 [3.16, toxicodynamics; 3.3, toxicokinetics]
UF_H (intraspecies variability) = 6.32 [3.16, toxicodynamics; 2.0, toxicokinetics]
UF_L (LOAEL to NOAEL) = 1
UF_{Sub} (subchronic to chronic) = 1
UF_D (database uncertainty) = 1
Oral RfD = 10.3/(7.9 × 6.3 × 1 × 1 × 1) = 10.3/66 = 0.2 mg B/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 = (0.2 × 70 × 0.1)/2 = 0.7 mg/L

B. Cancer

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

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Disodium octaborate tetrahydrate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Disodium octaborate tetrahydrate has 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

Table 3 lists the results of acute aquatic toxicity studies conducted on disodium octaborate tetrahydrate.

Table 3 Acute aquatic toxicity studies on disodium octaborate tetrahydrate

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Fathead minnow	96-hr LC_{50}	79.7	2	ECHA
Stonefly, Shortwing snowfly	96-hr LC_{50}	476	2	ECHA
Pseudokirchneriella subcapitata	72-hr 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 LC10 of 21.6 mg B/L was found for the fresh water fish *P. promelas* in a study according to EPA OPPTS 850.1400 (ECHA) [Kl.score=2].

Long-term effects (LC10/NOEC) on reproduction on freshwater vertebrates ranged from 6.6 to 32 mg B/L based on several well-accepted guideline studies (ECHA) [Kl.scores= 1 or 2].

Boric acid 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 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 below. 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/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*, LC10 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 (Warne et al. 2018), in this instance, a reliable NOEC of 2.8 mg/L was the most sensitive toxicity value for *P. subcapitata* (ANZG, 2021).

C. 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).

The avian toxicity studies conducted on disodium octaborate and boric acid are presented in Table 5.

Table 5: Avian toxicity studies on disodium octaborate and boric acid

Test Species	Test Substance	Endpoint	Results	Klimisch score	Reference
Mallard duck	Disodium octaborate	dietary LC_{50}	>2,100 mg B/kg food	1	EU, 2007
Bobwhite quail	Boric acid	dietary LC_{50}	>983 mg B/kg food	1	EU, 2007
Bobwhite quail	Disodium octaborate	Oral gavage LD_{50}	>527 mg B/kg bw	4	EU, 2007
Bobwhite quail	Disodium octaborate	dietary LC_{50}	>2,100 mg B/kg food	1	EU, 2007

D. Calculation of PNEC

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

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

No experimental toxicity data on sediment organisms are available. Due to the high water solubility of disodium octaborate tetrahydrate and its low partitioning to sediment, sediment toxicity testing for boron compounds is particularly challenging. 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 disodium octaborate tetrahydrate. 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 (IChEMS, 2022; ECHA, 2023).

Disodium octaborate tetrahydrate 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 to disodium octaborate tetrahydrate.

Disodium octaborate tetrahydrate is a water-soluble substance that is not expected to bioaccumulate. Limited data indicate that bioaccumulation (BCF values are low) is not significant in aquatic and terrestrial food chains. Thus, it does not meet the criteria for bioaccumulation.

The chronic aquatic toxicity data on disodium octaborate tetrahydrate has a NOEC > 0.1 mg/L. Thus, disodium octaborate tetrahydrate does not meet the criteria for toxicity.

The overall conclusion is that disodium octaborate tetrahydrate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H360FD:Reproductive Toxicant Category 1B

B. Labelling

Danger

According to the harmonised classification and labelling (ATP09) approved by the European Union, this substance may damage fertility and may damage the unborn child.

C. Pictogram

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

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

Swallowing small quantities (one teaspoon) will not cause any harm to adults. If larger amounts are swallowed, give two glasses of water to drink and seek medical attention. Never give anything by mouth to an unconscious person.

Notes to Physician

Observation only is required for adult ingestion of <5 grams. For ingestion of >5 grams, maintain adequate kidney function and force fluids.

B. Firefighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Disodium octaborate tetrahydrate is a flame retardant. It is not flammable, combustible, or explosive.

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.

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

Workplace Australia has not established an occupational exposure standard for disodium octaborate tetrahydrate.

[The workplace exposure standard for disodium tetraborate decahydrate (borax) in Australia is 5 mg/m^3 as an 8-hour TWA. The workplace exposure standard for disodium tetraborate pentahydrate in Australia is 1 mg/m^3 as an 8-hour TWA.]

Engineering Controls

Ensure adequate ventilation. Localized 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 exceed exposure limits.

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

Disodium octaborate tetrahydrate 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.

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ETHANOL

This dossier on ethanol presents the most critical studies pertinent to the risk assessment of ethanol in its use in coal seam gas extraction activities. This dossier does not represent an exhaustive or critical review of all available data. Ethanol consumption in alcoholic beverages is out of the scope of this dossier. 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Ethanol

CAS RN: [redacted]

Molecular formula: C_2H_6O

Molecular weight: 46.069

Synonyms: Ethyl alcohol, grain alcohol, alcohol, methylcarbinol, ethyl hydroxide, ethyl hydrate, algrain, alkohol, anhydrol

SMILES: CCO

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Ethanol

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colorless liquid with a mild odor.	2	ECHA
Melting point	-114°C	2	ECHA
Boiling point	78.2°C	2	ECHA
Density	0.789 g/cm^3 @ 20°C	2	ECHA
Vapor pressure	57.26 hPA @ 19.6°C	2	ECHA
Partition coefficient (log K_{ow})	-0.35 @ 24°C	2	ECHA
Water solubility	789 g/L @ 20°C	2	ECHA

Property	Value	Klimisch score	Reference
Flash point	13°C	2	ECHA
Auto flammability	>363 and <425°C	2	ECHA
Viscosity	1.17 mPa s @ 20°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Ethanol is readily biodegradable and not expected to bioaccumulate.

B. Biodegradation

Ethanol is readily biodegradable. The degradation of ethanol was approximately 74% and 84% (O_2 consumption) within 10 and 20 days, respectively, in a biodegradation test using a non-adapted domestic inoculum in a freshwater medium (ECHA) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for ethanol. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value from log K_{ow} of -0.35 is 2.199 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 1.045 L/kg.

D. Bioaccumulation

There are no bioaccumulation studies on ethanol. Ethanol is not expected to bioaccumulate based on a log K_{ow} of -0.35 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

Human health toxicological information was obtained from Inventory Multi-Tiered Assessment and Prioritisation (IMAP), which is an assessment framework conducted via Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS), unless otherwise cited. Statements regarding toxicity are based solely on the determination of applicable regulatory agency.

A. Summary

Ethanol has a low acute toxicity by the oral, dermal, and inhalation routes of exposure, as measured by lethality. Sublethal doses, however, have been shown to produce central nervous system depression, respiratory depression, and coma. Deaths were reported in rodent studies due to cardiorespiratory failure. Ethanol is not irritating to the skin, but it is slightly irritating to the eyes. Repeated exposures by the oral route have not resulted in any systemic toxicity to rodents, except from exposure to high doses. Evidence of the carcinogenicity of ethanol is confined to epidemiological studies assessing the impact of alcoholic beverage consumption. These do not indicate any such hazard exists from potential exposure to ethanol in the workplace or from the use of ethanol in consumer products (OECD, 2004). Ethanol is not genotoxic or mutagenic. Ethanol does not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity.

B. Acute Toxicity

Oral

The chemical has low acute toxicity by oral exposure in animal tests. The median lethal dose (LD50) in rats is >2000 mg/kg bw. Observed sub-lethal effects included central nervous system depression, e.g. inebriation, disturbances of gait, dose-related decreases in responses to painful stimuli, respiratory depression, and coma. Deaths were reported due to cardiorespiratory failure (OECD, 2005; HSDB; REACH).

Dermal

Few studies are available on the dermal toxicity of the chemical. A poorly documented rabbit study reported death in one of four animals following a dose of 20000 mg/kg bw. Although limited data are available, the apparent low dermal toxicity from this study is regarded as consistent with low uptake of ethanol through intact skin. The median lethal dose (LD50) in rats is greater than 2000 mg/kg bw. Observed sub-lethal effects were not reported for the study (OECD, 2005; REACH).

Inhalation

The chemical has low acute toxicity by inhalation exposure in animal tests. The lowest reported median lethal concentration (LC50) is 124.7 mg/L/four hours in rats. Observed sub-lethal effects included attempts to escape, reddish-watery eyes, nasal secretions, closing of eyelids, snout wiping, intermittent respiration, loss of pain reflex, abdominal position, and apathy (OECD, 2005; REACH).

C. Irritation

The chemical is not regarded as irritating to skin. The chemical is frequently applied to skin as a biocidal surgical wipe (70–80 % concentration) and as a component of

cosmetics, personal care, and household cleaning products. There appear to be few documented concerns regarding skin irritation arising from these uses. Direct contact of the eye with the liquid chemical causes immediate discomfort accompanied by reflexive closure of the eye. Even though the acute effect subsides rapidly and the recovery is complete, foreign body type discomfort may persist for a day or two. Although inhaling the chemical at 5000 ppm (9600 mg/m^3) has been reported as irritating in humans; lacrimation and coughing are only induced at a much higher concentrations (OECD, 2005).

Concentrations of the chemical attained in humans in the upper gastrointestinal tract after consumption of alcoholic beverages can cause local irritation.

The chemical produced irritant effects in several eye irritation studies in rabbits. While the severity of these effects was not consistent across all the studies, these were sufficiently severe in some studies to support classification, particularly under the Globally Harmonised System of Classification and Labelling of Chemicals.

D. Sensitization

The available data indicate that the chemical does not induce skin sensitisation in animals. An ear swelling study was used to examine the skin sensitising potential of ethanol. Ethanol was applied twice on the right ear after an induction procedure involving two scapular subcutaneous injection of adjuvant and multiple topical ethanol applications to the abdomen over a period of 14 days. The degree of contact hypersensitivity is deduced from ear swelling measured 24 and 48 hours after application. Ethanol was found not to cause any statistical increase in ear swelling, in contrast to 3 positive controls which all caused a statistically significant increase.

Data is also available from studies using ethanol as a vehicle. In a guinea pig maximisation study that used ethanol as a carrier solvent for the substance being tested (polyakylene glycol block copolymers) no positive reactions were obtained. It can be concluded that ethanol cannot have any significant skin sensitising properties since it was used as a solvent in this study at levels of up to 75%. A study was carried out to evaluate the effect of vehicles (e.g. ethanol) for use in the mouse local lymph node assay (LLNA), and their influence on the skin sensitization potential of fragrance materials. Groups of mice were treated with each test fragrance in ethanol (1:3 or 3:1 mixtures of the two), or with ethanol alone. Although there were no true control data for comparison with the ethanol-alone treated animals, the level of induced T-lymphocyte proliferation was low for ethanol when compared with that for fragrance materials known to be mild to moderate skin sensitizers, and comparable to other inert vehicles tested.

E. Repeated Dose Toxicity

Oral

Many repeated dose studies of chemical have been conducted in many species, predominantly with the aim of assessing adverse effects associated with the consumption of alcoholic beverages. Consequently, these are mostly conducted through oral exposure and with doses well in excess of those that might be encountered in occupational exposure or consumer products (OECD, 2005), or unintentional public exposures from environmental contamination.

In a 90-day study, SD rats were fed a mixture containing 16.25% USP ethanol at 3 dose levels (Kl =2). A single dose of 4 ml/kg of pure ethanol and water were used as controls. No significant differences were noted in body weight, haematology, opthamology, clinical chemistry or urine chemistry. Dose-related increases in liver to body weight ratios of female rats were seen at final sacrifice although the absolute liver weights of the high dose ethanol treated group, while significantly increased relative to the 100% ethanol treated group, was not different from the water control group. In addition, increased liver weights were observed in the male rats. Significant increases in kidney weights were observed in the mid and high dose groups. No histopathologic findings were attributed to ethanol treatment with exception of increased minimal focal to multifocal renal tubular epithelial hyperplasia in the high dose 20 ml/kg mixture containing 16.25% ethanol and the 100% USP ethanol control treated rats versus the water treated controls. It should be noted however that renal tubular epithelial hyperplasia is a common incidental finding in laboratory rats and it is uncertain whether the higher incidence of this lesion in the ethanol dosed rats compared with water controls is due to a random variation or to ethanol. Gonadal tissues were examined for both gross pathology and histopathology and no treatment-related effects were detected. The NOAEL for the study was determined at 10 ml/Kg for a mixture containing 16.25% ethanol for increased kidney weight and renal tubular epithelial hyperplasia in males (equivalent to 1.73g/kg). The LOAEL for this study was determined at 4 ml/kg for 100% USP ethanol (3.16g/kg) for increased kidney weight and renal tubular epithelial hyperplasia in males.

Inhalation

As properly conducted studies in animals are not available, there are no valid data on the effects of repeated inhalation exposure to the chemical. However, limited information is presented below to indicate that the chemical is likely to be of low toxicity following repeated inhalation exposure.

Dermal

No data are available.

F. Genotoxicity

Overall, ethanol is not considered to be mutagenic or genotoxic (OECD, 2005; REACH).

In Vitro Studies

Table 2: *In vitro* Genotoxicity Studies on Ethanol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	1	Zeiger et al., 1992
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	-	2	Wangenheim and Bolcsfoldi, 1988

*+, positive; -, negative;

In Vivo Studies

Several in vivo micronucleus assays have assessed the potential for the chemical to induce damage to chromosomes of erythroblasts. No effect was reported in rats when administered 5 % of the chemical (approximately 4 g/kg bw/day) in drinking water, or in mice at up to 40 % (approximately 31 g/kg bw/day). Chemical-related mortality was observed in the latter study. Marginally statistically significant increases in the incidence of micronucleated bone marrow erythrocytes were reported in rats fed for six weeks with a diet containing ethanol at 12–16 g/kg/day. Although there is very limited evidence that the chemical induces micronuclei in the bone marrow of rodents, the chemical has the potential to induce micronuclei in bone marrow erythrocytes at very high doses. KI scores were not listed for these studies (IMAP, 2014).

G. Carcinogenicity

Oral

A significant number of carcinogenicity studies have been identified, but the majority of these are only partial studies designed to look at aspects of the carcinogenic hazard resulting from drinking ethanol containing beverages and are judged unreliable for assessing the cancer hazard of ethanol as a chemical substance. Only two studies were identified as reliable.

In a study to assess the carcinogenic potential of ethanol, groups of rats were exposed to ethanol at concentrations of 1% and 3% in a liquid semi-synthetic diet for a period of 2 years, approximately equivalent to 1 and 3g/kg respectively. Each dose group used a control matched for caloric content using glucose. From the data it was possible to conclude that ethanol did not cause any treatment related increase in tumours and the no effect level was identified as > 3g/kg.

In a study designed and conducted to determine the long-term toxicity and carcinogenicity of urethane in ethanol, groups of mice were exposed to ethanol at concentrations up to 5% in drinking water for a period of 2 years, with control groups consuming drinking water alone. The only significant cancer finding was a dose related increase in the rate of hepatocellular adenomas for male mice in comparison with the concurrent controls. The species of mouse used in this study is known to have a high spontaneous incidence of these tumours. In comparison to historic controls, the incidence rate in the ethanol dosed animals was not high and the controls were significantly lower (although it should be noted that no historic control information was available for animals on the study diet used.) Analysis of the data using the Benchmark dose approach showed a BMDL10 of 1400mg/kg for liver adenomas in males. There was no significant increase in tumour rates (including mammary tumours) in females.

The International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence in humans and experimental animals to establish carcinogenicity of alcohol consumption and ethanol, respectively. It was also concluded that there is sufficient evidence in experimental animals to establish carcinogenicity of acetaldehyde (major metabolite of ethanol). Consequently, IARC has classified that 'alcohol consumption is carcinogenic to humans (Group 1)' and that 'ethanol in alcoholic beverages is carcinogenic to humans (Group 1)'. This conclusion was supported by an analysis of the expanded human dataset that carcinogenic effects appeared independent of the type of alcoholic beverage (IARC, 2010; IARC, 2012). As the use of the chemical in alcoholic beverages is not considered in this report, the above assessment of carcinogenicity of alcohol beverages may not be relevant to occupational exposure to the chemical or from using the chemical in consumer products (OECD, 2005). Furthermore, studies in animals conducted mostly through oral exposure at very high doses, exceeding the 'maximum tolerated dose', may be of little relevance when assessing risks associated with occupational exposure or using consumer products containing the chemical (OECD, 2005). Thus, classification as a carcinogen is not considered appropriate (IMAP).

Inhalation

No information available (IMAP, REACH).

H. Reproductive and Developmental Toxicity

The chemical does not show specific reproductive or developmental toxicity. Any reproductive and developmental effects were only observed secondary to maternal toxicity. As results of inhalation studies showed no developmental toxicity from chemical exposures even at maternally toxic doses, it can be concluded that deliberate oral consumption of alcoholic beverages is required for any reproductive or developmental toxicity (OECD, 2005).

The most reliable study (Kl = 1) performed to the most appropriate protocol and the one given the greatest weight as well as the key study is a two-generation study investigated the effects of 5%, 10% and 15% ethanol in drinking water in reproduction and fertility. Male and female CD-1 mice were continuously treated for 1 week prior to mating and for a 14-week breeding period followed by a 21-day holding period when they were separated and housed individually. The F1 offspring of the 15% ethanol pairs had fewer live pups per litter but ethanol treatment had no effect on the proportion of breeding pairs producing at least 1 litter during the continuous breeding phase or the number of litters per pair. The F1 offspring from the 15% group had decreased bodyweight at weaning and mating, and a decreased weight of testis, epididymides and seminal vesicles which was no longer evident when these were adjusted for body weight. There was also a significantly decreased percentage motile sperm but no changes in sperm concentration, and percentage of abnormal sperm or tailless sperm. When reproductive performance of F1 control and 15% ethanol-treated breeding pairs was assessed at 74 days of age, there was no significant difference in mating and fertility between the groups. However, adjusted live pup weight for the ethanol group was significantly reduced compared to controls which was likely due to generalized maternal toxicity.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for ethanol 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 lowest NOAEL from these studies is 1,730 mg/kg-day based on increased relative and absolute liver weight and absolute heart, liver, kidney and lung weight in male mice from a 90-day dietary study (1996). The NOAEL of 1,730 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) = 3
UF_D (database uncertainty) = 1

Oral RfD = 1730/(10 x 10 x 1 x 3 x 1) = 1730/300 = 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, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (6 x 70 x 0.1)/2 = 21 mg/L

B. Cancer

Evidence of the carcinogenicity of ethanol is confined to epidemiological studies assessing the impact of alcoholic beverage consumption. These do not indicate any such hazard exists from potential exposure to ethanol in the workplace or from the use of ethanol in consumer products (OECD, 2004). Therefore, no cancer reference value was derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Ethanol is a flammable liquid.

Ethanol does not exhibit the following physico-chemical properties:

- Explosivity
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Acute aquatic toxicity ranges from 275 to 15,300 mg/L, depending on species and exposure durations. While chronic toxicity ranges from 9.6 to 250 mg/L.

B. Aquatic Toxicity

<u>Acute Studies</u>

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

Table 3: Acute Aquatic Toxicity Studies on Ethanol

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-hr LC_{50}	15,300	2	ECHA
Pimephales promelas	96-hr LC_{50}	14,200	2	ECHA
Ceriodaphnia dubai	48-hr EC_{50}	5012	2	ECHA
Chlorella vulgaris	72-hr EC_{50}	275	2	ECHA

Chronic Studies

The 5-d NOEC to *Brachydanio rerio* in an OECD 212 embryo and sac-fry stage test is 250 mg/L (ECHA) [Kl. score = 2].

The 10-d NOEC to *Ceriodaphnia dubia* in a *Daphnia* reproduction test is 9.6 mg/L (ECHA) [Kl. score = 2].

The 72-hr EC_{10} to algae *Chlorella vulgaris* is 11.5 mg/L (ECHA) [Kl. score = 2].

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

The PNEC calculations for ethanol 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 (14,200 mg/L), invertebrates (5,012 mg/L), and algae (275 mg/L). Results from chronic studies are available for fish (250 mg/L), invertebrates (9.6 mg/L), and algae (11.5 mg/L). On the basis that the data consists of short- and long-term results from three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC or EC_{10} value of 9.6 mg/L for invertebrates. The $PNEC_{aquatic}$ is 0.96 mg/L.

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 0.013 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.02/1500) \times 1000 \times 0.96$
$= 0.013$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 1.05 \times 0.02$
$= 0.02$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for ethanol based on the molecular connectivity index (MCI) is 1.05 L/kg (EPA, 2019).
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).

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

Based on a measured log K_{ow} of -0.35, ethanol does not meet the screening criteria for bioaccumulation.

No chronic aquatic toxicity studies are available on ethanol. The acute $E(L)C_{50}$ values for ethanol are >1 mg/L. Thus, ethanol does not meet the criteria for toxicity.

Therefore, ethanol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable liquid, Category 2
Eye irritation, Category 2B
Acute Toxicity, Category 3
Reproductive toxicity, Category 2

Specific target organ toxicity – Repeated exposure, Category 2
Specific target organ toxicity – Single exposure, Category 3

B. Labelling

Danger

C. Pictogram

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

A. First Aid

Eye Contact
Protect unexposed eye. Rinse/ flush exposed eye(s)s gently using water for 15-20 minutes. Remove contact lens(es) if able to do so during rinsing. Seek medical attention if irritation persists or if concerned.

Skin Contact
Wash affected area with soap and water. Rinse thoroughly. Seek medical attention if irritation, discomfort, or vomiting persists.

Inhalation
Move exposed individual to fresh air. Loosen clothing as necessary and position individual in a comfortable position. Seek medical advice if irritation persists.

Ingestion
Rinse mouth thoroughly. Do not induce vomiting. Have exposed individual drink sips of water. Seek medical attention if irritation, discomfort, or vomiting persists.

B. Fire Fighting Information

Extinguishing Media

For small fires, use dry chemicals, CO_2, water spray or alcohol-resistant foam. For large fire, use water fog or alcohol-resistant foam. Use appropriate fire suppression agents for adjacent combustible materials or sources of ignition.

Specific Exposure Hazards
Combustion products may include carbon oxides or other toxic vapors. Dangerous fire hazard when exposed to hear, sparks, and open flames.

Special Protective Equipment for Firefighters
Wear protective equipment. Use NIOSH-approved respiratory protection/ breathing apparatus. Use spark-proof tools and explosion-proof equipment. Move product containers away from fire or keep cool with water spray as a protective measure, where feasible.

C. Accidental Release Measures

Personal Precautions
Beware of vapors accumulating to form explosive concentrations. Vapors can accumulate in low areas. Keep unprotected persons away.
Wear protective equipment. Use respiratory protective device against the effects of fumes/ dust/ aerosol. Ensure adequate ventilation. Keep away from ignition sources. Protect from heat.
For large spills, wear splash goggles, full suit, respirator, boots and gloves and use self-contained breathing apparatus.

Environmental Precautions
Prevent from reaching drains, sewer, or waterway. Collect contaminated soil for characterisation. Collect spilled liquid for recovery, treatment, or disposal.

Steps to be Taken if Material is Released or Spilled
Eliminate sources of ignition. Stop the spill, if possible. Contain spill material by diking or using inert absorbent. Spill may also be contained by using electrically protected vacuum cleaner or by wet-brushing. Transfer to a disposal or recovery container.

D. Storage And Handling

General Handling
Prevent formation of aerosols. Use only in well ventilated areas. Avoid splashes or spray in enclosed areas. Prevent exposure to ignition sources; use non-sparking tools and explosion-proof equipment.

Other Handling Precautions

Avoid contact with eyes, skin, and clothing. Avoid breathing vapor. Follow good hygiene procedures when handling chemical materials. Do not eat, drink, smoke, or use personal products when handling substances. Wash hands before breaks and at the end of work.

Storage

Store in a cool location. Provide ventilation for containers. Avoid storage near extreme heat, ignition sources, or open flame. Store away from foodstuffs. Store away from oxidizing agents. Store in cool, dry conditions in well-sealed containers. Keep containers tightly sealed. Store in secure flammable storage area away from sources of ignition. Protect from freezing and physical damage.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

The workplace exposure standard for ethanol in Australia is 1000 ppm (1880 mg/m^3) as an 8-hr TWA. No STEL is listed.

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. Avoid storage near extreme heat, ignition sources, or open flame. Use non-sparking tools and explosion-proof equipment.

Personal Protection Equipment

Respiratory Protection: Not required under normal conditions of use. Use suitable respiratory protective device when high concentrations are present. Use suitable respiratory protective devise when aerosol mist is formed. For spills, respiratory protection may be advisable.

Hand Protection: Gloves that are impermeable and resistant to the substance

Skin Protection: Wear chemical resistant gloves (rubber, neoprene or vinyl). Use personal protection equipment that is chemical resistant and prevents skin contact.

Eye protection: Goggles or safety glasses with side shields

Other Precautions:

- Use other PPE as required by the situation.
- Ethanol is a flammable liquid; keep away from ignition sources. 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: 1170
UN proper shipping name: Ethanol (mixture)

Transport hazard class: 3 Flammable liquids
Packing group: II

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

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ALCOHOLS, C11-14-ISO-, C13-RICH, ETHOXYLATED

This dossier on alcohols, C11-14-iso-, C13-rich, ethoxylated 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 primarily from the Human & Environmental Risk Assessment on Ingredients of European Household Cleaning Products: Alcohol Ethoxylates (HERA, 2009). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Alcohols, C11-14-iso-, C13-rich, ethoxylated

CAS RN: [redacted]

Molecular formula: Not available (UVCB substance)

Molecular weight: 233.46 g/mol

Synonyms: Ethoxylated branched C11-14, C13-rich alcohols; alpha-Alkyl-omega-hydroxypoly(oxypropylene) and/or poly(oxyethylene) polymers where the alkyl chain contains a minimum of six carbons, minimum number average molecular weight (in amu) 1,100

SMILES: C.C.[*]C.CCCCCCCCCCOCC

II. PHYSICO-CHEMICAL PROPERTIES

Alcohol ethoxylates (AEs) are a class of non-ionic surfactants that have the basic structure $C_{x-y}AE_n$. The subscript (x-y) following the 'C' indicates the range of carbon chain units. The hydrocarbon chain can be either linear or branched. AEs also contain an ethylene oxide (E) chain attached to the alcohol. The degree of ethylene oxide polymerization is indicated by the subscript (n) which indicates the average number of ethylene oxide units. Alcohols, C11-14-iso-, C13-rich, ethoxylated has an average number of 7 moles of ethylene oxide units.

No information is available on alcohols, C11-14-iso-, C13-rich, ethoxylated. Thus, data were read across from a similar substance, alcohols, C12-15, ethoxylated, as shown below.

Table 1: Overview of the Physico-Chemical Properties of Alcohols, C11-14-iso-, C13-rich, ethoxylated[1]

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 @ 101.3 kPa	2	ECHA
Boiling Point	287°C @ 101.3 kPa	1	ECHA
Density	926 kg/m^3 @ 15.56°C	1	ECHA
Vapour Pressure	Negligible	-	ECHA

Property	Value	Klimisch score	Reference
Partition coefficient (log K_{ow})	5.06* @25 °C	2	ECHA
Water Solubility	0.007 – 0.063 g/L @ 25 °C	1	ECHA
Flash Point	165.56 °C	2	ECHA
Auto Flammability	235 °C	2	ECHA
Viscosity	28.1 mPa s (dynamic) @ 20°C	1	ECHA

1 – Based on alcohols, C12-C15, ethoxylated (1 to 2.5 EO) [CAS RN [redacted]

*Based on alcohols, C12-14, ethoxylated (1 to 2.5 EO) [CAS RN [redacted]

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Alcohols, C11-14-iso-, C13-rich, ethoxylated is readily biodegradable. They are slightly soluble and have high adsorption potential to soil and sediment. However, they have a low potential to bioaccumulate.

B. Biodegradation

No studies are available on alcohols, C11-14-iso-, C13-rich, ethoxylated.

AEs with a typical alkyl chain (e.g., C12 to C15) will normally reach more than 60% ultimate degradation in standardized tests for ready biodegradability (HERA, 2009). For example, 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].

If a chemical is found to be inherently biodegradable or 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 alcohols, C11-14-iso-, C13-rich, ethoxylated.

Using KOCWIN in EPISUITE™ (USEPA, 2019), the estimated K_{oc} values for alcohols, C1.1-14-iso-, C13-rich, ethoxylated were 5649 L/kg (MCI) and 20,085 L/kg (K_{ow}). However, as described in ECHA, one should keep in mind that surfactancy (the fact that surfactants tend to stay in the boundary layer between the phases) and dissociation is not considered in the EPISUITE™ estimations. Therefore, calculated K_{oc} values should be used with caution.

If released to soil, these K_{oc} values indicate a high potential for both adsorption and low potential for mobility. If released to water, based on these K_{oc} values and slight solubility, this substance is expected to strongly adsorb to suspended solids or sediment.

D. Bioaccumulation

There are no bioaccumulation studies on this substance. The BCF values for AEs in fathead minnows have been reported to range from <5 to 387.5 (Toll et al., 2000). The uptake rates varied from 330 to 1,660 (L x kg/d) and elimination rates varied from 3.3 to 59 per day (Toll et al., 2000). The high concentrations in fish are thought to be prevented by an efficient biotransformation of the alcohol ethoxylates, leading to a high elimination rate. Thus, it can be stated that bioaccumulation of AEs is regarded to be negligible as the surfactants will be rapidly metabolised (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Overall, AEs are not expected to be systemically toxic. The available datasets for AEs ranging from C6–C18 and EO3–EO12 are considered representative of the AE category and were used to assess alcohols, C11-14-iso-, C13-rich, ethoxylated.

The acute toxicity of similar AEs is low by the oral and dermal routes. The skin irritation rabbit studies show that the degree of irritation depends on the testing conditions and length of the exposure period. Human patch studies on AEs do not support a skin irritant classification and alcohol ethoxylates in this group are not considered skin sensitisers. Alcohols, C11-14-iso-, C13-rich, ethoxylated is expected to be irritating to the eyes of rabbits. Repeated dose toxicity studies on AEs similar to alcohols, C11-14-iso-, C13-rich, ethoxylated in rats do not indicate any target organ effects. These AEs are not genotoxic, carcinogenic, and have a low potential for reproductive and developmental toxicity.

B. Metabolism

In rats, AEs are readily absorbed in the gastrointestinal tract (i.e., oral absorption has been estimated to be >75%) and rapidly excreted via the urine and faeces after oral application. The alkyl chain length appears to have an impact on the metabolism. AEs with longer alkyl chains are excreted at a higher proportion into expired air and less in urine. Also, ethoxy chain length impacts the proportions excreted via the urine, the faeces, and the expired air with more being excreted via the faeces and expired in the air with longer ethoxy chain length (HERA, 2009).

The same trends were observed when AEs were administered dermally, with the only difference being that adsorption was slower and less of the total administered compound was absorbed (HERA, 2009).

C. Acute Toxicity

No acute toxicity studies are available on alcohols, C11-14-iso-, C13-rich, ethoxylated.

The oral LD_{50} in rats for $C_{12\text{-}15}AE_3$ is >5,000 milligrams per kilogram (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 ethoxylate (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].

D. Irritation

Skin

Application of 0.5 millilitres (mL) $C_{12\text{-}13}AE_{<2.5}$ (CAS RN [redacted] to the skin of rabbits for 24 hours under occlusive conditions was considered irritating (ECHA) [Kl. score = 2].

Application of 0.5 mL alcohols $C_{12\text{-}13}$, branched and linear, <2.5 EO to the skin of rabbits for 4 hours under 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 AE should be classified as a skin irritant (Basketter et al., 2004) [Kl. score = 2].

Eye

Most AEs 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 AEs $C_{12\text{-}14}AE_3$, $C_{12\text{-}14}AE_6$, $C_{13}AE_6$, 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 AEs were reported to be practically or minimally irritating to the eyes of rabbits with EII scores of 0.5 to 15. These AEs 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).

E. Sensitisation

No sensitisation studies are available on alcohols, C11-14-iso-, C13-rich, ethoxylated.

In a guinea pig maximisation test, $C_{12\text{-}13}AE_{<2.5}$ (CAS RN [redacted] was not considered a skin sensitiser (ECHA) [Kl. score = 2].

F. Repeated Dose Toxicity

Oral

No repeated dose toxicity studies are available on alcohols, C11-14-iso-, C13-rich, ethoxylated.

Rats were given 0%, 0.0313%, 0.0625%, 0.125%, 0.25%, 0.5% or 1.0% $C_{12\text{-}15}AE_7$ in their diet for 90 days. The animals in the $\geq$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 $\geq$0.5% male rats and $\geq$0.25% females. Histopathologic examination showed hepatocytic enlargement in the $\geq$0.125% groups, suggesting increased liver metabolism on the basis of increased alkaline phosphatase activity at the higher dose levels. The no observed

adverse effect level (NOAEL) was established at 0.0625% in the diet or 102 mg/kg/day (HERA, 2009) [Kl. score = 2].

Rats were fed $C_{12-14}AE_7$ 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].

Rats were given 0%, 0.1%, 0.5% or 1% $C_{12-13}AE_{6.5}$ in their diet 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 incidence 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].

Inhalation

No studies are available.

Dermal

No adequate studies are available.

G. 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, C11-14-iso-, C13-rich, ethoxylated are presented in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Selected Alcohol Ethoxylates

Test Substance	Test System	Results*		Klimisch Score	Reference
		-S9	+S9		
$C_{14-15}AE_7$	Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	HERA, 2009
$C_{14-15}AE_7$	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 $C_{12-15}AE_3$ or $C_{12-14}AE_9$. 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 $C_{14-15}AE_7$. There were no increases in chromosomal aberrations in the bone marrow cells (HERA, 2009) [Kl. score = 2].

H. Carcinogenicity

No studies are available on alcohols, C11-14-iso-, C13-rich, ethoxylated. Based on the available data, chemicals in this group are not considered carcinogenic.

Male and female Sprague-Dawley rats were given $C_{12-13}AE_{6.5}$ in their 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 0, 0.1, 0.5 or 1% $C_{14-15}AE_7$ in their diet 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 $C_{14-15}AE_7$ in their diet 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].

I. Reproductive Toxicity

No studies are available on alcohols, C11-14-iso-, C13-rich, ethoxylated. Based on the data available, the chemicals of this group are not considered to cause reproductive toxicity.

CD rats were given 0%, 0.05%, 0.1% or 0.5% (approximately 0, 25, 50, or 250 mg/kg/day) $C_{12}AE_6$ in their diet 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 0%, 0.05%, 0.1% or 0.5% $C_{14-15}AE_7$ in their diet (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].

J. Developmental Toxicity

No studies are available on alcohols, C11-14-iso-, C13-rich, ethoxylated. Based on the data available, the chemicals of this group are not considered to cause developmental toxicity.

In a two-generation reproductive toxicity study, Charles River rats were given 0, 0.05, 0.1 or 0.5% (about 0, 25, 50 or 250 mg/kg/day) $C_{12}AE_6$ in their diet. 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 0, 50, 100 or 200 mg/kg $C_{12}AE_6$ by oral gavage 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].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for alcohols, C11-14-iso-, C13-rich, 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>

A two-year dietary study in rats has been conducted on $C_{12\text{-}13}AE_{6.5}$ (HERA, 2009). The NOAEL from this study is 50 mg/kg/day based on increased organ weights. 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

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 = 0.5 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 = (0.5 x 70 x 0.1)/2 = 1.8 mg/L

B. Cancer

The AEs $C_{12-13}AE_{6.5}$ and $C_{14-15}AE_7$ were not carcinogenic to rats in a two-year dietary study. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Alcohols, C11-14-iso-, C13-rich, ethoxylated does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Alcohols, C11-14-iso-, C13-rich, ethoxylated has moderate chronic toxicity concern to aquatic life.

B. Aquatic Toxicity

Acute Studies

There are no acute aquatic toxicity studies for ethoxylated C12-C16 alcohol. The aquatic toxicity of other AEs has been extensively evaluated in numerous studies on fish, daphnids and algae as well as microorganisms. Table 3 lists the results of acute aquatic toxicity studies on read across substance alcohols, C12-C15, ethoxylated (1 to 2.5 EO) [CAS RN [redacted] alcohols, C12-C14, ethoxylated (2 EO) [CAS RN [redacted] and alcohols, C12-C15, branched and linear, ethoxylated [CAS RN [redacted]

Table 3: Acute Aquatic Toxicity Studies on Ethoxylated C12-C16 Alcohol[a,b,c]

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Oncorhynchus mykiss (Rainbow Trout)	96-hr LC_{50}	1.3 – 1.7[a]	2	ECHA
Danio Rio	96-hr LC_{50}	1.2[b]	2	ECHA
Danio Rio	96-hr LC_{50}	2[b]	2	ECHA
Zebrafish	96-hr LC_{50}	>2[c]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.14[a]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.23[a]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.53[b]	2	ECHA
Daphnia magna	48-hr EC_{50}	2.84[b,d]	2	ECHA
Daphnia magna	48-hr EC_{50}	1.2[e]	1	ECHA
Daphnia magna	48-hr EC_{50}	>2[b]	2	ECHA
Daphnia magna	48-hr EC_{50}	>2[c]	2	ECHA
Daphnia magna	48-hr EC_{50}	0.23	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	0.75[a]	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	>2[c]	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	0.41[b]	2	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	0.778[b]	2	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	0.87[e]	1	ECHA
Desmodesmus subspicatus (green algae)	72-hr EC_{50}	1.3[e]	1	ECHA

a: Read across to alcohols, C12-C15, ethoxylated (1 to 2.5 EO) CAS No. [redacted]
b: Read across to alcohols, C12-C14, ethoxylated (EO 2) CAS No. [redacted]
c: Read across to alcohols, C12-C15, branched and linear, ethoxylated (CAS No. [redacted]
d: alcohols, C12-C14, ethoxylated (EO 1) CAS No. [redacted] as WAF (water accommodated fraction)
e: alcohols, C12-C14, ethoxylated (EO 4 or EO 6) CAS No. [redacted]

A review of the acute studies indicates that invertebrates are somewhat more sensitive to AEs than fish and algae. As concluded in HERA (2009), the Danish EPA (2001) found that the acute toxicity of AE to invertebrates varies, with EC50 values from 0.1 mg/L to more than 100 mg/L for linear AE and from 0.5 mg/L to 50 mg/L for branched AE. The toxicity is species specific and may vary between 0.29 mg/L and 270 mg/L for the same linear AE (Lewis and Suprenant 1983, quoted in Danish EPA 2001). The most commonly used invertebrates for testing are Daphnia magna and Daphnia pulex, and they are also among the most sensitive invertebrates to AE. The Danish EPA (2001) found that some AEs are very toxic to invertebrates (i.e., linear AE of C12-15 EO1-8 and branched AE with a low degree of branching, < 10-25%). They concluded that branching of the alkyl chain reduces the toxicity of AE to invertebrates, as also observed for algae (Danish EPA, 2001). However, the data used to reach this conclusion is from specially synthesised AEs, which have been shown to have a significantly higher toxicity than the AE made from a technical alcohol which are used commercially (Kaluza and Taeger, 1996).

Chronic Studies

In developing a water quality guideline for AEs (ANZG, 2018), the toxicity data was normalised for a specific alkyl chain length or a specific number of EO groups. The no observed effect concentrations (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 micrograms per litre (μg/L).

Freshwater crustaceans: 2 species, 590 to 860 μg/L.

Freshwater rotifers: 1 species, *Brachionus calyciflorus*, 1,300 μg/L

Freshwater algae, diatoms and blue-green algae: 6 species, 200 to 8,700 μg/L.

Freshwater mesocosms: 4 NOEC data for multiple species tests were 80, 80, 320, and 330 μg/L, although replication was insufficient to meet OECD (1992) requirements. Normalised data were 380, 380, 320, and 1,520 μg/L.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for alcohols, C11-14-iso-, C13-rich, ethoxylated follow the methodology discussed by DEWHA (2009).

PNEC Water

The ANZG water quality guideline (2018) for freshwater is: "*A high reliability trigger value of 140 μg/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 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 11.95 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (109/1280) \times 1000 \times 0.14$
$= 11.95$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (cubic metre per cubic metre [m^3/m^3])
BD_{sed} = bulk density of sediment (kilograms per cubic metre [kg/m^3]) = 1,280 [default]

$K_{sed\text{-}water}$ = 0.8 + [(0.2 x Kp_{sed})/1,000 x BD_{solid}]
= 0.8 + [(0.2 x 226/1,000 x 2,400]
= 109 m^3/m^3

Where:
Kp_{sed} = solid-water partition coefficient (litres per kilogram [L/kg])
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

Kp_{sed} = K_{oc} x f_{oc}
= 5,649 x 0.04
= 226 L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for alcohols, C11-14-iso-, C13-rich, ethoxylated calculated from EPISUITE™ using the MCI is 5,649 L/kg. The MCI method is preferred to the K_{ow} method due to the surfactant properties of the substance.
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 10.54 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil}$ = (Kp_{soil}/BD_{soil}) x 1,000 x $PNEC_{water}$
= (113/1,500) x 1,000 x 0.14
= 10.54 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}
= 5,649 x 0.02
= 113 m^3/m^3

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for alcohols, C11-14-iso-, C13-rich, ethoxylated calculated from EPISUITE™ using the MCI is 5,649 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, 2017).

Alcohols, C11-14-iso-, C13-rich, ethoxylated is readily biodegradable and thus does not meet the screening criteria for persistence.

The measured BCF in fish for AEs, which includes alcohols, C11-14-iso-, C13-rich, ethoxylated, have been reported to range from <5 to 387.5. Thus, alcohols, C11-14-iso-, C13-rich, ethoxylated does not meet the screening criteria for bioaccumulation.

The chronic NOEC values for AEs are >0.1 mg/L. Thus, alcohols, C11-14-iso-, C13-rich, ethoxylated does not meet the criteria for toxicity.

The overall conclusion is that alcohols, C11-14-iso-, C13-rich, ethoxylated is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Eye Irritant Category 2

Aquatic Chronic Toxicity Category 3

B. Labelling

Danger! According to the classification provided by companies to ECHA in Classification, Labelling and Packaging (CLP) notifications, this substance is very toxic to aquatic life, causes serious eye damage, is harmful if swallowed, is harmful to aquatic life with long lasting effects and causes skin irritation.

A. 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

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. 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

Self-contained breathing apparatus and full protective clothing must be worn in case of fire.

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

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.

Wash hands thoroughly after handling. Avoid breathing mists or aerosols.

Storage

Keep container tightly closed.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for alcohols, C11-14-iso-, C13-rich, ethoxylated.

Engineering Controls

Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection: Respiratory protection is not required if ventilation is adequate.

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

Alcohols, C11-14-iso-, C13-rich, ethoxylated 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

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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.

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Fatty acids, tall-oil, ethoxylated

This dossier on Fatty acids, tall-oil, ethoxylated (FAT) 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 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: Fatty acids, tall-oil, ethoxylated

CAS RN: [redacted]

This CAS RN is broadly defined as "A complex combination of hydrocarbons obtained by treating a petroleum fraction with hydrogen in the presence of a catalyst. Tall oil fatty acids (TOFA), generally any product containing 90% or more fatty acids and 10% or less of rosin, have grown in annual volume ever since, until they amount to 398.8 million pounds annual production in the U.S. in 1978. Crude tall oil is a byproduct of the Kraft process for producing wood pulp from pine wood. Crude tall oil is about 50% fatty acids and 40% rosin acids, the remainder unsaps and residues. Separative and upgrading technology involves: (a) recovery of the tall oil; (b) acid refining; (c) fractionation of tall oil; and occasionally (d) conversion to derivatives. TOFA of good quality and color of Gardner 2 corresponds to above 97% fatty acids with the composition of 1.6% palmitic & stearic acid, 49.3% oleic acid, 45.1% linoleic acid, 1.1% miscellaneous acids, 1.2% rosin acids, and 1.7% unsaponifiables.

Molecular formula: C(18-50)H(34-98)O(3-8) (UVCB substance)

Molecular weight: (UVCB substance)

Synonyms: IUPCA Name 2-[(10Z,13Z)-nonadeca-10,13-dienoyloxy]ethyl (10Z,13Z)-nonadeca-10,13-dienoate 2-hydroxyethyl (5Z,9Z,12Z)-octadeca-5,9,12-trienoate 2-hydroxyethyl (9Z)-octadec-9-enoate 2-hydroxyethyl (9Z,12Z)-octadeca-9,12-dienoate

SMILES: Not available (UVCB substance)

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Fatty acids, tall-oil, ethoxylated)

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Liquid.	2	ECHA
Melting point	-85 °C	2	ECHA
Boiling point	Not available. During the heating process the test item began to change its state at approximately 172 °C from liquid to highly viscous. This indicates a thermally caused change of the test item.	2	ECHA
Density	0.958 g/cm^3 @ 20°C	2	ECHA
Vapor pressure	The vapor pressure could not be determined.	2	ECHA
Partition coefficient (log K_{ow})	5.94	-	-
Water solubility	The test item can be mixed with water up to a ratio of 3:7 (m (test item) : :m (water)).	-	-
Flash point	Flash point at 101 325 Pa: 138 °C	2	ECHA
Auto flammability	377 °C at 1031 hPa	2	ECHA
Viscosity	58.0 mPa*s at 20 °C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

There are no biodegradation data on FAT. However, data on structurally similar substances suggest FAT is biodegradable with potential to sorb to soils. It is not expected to readily bioaccumulate.

B. Biodegradation

Data on the ready biodegradability of Fatty acids, tall oil, ethoxylated (EO > 1 < 2.5) (CAS [redacted] are not available. Therefore, data on the ready biodegradability of the structurally related analogue substance Fatty acids, tall oil, ethoxylated (EO 5) (CAS No. [redacted] is used as read-across in accordance with Regulation (EC) No. 1907/2006, Annex XI, 1.5.

This read-across is justified because both, target and source substance, are structurally identical (ethoxylated oleic acid) except for the fact that the source substance is slightly higher ethoxylated (5 EO) than the target substance (1-2.5EO). This difference might lead to a slightly lower water solubility of the target substance; however, since the solubility of both substances is rather high and not limiting the bioaccessibility of the substances to aquatic microorganisms this is not considered to influence the identical biodegradation behaviour of both substances. Both substances share the same functional groups and the same mode of action (baseline toxicity caused by the long lipophilic fatty acid chain). Thus, biotransformation can with very high certainty assumed to be identical.

The test with the source substance was conducted according to OECD Guideline 301B, under GLP conditions (BASF 2005). Domestic, non-adapted activated sludge was exposed to the test substance for 28 days at 22°C, and biodegradation was measured by CO2 consumption. After 28 days, the test substance reached a biodegradation of 90 - 100 %.

Based on the results for the read-across substance, Fatty acids, tall oil, ethoxylated (EO > 1 < 2.5) (CAS [redacted] is considered to be readily biodegradable.

C. Environmental Distribution

One study investigating the adsorption/desorption behaviour of Fatty acids, tall-oil, ethoxylated (CAS [redacted] is available. The study was performed according to GLP and OECD guideline 121 (BASF 2017). 6 different peaks were observed with log Koc values ranging from < 1.8 to > 5.63. The two main components (> 85%) show log Koc values > 4.

Thus, adsorption of Fatty acids, tall-oil, ethoxylated to solid soil is expected.

D. Bioaccumulation

The test substance consists of components with log Kow values in the range of 5 to > 10 (KOWWIN v1.68) indicating a potential for bioaccumulation. But due to rapid environmental biodegradation, metabolisation via enzymatic hydrolysis (monoesters and diesters) as well as sterical hindrance of crossing biological membranes (high molecular weight of diesters) a relevant uptake and bioaccumulation in aquatic organisms is not expected. This is supported by low BCF values of < 100 L/kg ww (BCFBAF v3.01, Arnot-Gobas, including biotransformation, upper trophic) calculated for different components of the UVCB (mono- and diester EO1 to EO5). Thus, taking all information into account, the test substance is not considered to be bioaccumulative.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The toxicity of fatty acids, tall-oil, ethoxylated is low by the oral and dermal routes. No data are available for evaluation of toxicity via the inhalation route. fatty acids, tall-oil, ethoxylated are not genotoxic; nor do they exhibit and evidence of reproductive or developmental toxicity in rats.

B. Acute Toxicity

In an acute oral toxicity study performed similar to OECD guideline 401 (BASF 1971), three groups of rats consisting of 10 animals/sex/dose were treated by single gavage application with an aqueous solution of the test substance (10000, 8000, 6400 mg/kg bw). The animals were observed for mortality and for clinical symptoms of toxicity over a period of 7 days. At the end of the observation period, the surviving animals were sacrificed for the purpose of necropsy. No mortality occurred at the tested concentrations. At all doses mastication, irregular breathing, redness of the eyes and closed eyes were seen immediately after dosing. The next morning mastication and irregular breathing was observed. On the following days, no clinical sings were observed. Pathological examination revealed hydrometra in 3 animals exposed to 10000 mg/kg bw, 2 animals exposed to 8000 mg/kg bw, and 3 animals exposed to 6400 mg/kg bw. Based on the results obtained under the test conditions of this study, the acute oral LD50 was determined to be > 10000 mg/kg bw.

In another acute oral toxicity study of similar design four groups of rats consisting of 5 animals/sex/dose were treated by single gavage application with an aqueous solution of the test substance (6400, 3200, 1600, 200 µL/kg). The animals were observed for mortality and for clinical symptoms of toxicity. At the end of the observation period, the surviving animals were sacrificed for the purpose of necropsy. No mortality occurred at the tested concentrations. At all doses on the day of the experiment, restless behaviour was observed after application. The animals had slightly accelerated breathing as well as ruffled fur. Four days after the application all animals were without clinical signs. In this study no pathological changes in the organs were observed. One animal showed bronchitis and bronchiectasis on both sides.

In an additional study a limit test was performed. 4 rats were treated by single administration with 2000 mg/kg of the test substance (2 animals/sex/dose). During the observation period of 14 days, no clinical symptoms of toxicity or mortality were observed.

The acute oral LD50 of the test substance was determined to be > 10000 mg/kg bw.

To evaluate the potential acute inhalation toxicity of the test substance an Inhalation Risk Test conducted according to a BASF internal testing method (BASF 1971). The test demonstrates the toxicity of an atmosphere saturated with vapours of the volatile components of a test substance at the temperature chosen for vapour generation (20 °C). Rats were exposed sequentially to the vapours, generated by bubbling 200 l/h air through a substance column of about 5 cm above a fritted glass disc in a glass cylinder. The animals were exposed for 8 hour. The exposure concentration was estimated to be 0.28 mg/L based on evaporated substance. In addition to mortality, clinical signs were recorded and necropsy on surviving animals performed. No mortality occurred and no clinical sign were noted during exposure and observation period. In one animal exposed for 8 hours hydrometra was observed after necropsy. Since no mortality occurred at the concentrations tested an LC50 estimation cannot be made.

In another Inhalation Risk Test of similar design, Rats (12 animals) were exposed sequentially to the vapours, generated by bubbling 200 l/h air through a substance column of about 5 cm above a fritted glass disc in a glass cylinder. This time vapours were generated at 20 °C as well as 50 °C. The exposure concentrations were 0.04 mg/L and 0.34 mg/L. Rats were exposed for 8 hour. As in the previous study, no mortality occurred after exposure up to 8 hours. Clinical sings observed in the animals exposed to the vapor generated at 20°C included mild escape attempts when exposure began and at the end of the exposure period slight eye irritation was observed. The next day, the animals were without symptoms. In the animals exposed to the vapor generated at 50 °C escape attempts were noted in the first 60 minutes of exposure. Exposure to the saturated atmosphere caused slight eye irritation. At the end of the exposure period, all clinical signs were resolved. Since no mortality occurred at the concentrations tested an LC50 estimation cannot be made.

Based on the inhalation studies, no conclusion on LC50 can be drawn, because the tested concentrations are too low in relation to the classification criteria.
There are no data to evaluate dermal toxicity of the substance to test animals.

C. Irritation

SKIN: Non-irritating

By using the currently available methods a single in vitro assay is not sufficient to cover the full range of skin irritating/corrosion potential. Therefore, two in vitro assays were part of an in vitro skin irritation and corrosion test strategy (BASF 2017): The Skin Corrosion Test (SCT) and Skin Irritation Test (SIT). However, the results derived with SIT (performed in a GLP-compliant study according to OECD 431, OECD 439, EU method B.40 BIS. And EU method B.46) alone were sufficient for a final assessment. Therefore, further testing in SCT was waived.

The potential of the test substance to cause dermal irritation was assessed by a single topical application of 30 µL of the undiluted test substance to a reconstructed three-dimensional human epidermis model (EpiDerm™). The irritation test was performed with three EpiDerm™ tissues which were incubated with the test substance for 1 hour followed by a 42-hour post-incubation period.

Tissue destruction was determined by measuring the metabolic activity of the tissue after exposure/post-incubation by using a colorimetric test. The reduction of mitochondrial dehydrogenase activity measured by reduced formazan production after incubation with a tetrazolium salt (MTT) was chosen as endpoint. The formazan production of the epidermal tissues treated with the test substance is compared to that of negative control tissues. The quotient of the values indicates the relative tissue viability.

The following results were obtained in the EpiDerm™ skin irritation test: 1) The test substance is able to directly reduce MTT. Therefore, an additional MTT reduction control KC (freeze-killed control tissues) was introduced. 2) The final mean viability of the tissues treated with the test substance determined after an exposure period of 1 hour with an about 42-hour post-incubation was 100.7%.

Based on the results observed and by applying the evaluation criteria, it was concluded that the test substance does not show a skin irritation potential in the EpiDerm™ in vitro skin irritation and corrosion test strategy under the test conditions chosen.
In a supporting skin irritation test two rabbits were treated for 1, 5, 15 min and 20 hours under occlusive conditions (BASF 1971). An application site of 2.5 x 2.5 cm was covered with the liquid test substance. After the application time (1, 5, 15 min and 20 h) the skin was washed with Lutrol (50%). The animals were observed for 8 days and skin changes were recorded daily. The report describes findings after 24 hours and at the end of the observation period (8 days). After 20 hours exposure to the test-substance one animals showed slight erythema after 24 hours (score 2). The observed redness was resolved by the end of the observation period, but a slight scaling was still present. The other animal exposed for 20 hours showed only some questionable erythema effect after 24 hours (score 1) which was fully reversible within 72 hours. No other effects were noted in the animals exposed for 20 hours. Of the animals exposed for shorter periods (1, 5, or 15 minutes) only one animal exposed for 15 minutes showed some questionable erythema which was fully reversible.

In another similar performed skin irritation test showed stronger effects (BASF 1966). The animals exposed for 20 hours showed strong to very strong erythema across the whole exposed area. After 8 days the redness in one animal was decreased to slight and had disappeared in the other. However, strong scaling was observed in both animals. In addition to the erythema a slight swelling was seen at 24 hours which also had disappeared after 8 days. The animals exposed for 15 minutes showed questionable erythema which was fully reversible. No ulcers, bleeding, or bloody scabs were observed. Animals exposed for shorter period did not show any signs of irritation. The OECD guideline 404 (Acute Dermal Irritation/Corrosion) states a typical exposure duration of 4 hour under open or semi-occlusive conditions. Therefore the test employing 20 hours exposure under occlusive conditions is considered a worst case situation,

Severe skin irritating effects were only seen in one of the study, however considering the worst case conditions these effects are questionable. In contrast, the in vitro guideline study the test substance was considered not to be skin irritant, which is supported by the other in vivo study.

Based on these data, the substance is not considered a skin irritant.

EYE: Non-irritating

The eye irritating potential of the test substance was tested in vitro (BASF 2017). By using the methods currently available a single in vitro assay is not sufficient to cover the full range of eye irritating potential. Therefore, two in vitro assays were part of this in vitro eye irritation test strategy: The Bovine Corneal Opacity and Permeability Test (BCOP Test) and EpiOcular Eye Irritation Test. However, in the current case the results derived with the EpiOcular test alone (which was applied conforming GLP and in accordance with OECD 492) were sufficient for a final assessment. Therefore, further testing in BCOP was waived.

The potential of the test substance to cause ocular irritation was assessed by a single topical application of 50 µL undiluted test substance to a reconstructed three-dimensional, human cornea model (EpiOcular™). Two EpiOcular™ tissues were incubated with the test substance for 30 minutes followed by a 2-hour post-incubation period. Tissue destruction was determined by measuring the metabolic activity of the tissue after exposure/post-incubation by using a

colorimetric test. The reduction of mitochondrial dehydrogenase activity measured by reduced formazan production after incubation with a tetrazolium salt (MTT) was chosen as endpoint. The formazan production of the epidermal tissues treated with the test substance is compared to that of negative control tissues. The ratio of the values indicates the relative tissue viability. The following results were obtained in the EpiOcular™ eye irritation assay: 1) The test substance is able to directly reduce MTT. Therefore, an additional MTT reduction control (freeze-killed control tissues (KC)) was introduced. 2) The final mean viability of the tissues treated with the test substance was 109.3%.

Based on the results observed in the EpiOcular Test alone and by applying the evaluation criteria, it was concluded that the test substance does not show an eye irritation potential in the in vitro eye irritation test strategy under the test conditions chosen.

In a supporting eye irritation test (BASF 1971) 50 µL of the test substance were applied to the conjunctival sac of one eye in 2 animals. The adjacent eye served as saline-control. The animals were observed after 1 and 24 h 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. One hour after application of the test substance slight redness of the conjunctivae was observed in both animals. After 24 hours one animals still showed slight redness of the conjunctivae while the effects in the other animal were completely reversed. After 8 days both animals were without eye irritating effects.

In another supporting eye irritation test (BASF 1966) of the same design and exposure regime similar results were obtained. One hour after application of the test substance slight redness of the conjunctivae was observed in both animals. After 24 hours no eye irritation effect were observed until the end of the observation period.

Based on these results, the test substance is considered to be not irritating to the eyes.

D. Sensitization

The substance is considered to be a sensitizer based on results obtained via the Buehler test.

LLNA assay

The skin sensitising potential of the test substance was assessed using the radioactive Murine Local Lymph Node Assay in a GLP compliant study according to OECD no. 429, Commission Regulation (EC) No 440/2008 Part B, and EPA OPPTS 870.2600. The assay simulates the induction phase for skin sensitisation in mice. It determines the response of the auricular lymph nodes on repeated application of the test substance to the dorsal skin of the ears. Groups of 5 female CBA/J mice each were treated with 3%, 10% and 30% w/w preparations of the test substance in MEK (methyl ethyl ketone) or with the vehicle alone. The high concentration was selected based on the presence of ear irritation in a pretest using a 60% preparation. The study used 3 test groups and 1 control group. Each test animal was applied with 25 µL per ear of the respective test-substance preparation to the dorsum of both ears for three consecutive days. The control group was treated with 25 µL per ear of the vehicle alone. Three days after the last application the mice were injected intravenously with 20 µCi of 3H-thymidine in 250 µL of sterile saline into a tail vein. About 5 hours after the 3H-thymidine injection, the mice were sacrificed

and the auricular lymph nodes were removed. The weights of each animal's pooled lymph nodes were determined. Thereafter lymph nodes were pooled group wise and further evaluated by measuring their cellular content and 3H-thymidine incorporation into the lymph node cells (indicators of cell proliferation). Moreover, a defined area with a diameter of 0.8 cm was punched out of the apical part of each ear and for each test group the weight of the pooled punches was determined in order to obtain an indication of possible skin irritation. The stimulation indices (fold of change as compared to the vehicle control) for cell count, 3H-thymidine incorporation, lymph node weight and ear weight were determined. No signs of systemic toxicity were noticed. When applied as 3%, 10% and 30% preparations in MEK, the test substance did not induce a biologically relevant response (no increase to 1.5 fold or above of control value = stimulation index (SI) ≥ 1.5) in the auricular lymph node cell counts. There was no relevant increase in lymph node weights as well. Concomitantly, the increase of 3H-thymidine incorporation into the cells was not biologically relevant (no increase above the cut off stimulation index of 3) at this concentration. The 30% test-substance preparation caused a minimal increase in ear weights as indication of ear skin irritation. Thus, it is concluded that the test substance does not show a skin sensitising effect in the Murine Local Lymph Node Assay under the test conditions chosen.

Buehler test

The dermal sensitising potential of the test substance was investigated according to one of the methods recommended in the OECD Guideline No. 406, "Skin Sensitisation", 1992 and the EEC Guideline "EEC 92/69 part B6", 1992. The test used was the Buehler test.

The experiment was performed on 30 guinea pigs divided into a test group of 20 animals, and a control group of 10 animals. The study included an induction and a challenge phase. The animals in the test group were induced with the test article and the animals in the control group were induced with sterile distilled water. The induction procedure included a closed patch topical application for 6 hours once a week for 3 weeks.

The challenge procedure included a closed patch topical treatment of the test article on the flank 4 weeks after the first induction. All animals were challenged for 6 hours. The skin reactions were evaluated 24 and 48 hours after termination of the challenge application. The undiluted test article was used for the inductions as well as for the challenge application.

Slight erythema was observed in 8 and 6 animals after 24 and 48 hours, respectively. However, slight erythema was considered a marginal skin change due to other factors than skin sensitisation. After 24 hours a moderate erythema was seen in 1 animal and after 48 hours a moderate erythema was seen in 5 animals. Based on these results, the test substance is considered to be sensitising to the skin.

E. Repeated Dose Toxicity

Oral

An OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) was performed in 2015. The rat is the preferred animal species for reproduction studies according to the various test guidelines and the Wistar strain

was selected. This Wistar rat strain (Crl:WI(Han)) was selected since extensive historical control data were available for this strain.

Male and female rats were dosed with the substance by oral gavage with 0, 100, 300, 1000 mg/kg/day. No clinical effects were observed , no mortality was observed comma and body weight changes we're not significantly different from controls. There were no treatment related changes in food consumption during the entire study. Water consumption was not affected. There were no haematological effects nor effects on clinical biochemistry parameters. An assessment of functional observation battery indicated no effects no test substance related deviations relative to motor activity were noted. Organ Weights were not affected by exposure to the substance at any dose level. Gross pathological and histopathological findings did not indicate any adverse effects.

The NOAEL for general systemic toxicity was determined to be 1000 milligram per kilogram body weight per day.

Inhalation
No studies are available.

Dermal
No studies are available.

F. Genotoxicity

In Vitro Studies

The test substance is not mutagenic in bacteria or mammalian cell lines. The key *in vitro* genotoxicity studies are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on C9-C14 Aliphatic Hydrocarbons (≤2% Aromatics)

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	1	ECHA
Mammalian cell gene mutation (Chinese hamster V 79 cells)	-	-	1	ECHA
Chromosomal aberration (human lymphocytes)	-	-	1	ECHA

*+, positive; -, negative

In Vivo Studies

No studies were available.

G. Carcinogenicity

No carcinogenicity studies are available on the substance.

H. Reproductive Toxicity

The substance - was tested in a combined repeated dose toxicity study with a reproductive/developmental toxicity screening test (OECD 422). Male and female Wistar rat strain (Crl:WI(Han)) rats were given oral gavage doses of 0, 100, 300, or 1,000 mg/kg-day. There was no indication of reproductive toxicity or any effects on tested endocrine system related parameters (T4 and TSH levels) at any dose level. The NOAEL for reproductive toxicity is 1,000 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 1].

I. Developmental Toxicity

The substance was tested in a combined repeated dose toxicity study with a reproductive/developmental toxicity screening test (OECD 422). Male and female Wistar rat strain (Crl:WI(Han)) SD rats were given oral gavage doses of 0, 100, 300, or 1,000 mg/kg-day. There was no indication of teratogenic toxicity at any dose level. The NOAEL for developmental toxicity is 1,000 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 1].

The NOAEL for reproductive toxicity is 1,000 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for C12-C15 aliphatic hydrocarbons (<2% aromatics) 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

Under the conditions of this Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, the oral administration by gavage of test substance to Wistar rats revealed no adverse signs of toxicity in male and female animals at a dose level of 1000 mg/kg bw/d. Thus, the no observed adverse effect level (NOAEL) for general systemic toxicity was 1000 mg/kg bw/d for male and female Wistar rats.

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) = 3
UF_D (database uncertainty) = 1

Oral RfD = 1,000/(10 x 10 x 1 x 3 x 1) = 1,000/300 = 3 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 = (3 x 70 x 0.1)/2 = 11 mg/L

B. Cancer

No carcinogenicity studies are available on C9-C14 aliphatic (<2% aromatic) hydrocarbon fluids. Thus, a cancer reference value was not derived for C12-C15 aliphatic hydrocarbons (<2% aromatics).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

The substance does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The substance is of low acute toxicity concern to aquatic life.

B. Aquatic Toxicity

Acute Studies
There are no aquatic toxicity data on the substance are listed on Table 3.

Table 3: Acute Aquatic Toxicity Studies on Fatty acids, tall-oil, ethoxylated*

Test Substance	Test Species	Endpoint	Results (mg/L) [WAF]	Kl. score
Fatty acids, tall-oil, ethoxylated	*Danio rerio*	96-h LL_{50}	>100	1
Fatty acids, tall-oil, ethoxylated	*Daphnia magna*	48-h LL_{50}	12.41	1
Fatty acids, tall-oil, ethoxylated	*Pseudokirchnerella subcapitata*	72-h LL_{50}	39.7	1

*All studies used the water accommodated fractions (WAFs) of the test substance.

Chronic Studies
No chronic data were available

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

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

PNEC water

Experimental results from acute toxicity studies are available for three trophic levels.

By applying an assessment factor of 100 to the daphnid E(L)C50 value of 12.41 the derived PNECaquatic for the substance of 0.12 mg/L.

PNEC sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the PNECsed was calculated using the equilibrium partitioning method. The PNECsed is 6 mg/kg sediment wet weight.

The calculations are as follows:

PNECsed = (Ksed-water/BDsed) x 1000 x PNECwater
= (65/1280) x 1000 x 0.12
= 6 mg/kg

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 133/1000 x 2400]
= 65

Where:
Kpsed = solid-water partition coefficient (L/kg).
BDsolid = bulk density of the solid phase (kg/m3) = 2,400 [default]

Kpsed = Koc x foc = 3321 x 0.04 = 133 L/kg

Where:
Koc = organic carbon normalized distribution coefficient (L/kg). The Koc for the substance acid calculated from EPISUITE™ using the Kow method is 3321 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 mg/kg soil dry weight. The calculations are as follows:

PNECsoil = (Kpsoil/BDsoil) x 1000 x PNECwater
=
= 66/1500 x 0.12 = 5 mg/kg

Where:
Kpsoil = soil-water partition coefficient (m3/m3)
BDsoil = bulk density of soil (kg/m3) = 1,500 [default]

Where:
Kpsoil = Koc x foc = 3321 x 0.02 = 66 mg/kg

Koc = organic carbon normalised distribution coefficient (L/kg). The Koc for the substance calculated from EPISUITE™ using the Kow method is 3321 L/kg.
Foc = 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).

FAT was noted to be readily biodegradable. Thus, the substance is not expected to meet the screening criteria for persistence.

Modeling of a representative structure indicates FAT does not have the potential to bioaccumulate. Thus, FAT does not meet the screening criteria for bioaccumulation.

FAT did not exhibit substantial acute toxicity to fish, invertebrates, or algae. Thus, FAT is not expected to meet the screening criteria for toxicity.

The overall conclusion is that FAT is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Skin Irrit. 2

Eye Irrit. 2

Skin Sens. 1B

B. Labelling

Warning

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. If irritation occurs, get medical attention.

Skin Contact
Wash the contaminated area of with soap and water. Remove and isolate contaminated clothing. 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.

Ingestion
Do not induce vomiting. Get medical attention immediately.

Notes to Physician
If ingested, material may be aspirated into the lungs and may 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
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
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, vapors, or spray Avoid contact with skin, eye, and clothing.

Environmental Precautions
Prevent from entering sewers, waterways, or low areas.

Steps to be Taken if Material is Released or Spilled
Pick up with non-combustible 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
Avoid breathing vapor or aerosol. Keep away from open flames, hot surfaces and sources of ignition. Provide sufficient ventilation in work area.

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

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Workplace Australia has not established an occupational exposure standard for C12-C15 aliphatic hydrocarbons (<2% aromatics).

Engineering Controls
Use adequate ventilation to control air-borne concentrations.

Personal Protection Equipment
Respiratory Protection:
If workers are exposed to concentrations at a level that is not adequate to protect work health, they must use appropriate, certified respirators. The following type of respirator should be considered for this material: particulate, dust or mists. For high airborne concentrations, use an approved supplied-air respirator, operated in positive pressure mode.

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

C12-C15 aliphatic hydrocarbons (<2% aromatics) 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

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FATTY ACIDS, C8-C16, 2-ETHYLHEXYL ESTERS

This dossier on fatty acids, C8-C16, 2-ethylhexyl esters presents the most critical studies pertinent to the risk assessment of fatty acids, C8-C16, 2-ethylhexyl esters 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: Fatty acids, C8-C16 (even numbered), 2-ethylhexyl esters

CAS RN: [redacted]

Molecular formula: $C_{16}H_{32}O_2$ to $C_{24}H_{48}O_2$

Molecular weight: 256 to 352

SMILES:

Octanoic acid, 2-EH ester
O=C(OCC(CCCC)CC)CCCCCCC

Decanoic acid, 2-EH ester
O=C(OCC(CCCC)CC)CCCCCCCCC

Dodecanoic acid, 2-EH ester
O=C(OCC(CCCC)CC)CCCCCCCCCCC

Fatty acids, C8-C16, 2-ethylhexyl esters is an UVCB substance (substance of Unknown or Variable Composition, Complex Reaction Products or Biological Materials).

The main components of fatty acid, C8-C16, 2-ethylhexyl esters produced by BASF are 2-ethylhexyl laurate [C12] (CAS No. [redacted] and 2-ethylhexyl octanoate [C8] (CAS No. [redacted]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Fatty Acids, C8-C16, 2-Ethylhexyl Esters

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Clear, slightly yellow liquid	2	ECHA
Melting Point	-53 to -30°C	1	ECHA
Boiling Point	-	-	-
Density	870 kg/m^3 @ 20°C (calculated)	2	ECHA
Vapor Pressure	<0.029 Pa @ 20°C (calculated)	2	ECHA
Partition Coefficient (log K_{ow})	6.68 to 8.65* (calculated)	2	ECHA
Water Solubility	<0.05 mg/L @ 20°C (measured)	2	ECHA
Flash Point	186°C	1	ECHA
Auto flammability	235°C	2	ECHA
Viscosity	7.4 mPa s @ 20°C	2	ECHA

*Calculated from KOWWIN v 1.67 in EPISUITE™ v. 4.00 (EPA, 2017). Due to the fact that this substance is a long-chain hydrocarbon which exceeds the applicability domain of KOWWIN, the value for log K_{ow} is reported with restrictions. The applicability domain covers log K_{ow} up to 10 (maximum), so these values should be given as log K_{ow} >10. The concrete value is reported to show the high lipophilic nature of the substance.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Fatty acids, C8-C16, 2-ethylhexyl esters are readily biodegradable. They have a low potential to bioaccumulate. They are highly insoluble in water and have high adsorption potential; thus, sediment and soil are expected to be the main targets for environmental distribution.

B. Biodegradation

In an OECD 301 D test, 97% (2 mg/L) and >65% (5 mg/L) were degraded after 30 days, indicating that fatty acids, C8-C16, 2-ethylhexyl esters are readily biodegradable (ECHA) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption
No experimental studies are available on fatty acids, C8-C16, 2-ethylhexyl esters. Using KOCWIN in EPISUITE™ (EPA, 2017), the estimated K_{oc} values of the surrogate dodecanoic acid, 2-ethylhexyl ester from the molecular connectivity index (MCI) and from log K_{ow} are 79,726 and 200,032 L/kg, respectively (ECHA). [Kl. score = 2]

D. Bioaccumulation

No experimental studies are available on fatty acids, C8-C16, 2-ethylhexyl esters. Using BCFBAF in EPISUITE™, the estimated BCF of the surrogate dodecanoic acid, 2-ethylhexyl ester is 1,054 L/kg based on a regression based estimate and 39.76 L/kg based on the Arnot-Gobas model which includes biotransformation and upper trophic. There would be rapid metabolism of fatty acid esters (initial hydrolysis by carboxylesterases) and excretion of linear aliphatic fatty acid esters from fish. Thus, bioaccumulation is not expected (ECHA). [Kl. score = 2]

IV. HUMAN HEALTH HAZARD ASSESSMENT

Information can be found in the ECHA database under fatty acids, C8-C16, 2-ethylhexyl esters (CAS No. [redacted] as well as under 2-ethylhexyl laurate (CAS No. [redacted]

A. Summary

Fatty acids, C8-C16, 2-ethylhexyl ester has virtually no acute toxicity by the oral and dermal route. It is not irritating to the skin and eyes, and is not a skin sensitiser. No adverse effects were seen in animals given repeated doses by the oral route. Fatty acids, C8-C16, 2-ethylhexyl esters are not genotoxic when tested in both *in vitro* and *in vivo* assays. There is no indication that this substance will cause malformations or have an adverse effect on reproduction and development. Some of this information was derived from information in part from products of similar structures or composition.

B. Toxicokinetics/metabolism

Fatty acids, C8-C16, 2-ethylhexyl esters is expected to be hydrolyzed to 2-ethylhexanol and the corresponding saturated linear fatty acids in the body by serum carboxylesterases. The saturated linear fatty acids are metabolized via normal intermediary metabolism in the body. 2-Ethylhexanol is oxidized to 2-ethylhexanoic acid, which is further metabolized primarily by oxidation to dicarboxylic acid metabolites.

C. Acute Toxicity

The oral LD_{50} in rats of fatty acids, C8-C16, 2-ethylhexyl esters is >2,000 mg/kg (ECHA). [Kl. score = 2]. The oral LD_{50} in rats of 2-ethylhexyl laurate is >2,000 mg/kg (ECHA). [Kl. score = 2]

The inhalation 4-hour LC_{50} of 2-ethylhexyl oleate (as an aerosol) in rats is > 5.7 mg/L (ECHA). [Kl. score = 2]

No acute dermal studies are available.

D. Irritation

Application of 0.5 ml of fatty acids, C8-C16, 2-ethylhexyl esters to the skin of rabbits for 4 hours under occlusive conditions was slightly irritating; it was considered non-irritating according to GHS classification (ECHA). [Kl. score = 2]

Instillation of 0.5 ml of 2-ethylhexyl laurate into the eyes of rabbits was not irritating (ECHA). [Kl. score = 2]

E. Sensitization

Fatty acids, C8-C16, 2-ethylhexyl esters was not considered a skin sensitizer in a guinea pig maximization test (ECHA). [Kl. score = 2]

F. Repeated Dose Toxicity

Oral
Studies are not available for fatty acids, C8-C16, 2-ethylhexyl esters; however, a 28-day oral gavage study has been conducted on fatty acids, C8-C14, 2-ethylhexyl esters.

Male and female SD rats were dosed by oral gavage with 0, 100, 300, or 1,000 mg/kg fatty acids, C8-C14, 2-ethylhexyl esters 5 days/week for 28 days. There were no treatment-related effects on clinical signs, body weights, feed consumption, hematology and clinical chemistry parameters, neurotoxicity, necropsy observations, and histopathology. The NOAEL is 1,000 mg/kg-day, the highest dose tested (ECHA). [Kl. score = 2]

Inhalation
No studies are available.

Dermal
No studies are available.

G. Genotoxicity

In Vitro Studies

Fatty acids, C8-C14, 2-ethylhexyl esters were not mutagenic to *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in the absence or presence of metabolic activation (ECHA) [Kl. score = 2].

2-Ethylhexyl oleate was not mutagenic in a mouse lymphoma assay with or without metabolic activation (ECHA) [Kl. score = 2].

There was no increase in chromosomal aberrations when peripheral human lymphocytes were treated with 2-ethylhexyl oleate with or without metabolic activation (ECHA) [Kl. score = 2].

In Vivo Studies

There were no increases in the incidence of micronucleated cells in the bone marrow of male and female CD-1 mice given a single intraperitoneal injection of 0, 1,075, 2,150, or 4,300 mg/kg fatty acids, C8-C16, 2-ethylhexyl esters (ECHA). [Kl. score = 2]

H. Carcinogenicity

No studies are available.

I. Reproductive Toxicity

Male and female SD rats were given in their diet ethyl oleate for 91 days. The estimated daily intakes are 0, 1,800, 3,600, and 5,500 mg/kg-day for males; and 0, 2,000, 3,900, and 6,100 mg/kg-day for females. There were no treatment-related effects on estrus cycles in females, sperm characterization in males, and histologic examination of male and female reproductive organs. The NOAEL for reproductive toxicity is 5,500 and 6,100 mg/kg-day for males and females, respectively (Bookstaff *et al.*, 2004; ECHA). [Kl. score = 2]

J. Developmental Toxicity

Female pregnant SD rats were dosed by oral gavage with 0, 100, 300, or 1,000 mg/kg 2-ethylhexyl stearate on gestational days 6 to 15. There was no maternal or developmental toxicity, with the NOAEL being 1,000 mg/kg-day, the highest dose tested (ECHA). [Kl. score = 2]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for fatty acids, C8-C16, 2-ethylhexyl esters 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>
No repeated dose toxicity studies have been conducted on fatty acids, C8-C16, 2-ethylhexyl esters. However, a 28-day oral gavage study with rats was conducted on a similar material: fatty acid, C8-C14, 2-ethylhexyl esters. No effects were seen in this study and the NOAEL was 1,000 mg/kg-day, the highest dose tested (ECHA). The NOAEL from this study 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 = 1,000/(10 x 10 x 1 x 10 x 1) = 1,000/1,000 = 1.0 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 = (1.0 x 70 x 0.1)/2 = 3.5 mg/L

B. Cancer

There are no carcinogenicity studies on fatty acids, C8-C16, 2-ethylhexyl esters. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Fatty acids, C8-C16, 2-ethylhexyl esters do not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Fatty acids, C8-C16, 2-ethylhexyl esters are of low acute concern to aquatic organisms, at least in the range of its water solubility.

B. Aquatic Toxicity

Acute Studies
Table 2 lists the results of acute aquatic toxicity studies on fatty acid, C8-C16, 2-ethylhexyl esters.

Table 2: Acute Aquatic Toxicity Studies on Fatty Acids, C8-C16, 2-Ethylhexyl Esters

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Zebrafish	96-h LC_{50}	>10,000*	2	ECHA
Daphnia magna	48-h EC_{50}	>100** >100 (filtered test solution)[1]	1	ECHA
Daphnia magna	48-h EL_{50}	>100 (WAF)	1	ECHA
Scenedesmus subspicatus	72-h EC_{50}	<100 >100 (filtered test solution)[1]	2	ECHA

*There was increased turbidity of the test solutions with increasing concentrations; this indicates that effect concentrations exceeded the solubility of the test substance in the test medium.
**An average of 50% of the Daphnia were glued to oil drops at the surface or remained glued to the vessel walls.
[1]NOEC = 100 mg/L.

It should be noted that the water solubility of fatty acids, C8-C16, 2-ethylhexyl esters is <0.05 mg/L (ECHA).

Chronic Studies

A 21-day *Daphnia* reproduction test was conducted on fatty acids, C8-C16, 2-ethylhexyl esters. The test substance was stirred for 16 hours to 7 days; after a settling period of 2 hours, the solution was filtered through a glass fiber filter (activated with 1 mL NaOH and washed with deionized water). There was 10% mortality at 100 mg/L, but no mortality in control and at 1 mg/L. For reproduction, the EC_{50} and NOEC were >100 and >1 mg/L, respectively (ECHA) [Kl. score = 1].

C. Terrestrial Toxicity

The 14-day LC_{50} of isopropyl myristate (CAS No. 110-27-0), a surrogate for fatty acids, C8-C16, 2-ethylhexyl esters, to earthworms was >20,000 mg/kg soil dry weight (ECHA). [Kl. score = 2]

D. Calculation of PNEC

The PNEC calculations for fatty acids, C8-C16, 2-ethylhexyl esters follow the methodology discussed in DEWHA (2009).

PNEC water

Experimental results are available for three trophic levels. For the invertebrate and algal studies, there were no effects at the WAF loading rate or filtered test solution (100 mg/L

nominal). Long-term studies are also available for two trophic levels. For the chronic Daphnia study, the EC_{50} for reproduction is greater than the filtered tested solution at 100 mg/L (nominal), which is likely to be close to or at the water solubility limit. Assuming that the exposure concentration in the filtered test solutions (100 mg/L nominal) and WAF is the water solubility limit (saturation) for fatty acid, C8-C16, 2-ethylhexyl esters, the EC_{50} values and NOECs are >0.05 mg/L. On the basis that the data consists of short-term studies from three trophic levels and long-term studies from two trophic levels, an assessment factor of 50 has been applied to water solubility of fatty acids, C8-C16, 2-ethylhexyl esters of 0.05 mg/L. The $PNEC_{aquatic}$ is 0.001 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 1.2 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (1532/1280) \times 1000 \times 0.001$
$= 0.019$

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]

$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 3189/1000 \times 2400]$
$= 1,532$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$
$= 79,726 \times 0.04$
$= 3,189$

Where:
K_{oc} = organic carbon normalized distribution coefficient (L/kg). The K_{oc} for fatty acids, C8-C16, 2-ethylhexyl esters calculated from EPISUITE™ using the MCI is 79,726 L/kg.
F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC soil

Experimental results are available for one trophic level on a surrogate of fatty acids, C8-C16, 2-ethylhexyl esters. The acute LC_{50} value to earthworms is >20,000 mg/kg soil dry weight. On the basis that the data consist of one short-term result from one trophic level, an assessment factor

of 1,000 has been applied to the acute LC_{50} value of 20,000 mg/kg for earthworms. The $PNEC_{soil}$ is 20 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).

Fatty acids, C8-C16, 2-ethylhexyl esters are readily biodegradable; thus they do not meet the screening criteria for persistence.

Based on the estimated BCF values, fatty acids, C8-C16, 2-ethylhexyl esters do not meet the screening criteria for bioaccumulation.

The NOEC values from chronic aquatic toxicity studies on fatty acids, C8-C16, 2-ethylhexyl esters are greater than its water solubility. Thus, it does not meet the screening criteria for toxicity.

The overall conclusion is that fatty acids, C8-C16, 2-ethylhexyl esters are not PBT substances.

IX. CLASSIFICATION AND LABELLING

A. Classification

No classification.

B. Labelling

No signal word.

C. Pictogram

None.

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

A. First Aid

Eye Contact
Rinse immediately with plenty of running water. If easy to do, remove contact lenses. Get medical attention if symptoms persist.

Skin Contact
Wash with soap and water. Get medical attention if symptoms occur.

Inhalation
Treat symptomatically. Move to fresh air. Get medical attention if symptoms persist.

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, carbon dioxide.

Specific Exposure Hazards
None known.

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.

Environmental Precautions
Not regarded as dangerous to the environment.

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
No special precautions are necessary beyond normal good hygiene practices.

Other Handling Precautions
Wash hands thoroughly after handling.

Storage
Keep container closed.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Workplace Australia has not established an occupational exposure standard for fatty acids, C8-C16, 2-ethylhexyl esters.

Engineering Controls
Good general ventilation should be used.

Personal Protection Equipment

Respiratory Protection:
Respiratory protection is not required.

Hand Protection:
Minimize skin contact.

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

Eye protection*:*
Minimize eye contact.

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

F. Transport Information

Fatty acids, C8-C16, 2-ethylhexyl esters 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

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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.

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GLYCERINE
[GLYCEROL]

This dossier on glycerine presents the most critical studies pertinent to the risk assessment of glycerine 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 glycerol (OECD, 2002), 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): Glycerol

CAS RN: [redacted]

Molecular formula: $C_3H_8O_3$

Molecular weight: 92.09

Synonyms: Glycerine; glycerin; glycerol; glycyl alcohol; 1,2,3-propanetriol; trihydroxypropane

SMILES: C(C(CO)O)O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Glycerine[1]

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Clear, water-white, viscous, sweet-tasting hygroscopic liquid.	2	ECHA
Melting Point	18.17°C	2	ECHA
Boiling Point	290°C	2	ECHA
Density	1.2611 g/ml or g/cm^3 @ 20°C	2	ECHA
Vapor Pressure	<0.001 mm Hg at room temperature	2	ECHA
Partition Coefficient (log K_{ow})	-1.75 @ 25°C (measured)	2	ECHA

[1] Substance is known to be on the EEA market in nanomaterial form.

Property	Value	Klimisch score	Reference
Water Solubility	Completely miscible @ 25^{o}C	2	ECHA
Flash Point	195.6^{o}C; 177^{o}C; 199^{o}C	2	ECHA
Auto flammability	370^{o}C; 429^{o}C	2	ECHA
Viscosity	1.41 Pa s @ 20^{o}C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Glycerine is readily biodegradable. It is not expected to bioaccumulate. Based on the estimated K_{oc} value, glycerine is expected to be highly mobile in sediment and soil.

B. Biodegradation

Glycerine was readily biodegradable in an OECD 301D test. Degradation was 57% after 5 days, 84% after 15 days, and 92% after 30 days (OECD, 2002) [Kl. score = 2].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for glycerine. Using KOCWIN in EPISUITE™ (EPA, 2017), the estimated K_{oc} value from log K_{ow} is 0.1345 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 1 L/kg.

D. Bioaccumulation

No bioconcentration studies have been conducted on glycerine. Glycerine is not expected to bioaccumulate based on the experimental log K_{ow} of -1.75 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Glycerine has virtually no acute toxicity by the oral and dermal routes. It is non-irritating to the skin and eye and is not a skin sensitizer. No systemic toxicity was seen in animals repeatedly exposed by the dermal and inhalation routes, but liver effects were seen in rats given very high doses in the diet. Glycerine is not genotoxic. Lifetime dietary studies showed no carcinogenic effects in rats. No reproductive or developmental effects were seen in animals given high doses of glycerine in the diet.

B. Toxicokinetics/Metabolism

Glycerol is an intermediate in carbohydrate and lipid metabolism in living organisms.

C. Acute Toxicity

The oral LD_{50} values are >5,000 to 58,400 mg/kg in rats, 4,250 to 38,000 mg/kg in mice, 7,750 and 10,000 mg/kg in guinea pigs (OECD, 2002). The oral LD_{50} value of 4,250 mg/kg in mice is not consistent with the range of values found in the available literature and is considered unreliable because of the lack of documentation of the study (OECD, 2002).

All rats died following a 2-hour exposure to saturated vapors of glycerine, while there was no mortality when the exposure was for only one hour (ECHA) [Kl. score = 2].

No deaths were seen in rabbits following dermal application for 8 hours under occlusive conditions. The dermal LD_{50} is >18,700 mg/kg (Hine *et al.*, 1953).

D. Irritation

Application of 0.5 ml glycerine to the skin of rabbits for 24 hours under occlusive conditions was not irritating (Weil and Scala, 1971; ECHA). [Kl. score = 2]

Instillation of 0.1 ml glycerine into the eyes of rabbits was non-irritating (Weil and Scala, 1971; ECHA).

E. Sensitization

Male guinea pigs were given ten 0.1 mL injections of a 0.1% solution of synthetic or natural glycerine in isotonic saline every other day over 20 days. Following a two-week period, an 0.05 mL injection was given of the 0.1% glycerine solution. There was no sensitizing response (Hine *et al.*, 1953).

F. Repeated Dose Toxicity

<u>Oral</u>
Male and female rats were given in their feed 0, 5, or 20% glycerine for 90 days. Glycerine samples from different companies were compared in separate groups of animals. Body weight gain was higher in the treated rats compared to the controls. The 20% males had increased liver weights relative to body weights with histopathologic changes of generalized cloudy swelling and hypertrophy of the parenchymal cells. The 20% females showed increased relative liver weights, but had generalized cloudy swelling in the liver. For the liver changes, there were no differences between the three glycerine samples. Relative heart weights were significant reduced in the 20% females from one glycerine sample, and relative kidney weights were increased in the 20% females from another glycerine sample; these changes were not accompanied by histopathological changes. The NOAEL for this study is 5% glycerine in the diet, which corresponds to an estimated daily intake of 4,580 and 6,450 mg/kg-day for males and females, respectively (ECHA). [Kl. score = 2]

Male and female Long-Evans rats were given in their feed 0, 5, 10, or 20% glycerine for two years (the 20% group were for 1 year only). The estimated daily intakes are 0, 2,000, 4,000, and 8,000 mg/kg-day for males; and 0, 2,500, 5,000, and 10,000 mg/kg-day for females. Treatment was discontinued after one year for the 20% animals for reasons that were not stated in the report. Data on mortality and clinical observations were not reported. There was a slight increase in food consumption in the ≥5% group males. No adverse effects were reported in males or females at any dose level. The NOAEL is 20% glycerine in the diet, which corresponds to 8,000 and 10,000 mg/kg-day for males and females, respectively (Hine et al., 1983; ECHA). [Kl. score = 2]

Female rats were given in their drinking water 0, 5% synthetic glycerine, or 5% natural glycerine for 6 months. There were no difference between the two glycerine samples. The treated rats gained more weight over the treatment period than the controls. There were no treatment-related hematological changes, and there were mild treatment-related kidney effects, as indicated by calcified masses in tubules near the junction of the cortex and medulla (Anderson et al., 1950; ECHA). [Kl. score = 2]

Inhalation

Male and female SD rats were exposed by inhalation (nose-only) to 0, 33, 165, or 660 mg/m^3 of aerosolized glycerine 6 hours/day, 5 days/week for 13 weeks. The mass median aerodynamic diameter (MMAD) was <2.0 µm (respirable). The only effect seen was localized irritation of the upper respiratory tract. The NOAEC for systemic toxicity is 660 mg/m^3, the highest exposure concentration tested. The NOAEC for localized effects (irritation) is 167 mg/m^3 (Renne, 1992; ECHA). [Kl. score = 2]

Dermal

Rabbits were given dermal applications of 0.5 to 5.4 ml/kg glycerine 8 hours/day for 45 weeks. No effects including irritation were noted. The NOAEL is 5.4 ml/kg, which is calculated to be 5,040 mg/kg-day (ECHA). [Kl. score = 2]

G. Genotoxicity

In Vitro Studies

The results of the *in vitro* studies on glycerine are presented below in Table 2.

Table 2: *In Vitro* Genotoxicity Studies on Glycerine

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	Haworth *et al.*, 1983; ECHA
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	Doolittle *et al.*, 1988; ECHA

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Mammalian cell gene mutation (CHO cells)		-	2	Doolittle *et al.*, 1988; ECHA
Sister chromatid exchange (human lymphocytes)	-	-	2	Doolittle *et al.*, 1988; ECHA
Unscheduled DNA synthesis (rat hepatocytes)	-	-	2	Doolittle *et al.*, 1988; ECHA
Chromosomal aberrations (CHO cells)	-	-	2	Doolittle *et al.*, 1988; ECHA

*+, positive; -, negative

In Vivo Studies

No studies are available.

H. Carcinogenicity

Oral

Male and female Long-Evans rats were given in their feed 0, 5, 10, or 20% glycerine for two years (the 20% group were for 1 year only). The estimated daily intakes are 0, 2,000, 4,000, and 8,000 mg/kg-day for males; and 0, 2,500, 5,000, and 10,000 mg/kg-day for females. Treatment was discontinued after one year for the 20% animals for reasons that were not stated in the report. Data on mortality and clinical observations were not reported. The tumor incidences were similar between treated and control animals (Hine et al., 1953; ECHA). [Kl. score = 2]

I. Reproductive Toxicity

In a two-generation reproductive toxicity study, male and female rats were dosed by oral gavage with 0 or 20% glycerine solution (in water). There were no treatment-related effects on growth, reproductive performance, fertility, and no histopathological changes in the tissues examined. The NOAEL for this study is 20% glycerine in water, which the daily intake was estimated to be 2,000 mg/kg-day (OECD, 2002; ECHA). [Kl. score = 2]

J. Developmental Toxicity

Pregnant female Wistar rats were dosed by oral gavage with 0, 13.1, 60.8, 282, or 1,310 mg/kg-day glycerine during gestational days 6 to 15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 1,310 mg/kg-day, the highest dose tested (ECHA). [Kl. score = 2]

Pregnant female CD-1 mice were dosed by oral gavage with 0, 12.8, 59.4, 276, or 1,280 mg/kg-day glycerine during gestational days 6 to 15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 1,280 mg/kg-day, the highest dose tested (ECHA). [Kl. score = 2]

Pregnant female Dutch rabbits were dosed by oral gavage with 0, 11.8, 54.8, 254.5, or 1,180 mg/kg-day glycerine during gestational days 6 to 18. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 1,280 mg/kg-day, the highest dose tested (ECHA). [Kl. score = 2]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for glycerine 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

Liver effects were seen in male and female rats in a 90-day dietary study, with a NOAEL of 5% glycerine in the diet. This dose corresponds to an estimate daily intake of 4,580 and 6,450 mg/kg-day for males and females, respectively (ECHA). In a two-year dietary study, no effects were seen in male or female rats at a dose of 20% glycerine in the diet. It should be noted, however, that the treatment at the dietary level of 20% was for only one year, while the lower doses (5 and 10%) were for two years. No liver effects were noted at any dose level. The NOAEL for the two-year dietary study is the 20% dietary level which corresponds to estimated daily intakes of 8,000 and 10,000 mg/kg-day, for males and females, respectively (Hines et al., 1953; ECHA).

The NOAEL of 4,580 mg/kg-day from the males rats in the 90-day dietary study 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 = 4,580/(10 x 10 x 1 x 10 x 1) = 4,580/1,000 = 4.6 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, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (4.6 x 70 x 0.1)/2 = 16 mg/L

B. Cancer

Glycerine was not carcinogenic to rats in a two-year dietary study. Therefore, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Glycerine does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Glycerine is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies
Table 3 lists the results of acute aquatic toxicity studies on glycerine.

Table 3: Acute Aquatic Toxicity Studies on Glycerine

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-h LC_{50}	54,000	2	ECHA
Sheepshead minnow	96-h LC_{50}	>11,000	2	ECHA

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Daphna magna	24-h EC_{50}	>10,000	2	ECHA
Scenedesmus quadricauda	8-d EC_0	>10,000	2	Bringmann, 1980; OECD, 2002

Chronic Studies
No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

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

PNEC water
Experimental results are available for three trophic levels, although the data on algae cannot be used for determining a PNEC value. Acute E(L)C_{50} values are available for fish (>11,000 mg/L) and *Daphnia* (>10,000 mg/L). On the basis that the data consists of short-term results from two trophic levels, an assessment factor of 100 has been applied to the lowest reported E(L)C_{50} value of 10,000 mg/L for *Daphnia*. The $PNEC_{aquatic}$ is 100 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 64 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.82/1280) \times 1000 \times 100$
$= 64$

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]

$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 0.04/1000 \times 2400]$
$= 0.82$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$
$= 1 \times 0.04$
$= 0.04$

Where:
K_{oc} = organic carbon normalized distribution coefficient (L/kg). The K_{oc} for glycerol calculated from EPISUITE™ using 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 1.3 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.02/1500) \times 1000 \times 100$
$= 0.13$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 1 \times 0.02$
$= 0.02$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for glycerol calculated from EPISUITE™ using 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).

Glycerine is readily biodegradable and thus does not meet the screening criteria for persistence.

No bioconcentration studies are available for glycerine. The measured log K_{ow} for glycerine is -1.75; thus glycerine does not meet the screening criteria for bioaccumulation.

The acute $E(L)C_{50}$ values for glycerine in fish, invertebrates, and algae are >1 mg/L. Thus glycerine does not meet the screening criteria for toxicity.

Therefore, glycerine is not a PBT substance.

IX. CLASSIFICATION AND LABELING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictogram

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 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.

Special Protective Equipment for Firefighters
Wear self-contained breathing apparatus for fire fighting.

C. Accidental Release Measures

Personal Precautions
Use appropriate protective equipment. Ensure adequate ventilation. Do not breathe vapors, mists, or gas.

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 and dispose of as hazardous waste.

D. Storage And Handling

General Handling
No special measures necessary provided product is used correctly.

Other Handling Precautions
Avoid inhalation of vapor or mist.

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 glycerine.

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 of closed work clothing is recommended.

F. Transport Information

Glycerol 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

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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 or shale 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. PHYSICO-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

Oral

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. 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

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]2C+

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 = <u>13 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, 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 = <u>46 mg/L</u>

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.

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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

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HYDROTREATED LIGHT PETROLEUM DISTILLATE

This dossier on hydrotreated light petroleum distillate (CAS RN [redacted] presents the most critical studies pertinent to the risk assessment of this substance in its use in coal seam or shale 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): 1,4-bis(propan-2-yl)benzene; 7,7-dimethylhexadecane; octadecane

CAS RN: [redacted]

Molecular formula: Not available (UVCB substance)

Molecular weight: Not available (UVCB substance)

Synonyms: Distillates, petroleum, hydrotreated light

SMILES: CC(C)C1=CC=C(C=C1)C(C)C.CCCCCCCCCCCCCCCCCC.CCCCCCCCCC(C)(C)CCCCCC

II. PHYSICO-CHEMICAL PROPERTIES

Hydrotreated light petroleum distillate is a UVCB substance (unknown variable composition or biological substance) containing aliphatic (linear, branched, and/or cyclic paraffins) molecules of carbon and hydrogen. Physical and chemical properties were not available for the UVCB hydrocarbon. As a result, information was obtained from a read-across substance (hydrodesulfurised kerosine). Key physical and chemical properties for the substance are shown in Table 1.

Table 1: Overview of the Physico-Chemical Properties of Hydrodesulfurised Kerosine (CAS RN [redacted])

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Liquid	2	ECHA
Melting Point	-49°C (pour point) @ 101.3 kPa.	2	ECHA
Boiling Point[1]	90 to 320°C @ 101.3 kPa	2	ECHA
Density	770 to 850 kg/m^3 @ 15°C	2	ECHA
Vapour Pressure	<1,000 to 37,000 Pa at 37.8°C	2	ECHA
Partition Coefficient (log K_{ow})	1.99 – 18.02 @ 20°C	2	ECHA
Water Solubility	0.000009 – 0.00645 g/L @ 25 °C	-	OECD
Viscosity	1.1 to 2.5 mm^2/s @ 20°C (kinematic)	2	ECHA
Auto flammability	220 - 250°C (for kerosines)	2	ECHA

[1] CAS numbers in this category indicate a boiling point range of 90-320 deg Celsius.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Representative substances are expected to be readily biodegradable. They are highly insoluble in water and have high adsorption potential. They have a low potential to bioaccumulate.

While sediment and soil are expected to be the main targets for environmental distribution, biodegradation potential is expected to offset sorption. In fact, fugacity modelling suggests that accumulation in sediment is expected to be several orders of magnitude less than 1%, relative to soil, water and air compartments.

B. Partitioning

Based on Henry's Law Constant values > 4.76 x 10^4 Pa-m^3/mol @25 ^oC, members of this group have the potential to volatilise from water or moist soil surfaces. These chemicals are unlikely to degrade by hydrolysis as they lack a functional group that is hydrolytically reactive. However, in the air, category members have the potential to rapidly degrade through indirect photolytic processes (OECD, 2012).

C. Biodegradation

Kerosine's are readily to inherently biodegradable. In the supporting OECD 301 study, naphtha solvents were readily biodegraded in 28 days but not within the 10-day window. The mean of three samples was 61% theoretical biological oxygen demand on Day 28. In a valid OECD 301F supporting study Kerosine Mid-Blend was not considered readily biodegradable in 28 days, with less than 60% degradation on day 28 (58.6%). However, according to USEPA guidance for biodegradability, it is considered inherently biodegradable because significant degradation occurred). Based on this and the known properties of hydrocarbons in the range C9 to C16, kerosines are often considered not readily biodegradable; but as they can be degraded by microorganisms, they are regarded as being inherently biodegradable.

If a chemical is found to be inherently or readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

D. Environmental Distribution

Standard adsorption/desorption studies are not applicable to petroleum UVCB substances. Mackay Level III modelling indicates that category member constituents partition mostly to the sediment and soil compartments rather than air compartment when an equal emission rate (1000 kg/hr) to the air, water, and soil compartment is assumed. When release occurs only to either the air, or soil compartment, constituents are indicated in the modelling to partition largely to the compartment to which they are released. When released to the water compartment, constituents are indicated by the model to partition to either water or sediment (HPVIS). However, based on the member category low solubility, partitioning to sediment would be expected.

E. Bioaccumulation

No experimental studies are available on the substance. Using BCFBAF in EPISuite™, the estimated BCF of a representative substance is 0.893 L/kg based on the Arnot-Gobas model that includes biotransformation and upper trophic. Thus, bioaccumulation is not expected (ECHA). [Kl. score = 2]

IV. HUMAN HEALTH HAZARD ASSESSMENT

The information presented within this Section was derived in part from read-across substances: hydrodesulfurised kerosine (CAS RN [redacted] and undiluted JP-8 jet fuel (CAS No. [redacted]

A. Summary

The substance has low acute toxicity by the oral and dermal route. It is not irritating to the skin and eyes, but it is a skin sensitiser. Aside from minor changes in body weight, no adverse effects were seen in animals given repeated doses by the oral route. The substance is not genotoxic when tested in both *in vitro* and *in vivo* assays. There is no indication that this substance will cause malformations or have an adverse effect on reproduction and development. This information was derived in part from products of similar structure or composition.

B. Toxicokinetics

The studies of the pharmacokinetics (i.e., absorption, distribution, metabolism and excretion) of kerosine are scarce. There are some *in vitro* and *in vivo* studies available on jet fuels. However, because jet fuel is a complex mixture, these studies use certain constituents of jet fuels as marker compounds to describe the total jet fuel's pharmacokinetics. There are more data available for a number of kerosine constituents, and these can be used as a basis for understanding the pharmacokinetics of kerosine as a whole. There are three ways in which humans are exposed to kerosine: by inhalation; ingestion; and dermal contact. Due to the relatively low volatility of kerosine and jet fuels, dermal exposure can be a more important route of exposure than exposure via inhalation. During many operations involving aircraft fuel tanks there is a significant potential for dermal exposure. Ingestion occurs primarily as a consequence of incidental ingestion.

Groups of five male C3H mice were dosed with a single dermal application of 15 or 60 µL kerosine (30% straight-run hydrotreated and 70% hydrocracked kerosine) spiked with radiolabelled naphthalene or tetradecane, and sacrificed after 96 h exposure (Mobil, 1994). Another group of five male C3H mice were exposed by air to the same compounds and doses in a metabolism cage to determine passive inhalation. The results of the dermal exposure show that 5% of the labelled tetradecane and 15% of the labelled naphthalene were absorbed over 96 h. The inhalation experiments showed that 2.8% of the labelled naphthalene was bioavailable. Comparison of these data with a similar dataset obtained with a 25% concentration of the test compounds diluted in mineral oil, revealed that dilution did not affect the absorption of the test compound.

Four groups of eight male Sprague-Dawley rats were exposed to 1, 4, 8, or 16 mL kerosine through the abdominal skin for 2 h at a skin area of 4, 8, 16 or 64 cm2, respectively (Tsujino et al., 2003). Before, during and after the experiment, blood samples were taken and analysed for trimethylbenzenes and aliphatic hydrocarbons. Trimethylbenzenes were detectable in blood within 5-20 min and showed a dose dependent absorption. High concentrations of aliphatic hydrocarbons were detected in the exposed skin as compared to the blood concentration. The aliphatic hydrocarbon levels were dependent on the amount of kerosine exposed per unit area.

The systemic distribution of kerosine components in the blood and tissues of rats following *in vitro* dermal exposures was investigated, using trimethylbenzenes and aliphatic hydrocarbons (C9-C16) as biomarkers (Tsujinoet al., 2002). The trimethylbenzenes were absorbed through the skin and detected in blood and tissues to a greater extent as compared to the aliphatics. The data indicate that kerosine components are absorbed percutaneously and distributed to the various organs via the blood circulation. Distribution of trimethylbenzenes in blood and tissues following dermal exposure

is (at decreasing concentrations): kidney > blood > liver > adipose > brain > spleen > lung = muscle. Distribution of aliphatics in blood and tissues following dermal exposure is (at decreasing concentrations): blood > adipose > muscle > lung > liver > kidney > spleen > brain.

The inhalation studies demonstrate that the volatile kerosine constituents are well absorbed (31 – 54%) and are distributed mainly in the fat tissue. Aromatics were metabolised at a higher rate than naphthenes, n-alkanes, isoalkanes and 1-alkenes. Dermal application of kerosine or jet fuel generally shows that the aromatics and aliphatics are well absorbed into the skin. Subsequently, the aromatics penetrate the skin at a higher rate than the alkanes. SKINPERM calculations indicate that although skin permeation rates of alkanes, naphthenes and aromatics are more or less comparable, the latency times of alkanes are longer than the latency times of naphthenes and aromatics. After absorption, the kerosine constituents are distributed via the blood circulation to the fat tissue and various organs. Studies with oral exposure to kerosine indicate that gastrointestinal absorption of kerosine is slow and incomplete, resulting in low bioavailability.

C. Acute Toxicity

Kerosines are of low acute toxicity, with an oral LD50 greater than 5,000 mg/kg (rat), a dermal LD50 greater than 2,000 mg/kg (rabbit), and an inhalation LC50 greater than 5.28 mg/L (rat). The most important effects in animals following very high oral doses were slight irritation of the stomach and the gastrointestinal tract. The only adverse effects observed in acute inhalation studies were decreased activity and breathing frequency at very high doses. Dermal application of kerosine did not lead to acute toxic systemic effects. Clinical effects observed were related to dermal irritation rather than to systemic toxicity. The acute toxicity of kerosine is not classified by EU CLP Regulation (EC No. 1272/2008).

Oral

In the key acute oral toxicity study (Klimisch score=1; ARCO, 1992a), groups of fasted (5 per sex), young adult, Sprague Dawley rats were given a single oral dose of undiluted thermocracked kerosine at a dose of 5,000 mg/kg bw and observed for 14 days. There were no treatment related mortalities. All of the study animals exhibited one or more of the following clinical signs: nasal discharge, ocular discharge, abnormal stools, lethargy, stained coat, and alopecia. All animals gained weight during study period. At necropsy, one of the ten animals exhibited visual lesions, the remaining nine showed signs of alopecia in the inguinal and/or perineal regions. The oral LD50 was determined to be greater than 5000 mg/kg in males and females.

In supporting studies conducted on kerosine substances, rats were administered single oral gavage doses of the test substance. The results supported an oral LD50 of > 5,000 mg/kg in males and females.

Inhalation

In the key acute inhalation toxicity study (Klimisch score = 1; API, 1987a), groups of Sprague-Dawley rats, five males and five females, were exposed by inhalation route to straight-run kerosine for 4 hours to their whole body at a single dose of 5.28 mg/L (vapour, analytical). All except one animal had normal growth rates throughout the study. The one exception on day 8 had a body weight less than its starting body weight but by the end of the study normal growth had resumed. All animals exhibited decreased activity during the exposure. Otherwise, there were no treatment-related clinical signs of toxicity. No macroscopic lesions were observed in any animal at post-mortem and no microscopic changes were observed in any lung section examined. The LC50 was greater than 5.28 mg/L.

In supporting studies conducted on kerosine substances, rats were administered single doses of the test substance via inhalation. The LC50s as measured based on mortality and systemic effects do not indicate classification of kerosine as an acute inhalation toxicant. One supporting study on deodorised kerosine showed a lack of systemic effects after repeated exposure to rats (6 hours each day for 4 days) and resulted in an LC50 of > 7.5 mg/L (Carpenter et al., 1976). Another supporting study on deodorised kerosine showed a lack of systemic effects after a single 6-hour exposure to cats and resulted in an LC50 of > 6.4 mg/L (Carpenter et al., 1976).

Dermal

In the key acute dermal toxicity study (Klimisch score=1; ARCO, 1992g), groups of young adult New Zealand White rabbits, five males and five females, were dermally exposed to undiluted thermocracked kerosine for 24 hours to 10% of their body surface area at a dose of 2,000 mg/kg. Animals were then observed for 14 days. There were no mortalities and all animals gained weight during the study. All of the animals exhibited one or more of the following clinical signs during the observation period: dermal irritation (erythema, oedema, eschar, fissuring and/or dried skin) and/or abnormal stools. Apart from skin irritation, there were no other abnormalities noted at necropsy. The dermal LD50 was determined to be greater than 2,000 mg/kg in both males and females.

In supporting studies conducted on kerosine substances, rabbits were administered single dermal doses of the test substance, and results supported a dermal LD50 of > 2,000 mg/kg in males and females.

D. Irritation

Skin

In the key study, young adult rabbits (6 females) were dermally exposed (occlusive coverage) to 0.5 mL of undiluted kerosine/heating oil for 24 hours on both intact and abraded skin sites. Each of the test sites was evaluated for skin responses for 9 days post-exposure and was scored using the Draize scale. The mean erythema score from 24 to 72 hours was 3.46/4 while the mean oedema score from 24 to 72 hours was 2.33/4. While this protocol deviates from current guidelines that state exposure should be semi-occlusive over 4 hours, and to intact skin only, this study is included as key to show the irritating nature of kerosine products.

In another guideline study conducted according to GLP and in accordance with current guidelines, young adult New Zealand White rabbits (3 per sex) were dermally exposed (semi-occlusive coverage) to 0.5 mL of undiluted odourless kerosine, for 4 hours. Animals were observed for seven days after exposure. Irritation was scored based on the Draize method (1959). The mean erythema score from 24 to 72 hours was 0.17/4 while the mean oedema score from 24 to 72 hours was 0/4.

Additional supporting studies are provided on straight run kerosine, odourless kerosine, hydrocracked kerosine, hydrodesulfurised kerosine, Jet Fuel A, Jet Fuel A1, JP-5, and Cherry Point Jet Fuel A. Most of the studies are valid in their methodology, but they differ from the current OECD guidelines in that animals were exposed under occluded conditions for 24 hours instead of semi-occluded conditions for 4 hours. Considering the conditions of the test, results must be interpreted carefully for the purposes of classification and labelling. The mean scores for erythema and oedema have been assessed against the deviations and provided the test would be conducted under standard conditions, the overall weight of evidence indicates that kerosines are irritating to skin. Kerosines are classified as irritating to the skin according to criteria in EU CLP Regulation (EC No. 1272/2008).

Effects on skin irritation/corrosion: irritating

Eyes

Several well-controlled (GLP) animal experiments performed on a variety of kerosines indicate that none of the kerosines and jet fuels tested were more than slightly irritating to the eyes. In addition, a number of short reports on eye irritation studies on JP-5 and JP-8 show no eye irritation whatsoever in rabbits (6 unwashed eyes; 3 washed eyes): all scores 0.0 for up to 7 days (end of the study). None of the hazard assessments of kerosine and jet fuel constituents have resulted in classification for eye irritation.

In the key study selected for primary eye irritation, 0.1mL of undiluted thermocracked kerosine was instilled into the conjunctival sac of the right eye of three female young adult New Zealand White rabbits and observed through 72 hours. Irritation was scored according to the Draize method (1959). There was no evidence of damage to the cornea or iris for all animals over all scoring periods. Mild conjunctivae indicators such as redness, chemosis, and discharge were evident at the one-hour scoring interval, but not at any of the other scoring intervals. Fluorescein staining scores were zero for all study animals over all scoring periods.

The average irritation score was 0.0 for the cornea, iris and conjunctivae.

Based on the evidence, kerosine is not an eye irritant.

E. Sensitisation

In animal assays for skin sensitisation such as the Magnusson-Kligman GPMT and the Buehler assay, kerosines and jet fuels did not trigger a positive response.

In the key dermal sensitisation study (Klimisch score=1; ARCO, 1992q), thermocracked kerosine in mineral oil was tested on male young adult Pig/Hartley guinea pigs using a modified Buehler technique. During the challenge phase, a second exposure of a 1:4 dilution of thermocracked kerosine to induced test animals did not yield higher response grades, severity, or incidence than those associated with the naive challenge control group exposed to thermocracked kerosine. During the challenge phase, exposure of 0.2% DNCB to induction positive control animals elicited significantly higher response grades, severity indices, and incidence over the naive DNCB challenge control group. The vehicle irritation control group was free of dermal irritation during the challenge phase. Therefore, under the conditions of this study, thermocracked kerosine is not considered a delayed contact sensitiser while DNCB induced an appropriate positive response.

Based on test data, there was no evidence of skin sensitisation; therefore, kerosine is not classified for skin sensitisation according to EU CLP Regulation (EC No. 1272/2008)

F. Repeated Dose Toxicity

Oral

In the key oral subchronic study (Klimisch score=1; Mattie et al., 2000), male rats were treated for 70 to 90 days with 0 (1mL of distilled water), 750, 1,500, or 3,000 mg/kg/day of undiluted JP-8 jet fuel, then mated to untreated females (one female at a time). Males were gavaged throughout the cohabitation period and were returned to their individual cage after successful mating. In the second part of the study, female rats were administered the test compound at doses of 0 (1mL of distilled water), 375, 750, or 1,500 mg/kg/day undiluted JP-8 jet fuel for 90-day prior to mating, through

mating, gestation, delivery, and lactation for a total of 21 week. During mating, they were housed with untreated males.

There were no effects on clinical signs or mortality in either sex. Haematology, clinical chemistry, and urinalysis were measured only in females without any effects noted. Body weights in male rats were decreased in a dose-dependent manner and was likely related to nephropathy, which is specific in male rats treated with hydrocarbons, and not relevant for human exposure. In females, body weight was only significantly reduced in the high-dose group. Absolute and relative liver weights were increased in mid- and high-dose females but were not likely biologically significant due to the lack of changes in clinical chemistry or histopathology in the liver. The test compound caused perianal dermatitis (high-dose only) and stomach hyperplasia (mid- and high-dose) in the female rats. There was a dose-related decrease in pup weight that was significant in the 750 mg/kg/day group on postnatal day 4 only and in the 1,500 mg/kg/day group from postnatal day 4 through postnatal day 21 but had recovered by postnatal day 90. There were no treatment-related effects on reproduction or sperm parameters in males. There were no effects on reproduction, gestation, or litter size in females.

The study low observed adverse effect level (LOAEL) for systemic effects is 1,500 mg/kg/day and the no observed adverse effects level (NOAEL) for systemic effects is 750 mg/kg/day, based on reduced body weight in dams and in pups. The LOAEL for adult male rats exposed to JP-8 orally was 750 mg/kg/day due to changes in clinical pathology, body weight, organ weights and the same irritation seen in female rats. The decrease in male rat bodyweight is very likely due to the male rat-specific nephropathy and is therefore not considered for the derivation of the oral NOAEL. The reproduction NOAEL was 3,000 and 1,500 mg/kg/day in males and females, respectively.

Inhalation

In a key subchronic inhalation toxicity study (Klimisch score=1; Mattie et al., 1991), JP-8 jet fuel was administered to 95 male Fisher 344 rats, 75 female Fischer 344 rats, and 100 male and female C57BL/6 mice by dynamic whole body vapour exposure at concentrations of 0, 500 or 1,000 mg/m3(0, 0.5, or 1.0 mg/L) as a vapour for 24 hours per day, 7 days/week for a total of 90 days. The male rats developed hydrocarbon-induced nephropathy at both treatment concentrations. Male rats had decreased body weight and decreased absolute and relative kidney weight at both treatment concentrations. Female rats were unaffected by treatment. In mice, no significant clinical signs of toxicity were noted that differentiated the groups that were treatment-related. The no observed adverse effect concentration (NOAEC) for male rats is difficult to establish, since potential adverse effects may be masked by male rat specific hydrocarbon nephropathy. However, based on the hydrocarbon-induced nephropathy and reduced body weights and increased kidney weights, the lowest observed adverse effects concentration (LOAEC) in male rats is 500 mg/m^3. The LOEC for male mice is also 500 mg/m^3, but it was not treatment related. The NOAEC for female rats and mice is greater than or equal to 1,000 mg/m3. This was the highest dose tested in the study.

In a subacute inhalation toxicity study (Klimisch score = 1; API, 1986), hydrodesulfurised kerosine vapour was administered to 20 Sprague-Dawley rats/sex/concentration by dynamic whole-body exposure at a concentration of 24 mg/m^3 (0.024 mg/L) for 6 hours per day, 5 days/week for 4 weeks. There were no compound related effects in mortality, clinical signs, body weight, haematology, clinical chemistry, organ weights, or gross and histologic pathology. Therefore, the NOAEC is greater than or equal to 24 mg/m^3. This was the highest dose tested in the study.

Dermal

In a key sub-chronic dermal study hydrodesulfurised kerosine was applied at concentrations of 20, 40 or 60% (v/v) at a rate of 1 ml/kg/day to the shorn intrascapular region of groups of 12 individually housed male and female, Sprague-Dawley rats (aged 7-9 weeks). This was equivalent to doses of test material of 165, 330 or 495 mg/kg/day. Dosing was continued for five days a week for 13 weeks. In addition, a group of 12 male and 12 female rats of similar age were administered mineral oil at a dose rate of 1 ml/kg/day; these animals served as vehicle controls. 12 rats/sex/group each in the vehicle controls and high dose group were maintained for a 4-week recovery period. Ingestion of the test material was prevented by using a collar and removal of any residual test or control material from the skin. Animals were observed for clinical signs prior to dosing and 1, 6 and 24 hours after the first dose. Subsequently, observations were made prior to each dose being applied.

Prior to the administration of each dose, the treated skin site was evaluated for dermal irritation using the Draize scoring method. Body weights were recorded prior to the first dose and weekly thereafter. An ophthalmic examination was conducted on each rat prior to application of the first dose and again prior to sacrifice at the end of the study. During the week prior to the first dose, each rat was subjected to a functional observation battery (FOB). The FOB was conducted again 1, 6 and 24 hours after the first dose and at 7 and 14 days. During the study, the FOB, motor activity and startle response testing was conducted on all rats at weeks 4, 8 and 12. At week 14 blood samples were collected from 12 animals/sex/group. Full necropsies were performed at week 14 on 6 rats/sex/group and at week 18 on the recovery rats (vehicle and high dose groups). Each full necropsy included an examination of the external surface of the body and its contents. The remaining six rats of each group were anesthetized with an intraperitoneal injection of Pentothal and transcardially perfused in-situ using 10% neutral-buffered formalin and given a limited necropsy. For these rats, no organs were weighed, and specific tissues were also collected for subsequent microscopic testing.

There was a generally dose-related increase in the incidence and severity of various skin conditions at the treated site. Males seemed to be more sensitive than females as they were affected at all doses, however, the effects indicated very little irritation. Recovery group animals revealed complete recovery in the females and minimal hyperkeratosis in the high dose group males. At necropsy no substance-related observations were made for males in any group. In the females there was a suggestion of a possible treatment-related effect which occurred in 7 rats across all groups and consisted of skin crusts or ulceration at the site of application of test material. Haematological and serum clinical parameters were unaffected by treatment.

All animals survived until scheduled termination. There were no test substance-related effects on survival, clinical observations (apart from skin irritation), neurobehavioral signs or ophthalmological findings. The NOEL for systemic toxicity was >495 mg/kg/day. The LOEL for slight dermal irritation was 165 mg/kg/day, equivalent to ~ 1 mg/cm^2.

G. Genotoxicity

In vitro Gene Mutation in Mammalian Cells

Key in vitro gene mutation studies in mammalian cells were identified. In a study by the American Petroleum Institute (API, 1984b), cultures of mouse lymphoma cells were exposed to hydrodesulfurised kerosine with or without metabolic activation by Aroclor 1254-induced rat liver S9 fraction. Under non-activation conditions the test material induced a good range of toxicities for evaluation (relative growths ranged from 2.8% to 65.3%). None of the assays induced a mutant

frequency that exceeded the minimum criterion (40.8 x 10-6). The test material was not mutagenic under non-activation conditions. In the presence of metabolic activation, a wide range of toxicities was induced (6.1 to 107.9% relative growths). The minimum criterion mutant frequency of 69.0 x 10-6 was not exceeded. The test material was therefore considered non mutagenic under activation conditions. In a study by API (1977) (Klimisch score = 1), mouse lymphoma L5178Y cells were exposed to straight-run kerosine in acetone vehicle at concentrations ranging from 0.04 to 0.065 µL/mL (with metabolic activation) or 0.006 to 0.13 µL/mL (without activation). There was no evidence that straight-run kerosine induced mutant colonies over background levels.

In vitro Cytogenicity in Mammalian Cells

Hydrodesulfurised kerosine was tested in the sister chromatid exchange assay using Chinese hamster ovary cells (API, 1988a). The assay was conducted with Aroclor-induced rat liver S-9 activation system. A small but statistically significant increase in the frequency of sister chromatid exchanges was observed at the high and low concentrations with metabolic activation. These increases appeared to be random and of no biological significance. There were no significant increases observed at any concentration in the absence of metabolic activation. Under the conditions of the study, hydrodesulfurised kerosine is negative in the sister chromatid exchange assay with Chinese hamster ovary cells.

In vivo Cytogenicity

Based on weight of evidence kerosine substances were found to be non-mutagenic through cytogenic investigations.

In six in vivo bone marrow cytogenetic studies in the rat, there were no indications of chromosomal aberrations. Although an in vivo Sister Chromatid Exchange study in the mouse gave positive findings in the male group (but not in the females) the positive findings in the males were associated with signs of toxicity (lethargy and weight loss) at the very high-top dose used in the study (4,000 mg/kg), both on the day of the administration of the kerosine and the day after (when they were sacrificed).

In a rat bone marrow micronucleus assay (API, 1985c, Klimisch score = 1), straight run kerosine (CAS RN [redacted] was administered to Sprague Dawley rats. Straight run kerosine was not considered to induce chromosomal aberrations in bone marrow cells of rats. In another bone marrow micronucleus assay (API, 1984b, Klimisch score = 1), hydrodesulfurised kerosine (CAS RN [redacted] was administered to rats. No clinical signs of toxicity were exhibited by the rats, and there was no significant increase in frequency of micronucleated polychromatic erythrocytes in bone marrow as compared to control. In a study by API (1977) (Klimisch score = 1), straight-run kerosine (CAS RN [redacted] was administered to 45 male rats. No significant increase in the frequency of micronucleated polychromatic erythrocytes was observed.

In vivo Gene Mutation

Key in vivo gene mutation studies were identified. In a sperm cell dominant lethal mutation assay (API, 1980b, Klimisch score = 1), Jet Fuel A was administered via inhalation route to male mice at concentrations of 100 or 400 ppm for a 6-hour exposure period, 5 days per week for 8 weeks. Males were mated with females, and the uteri of pregnant females were examined for living and dead implants. Jet Fuel A did not increase the incidence of post-implantation deaths. In another study by API (1973) (Klimisch score = 1), deodorised kerosine was administered subcutaneously to 10 male Swiss-Webster mice in corn oil vehicle or intraperitoneally to 10 Long-Evans rats undiluted at a dose of 1.0 mL/kg. Males were mated with females, and no pattern of decreased pregnancy rate or increased embryo loss was observed in the females.

H. Carcinogenicity

Kerosine is not carcinogenic when animals are exposed via the oral or inhalation route (ECHA).

Male mice were administered dermally 37.5µL of jet fuel A to the shaved backs of 50 mice per dose, twice a week for 2 years or intermittently so that application of the jet fuel was suspended when dermal irritation was noted in 20% of the group and was resumed when irritation resolved in all but 20% of the affected animals. There was a significant increase in tumours at the application site with continuous treatment compared to the control (0% versus 44%), but not with intermittent treatment (0% versus 2%). With continuous treatment, there was a treatment-related increase in dermal tumour incidence compared to controls. However, stopping treatment during dermal irritation nearly eliminated the carcinogenic effect (ECHA) [Kl. Score = 1].

Male and female mice were administered dermally 25 mg of petroleum-derived jet fuel A to the shaved backs of 25 mice, three times a week for 105 weeks. Due to high mortality, jet fuel A application was discontinued during week 62, but surviving animals were observed until study termination. There was a significant increase in tumours at the application site (0%, 26%, and 26% in the controls, JP-4, and jet A groups). The majority of the tumours were squamous cell carcinomas or fibrosarcomas. At the doses tested, there was a treatment-related increase in dermal tumour incidence when compared to controls. The results of the study indicate that there was a treatment-related increase in dermal tumour incidence when compared to controls, therefore it can be concluded that Jet fuel A has a carcinogenic effect on mice at 25 mg dosage (ECHA) [Kl. Score = 1].

Straight-run kerosine (CAS RN [redacted] and hydrodesulfurised kerosine (CAS RN [redacted] were tested in standard 2-year bioassays in mice. The animals, 50 per group, were treated twice weekly with 50 µl straight-run kerosine or with hydrodesulfurised kerosine. It was concluded that both straight-run and hydrodesulfurised kerosine were moderate skin carcinogens (ECHA) [Kl. Score = 2].

In the key carcinogenicity study from NTP, JP-5 navy fuel in acetone was administered to 50 mice dermally at dose levels of 0 (vehicle control), 250, or 500 mg/kg bw/day for up to 103 weeks. There was a significant decrease in survival in females at both treatment doses. Remaining high-dose females were sacrificed at week 90. There was no treatment-related effect on survival in male mice. The LOAEL is 250 mg/kg/day, based on dermatitis and decreased survival in females. No NOAEL can be determined. At the doses tested, there was not a treatment-related increase in tumour incidence when compared to controls (ECHA) [Kl. Score = 1].

The potential influence of skin irritation on tumour development in long-term mouse skin painting studies was investigated as part of the CONCAWE middle distillates programme. The study included straight run hydrotreated kerosine (MD3). The test material was applied to the shorn skin of three groups of 50 male mice for 104 weeks. For the straight run hydrotreated kerosine, skin tumours only developed in the group of animals in which substantial skin irritation occurred during the study. Since no polycyclic aromatic compounds were detected in the straight run kerosine it is concluded that the occurrence of tumours is likely to have been caused by a non-genotoxic mechanism. This conclusion is consistent with reports by others that lighter middle distillates are tumour promotors but not initiators and furthermore that skin irritation plays an important role in skin tumour development. These tumours are probably the consequence of a continuous cycle of cell damage and repair caused by chronic skin irritation. The conclusions gained from this study can be applied to other carcinogenicity studies on kerosines, and they show that tumours are noted in the presence of repeated dermal irritation, and that kerosines lack a genotoxic mechanism of carcinogenicity (ECHA) [Kl. Score = 1].

I. Reproductive Toxicity

There are no specific reproductive toxicity data for the substance but there are data available with ECHA as migrated information which is read-across based on grouping of substances (category approach).

An OECD Guideline 415 One-Generation Reproduction Toxicity study was conducted. This was a reproductive study performed in two parts. In the first part, males were treated for 70 to 90 days with 0 (1mL of distilled water), 750, 1,500, or 3,000 mg/kg/day of undiluted JP-8 jet fuel, then mated to untreated females (one female at a time). In the second part of the study, female rats were administered the test compound at doses of 0 (1mL of distilled water), 375, 750, or 1,500 mg/kg/day undiluted JP-8 jet fuel for 90 -day prior to mating, through mating, gestation, delivery, and lactation for a total of 21 weeks.

There were no changes in clinical signs or mortality in parental animals. Body weights in male rats were decreased in a dose-dependent manner. Terminal body weights were approximately 545 grams, 520 grams, 475 grams, and 315 grams in the control, 750, 1,500, and 3,000 mg/kg/day, respectively. In females, body weight was only significantly reduced in the high-dose group, but the differences were not significant at terminal sacrifice. The body weight in females at 20 weeks (1 week before sacrifice) was approximately 400 grams, 385 grams, 382 grams, and 335 grams in the control, 375, 750, and 1,500 mg/kg/day, respectively. Hematology was not measured in the males and no effects were noted in the females. Clinical chemistry was not measured in the males and no effects were noted in the females. Urinalysis was not measured in the males and no effects were noted in the females. Absolute and relative liver weights were increased in mid- and high-dose females but were not accompanied by any histological findings. The test compound caused perianal dermatitis (high-dose only) and stomach hyperplasia (mid- and high-dose) in the female rats.

There were no treatment-related effects on reproduction or sperm parameters in males. There were no effects on reproduction, gestation, or litter size in females. The lowest NOAEL based on parental body weight was determined to be 750 mg/kg/day.

The F1 generation was not examined for clinical signs though no mention would suggest no significant signs were noted. No mortality was observed. There were no effects on offspring viability. However, there was a dose-related decrease in pup weight that was significant in the 750 mg/kg/day group on postnatal day 4 only and in the 1,500 mg/kg/day group from postnatal day 4 through postnatal day 21. The 1,500 mg/kg/day group recovered by postnatal day 90. The NOAEL based on offspring body weight was determined to be 750 mg/kg/day.

J. Reproductive Toxicity/Developmental Toxicity

In a developmental toxicity study, undiluted JP-8 jet fuel was administered to 30 Sprague-Dawley (Crl:CD) rats/dose by gavage at various volumes to achieve dose levels of 0 (sterile water), 500, 1,000, 1,500, or 2,000 mg/kg bw/day from days 6 through 15 of gestation.

There was a significant decrease in maternal weight gain with doses of 1,000 mg/kg/day or greater. Maternal necropsy weight was significantly different than the control in the 1,500 and 2,000 mg/kg/day groups. There were no apparent clinical signs of toxicity. Reproductive endpoints were not assessed in this study because females were pregnant prior to treatment and did not deliver, so only developmental endpoints can be assessed. Thirteen females (one 1,000 mg/kg/day; three 1,500 mg/kg/day, and nine 2,000 mg/kg/day) were found dead. Although there appears to be a dose-dependent increase in the mortality, necropsy found the cause of death to be related to the

presence of the test compound in the lungs indicating dosing into the lungs instead of the gastrointestinal tract. The maternal LOAEL is 1,000 mg/kg/day, based on reduced body weight gain. The maternal NOAEL is 500 mg/kg/day.

There was a significant decrease in foetal weight in both male and female foetuses dosed with 1,500 and 2,000 mg/kg/day. The test compound did not significantly increase the incidence of malformations or variations compared to the control nor was the sex ratio altered. The developmental LOAEL is 1,500 mg/kg/day, based on reduced foetal weight. The developmental NOAEL is 1,000 mg/kg/day. It can be concluded that the test substance is not toxic to development.

This study received a Klimisch score of 1 and is classified as reliable without restrictions because it was carried out in a method equivalent/similar to OECD TG 414.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for the substance 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

The NOAEL for reduced maternal body weight is 500 mg/kg/day, based on reduced body weight in dams and in pups treated under a repeat dose regimen. The NOAEL from this study 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 = 500 /(10 x 10 x 1 x 10 x 1) = 500/1,000 = 0.5 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 = (0.500 x 70 x 0.1)/2 = 1.8 mg/L

Cancer

There are no carcinogenicity studies on the substance or related hydrocarbons. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

The substance does not exhibit the following physico-chemical properties:

- Explosivity
- Oxidising potential

The substance is classified as a "Flammable Liquid Category 3"

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The substance is of low acute concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies on hydrotreated light petroleum distillate surrogates.

Table 2: Acute Aquatic Toxicity Studies on Hydrotreated Light Petroleum Distillate Surrogate[2]

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Oncorhynchus mykiss	96-hour LL_{50}	2-5	1	ECHA
Daphnia magna	48-hour EL_{50}	1.4	1	ECHA
Raphidocelis subcapitata	72-hour EC_{50}	<1-3 (average of 2)	1	ECHA
Selenastrum capricornutum	72-hour EC_{50}	3.7	2	ECHA

Chronic Studies

There are no long-term toxicity studies on fish. A single long-term study on invertebrates is discussed below.

In a 21-day semi-static chronic reproductive toxicity test (OECD 211; KS = 1) on *Daphnia magna*, hydrodesulfurised kerosine was evaluated using water accommodated fraction methodology. The

[2] Hydrodesulfurised Kerosine (CAS RN [redacted]

actual loading rates were 0 (control), 0.08, 0.19, 0.48, 1.2 and 3.0 mg/L. Under the conditions of this test, the 21-day chronic reproductive NOEL for kerosine is 0.48 mg/L. The LOEL is 1.2 mg/L. The EL_{50} based on reproduction is 0.89 mg/L (ECHA).

C. Terrestrial Toxicity

There are no terrestrial toxicity studies for this substance.

D. Calculation of PNEC

The PNEC calculations for hydrotreated light petroleum distillate follow the methodology discussed in DEWHA (2009).

PNEC Water

Experimental results are available from acute tests on three trophic levels. There is one long term study on a single trophic level organism, *D. magna*.

On the basis that the data consists of short-term studies from three trophic levels and a long-term study from one trophic level, an assessment factor of 100 is applied to the 21-day chronic reproductive NOEL for kerosine of 0.48 mg/L. The $PNEC_{aquatic}$ is 0.005 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 0.36 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (93.4/1280) \times 1000 \times 0.005$
$= 0.36$ mg/kg

Where:
$K_{sed\text{-}water}$ = suspended matter-water partition coefficient (m^3/m^3) [calculated]
BD_{sed} = bulk density of sediment (kg/m^3) = 1,280 [default]

$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed}/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 193/1000 \times 2400]$
$= 93.4\ m^3/m^3$

And:
Kp_{sed} = solid-water partition coefficient (L/kg).[calculated]
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$
$= 4818 \times 0.04$
$= 193$ L/kg

Where:
K_{oc} = organic carbon normalized distribution coefficient (L/kg). The K_{oc} for hydrodesulfurised kerosine calculated from EPISUITE™ using the MCI is 4818 L/kg.
F_{oc} = fraction of organic carbon in sediment = 0.04 [default].

PNEC Soil

There are no experimental toxicity testing results available for the substance or its noted surrogates. Therefore, the $PNEC_{soil}$ was calculated using the equilibrium partitioning method. The $PNEC_{soil}$ is 0.32 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (96.4/1500) \times 1000 \times 0.005$
$= 0.32$ mg/kg

Where:
Kp_{soil} = soil-water partition coefficient (m3/m3)
BD_{soil} = bulk density of soil (kg/m3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 4818 \times 0.02$
$= 96.4\ m^3/m^3$

And:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for hydrodesulfurised kerosine calculated from EPISUITE™ using the MCI is 4818 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, 2017).

The substance or similar compounds are readily biodegradable; thus they do not meet the screening criteria for persistence.

Based on the estimated BCF values, derived from EPISuite estimates (BCF = 3.162 L/kg wet-weight) the substance does not meet the screening criteria for bioaccumulation.

The NOEC values from acute and chronic aquatic toxicity studies on the substance indicate it does not meet the screening criteria for toxicity.

Therefore, hydrotreated light petroleum distillates are not PBT substances.

IX. CLASSIFICATION AND LABELLING

A. Classification

Asp. Tox. 1

B. Labelling

Danger

C. Pictogram

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

A. First Aid

Eye Contact

Rinse immediately with plenty of running water. If easy to do, remove contact lenses. Get medical attention if symptoms persist.

Skin Contact

Wash with soap and water. Get medical attention if symptoms occur.

Inhalation

Treat symptomatically. Move to fresh air. Get medical attention if symptoms persist.

Ingestion

In case of ingestion, always assume that aspiration has occurred. Do not induce vomiting. 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

Foam (Specifically trained personnel only)- Water fog (Specifically trained personnel only)- Dry chemical powder- Carbon dioxide- Other inert gases (subject to regulations)- Sand or earth

Specific Exposure Hazards

None known.

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.

Environmental Precautions

Do not release to open drains or surface water. Not regarded as dangerous to the environment.

Steps to be Taken if Material is Released or Spilled

Collect free product with suitable means. Transfer collected product and other contaminated materials to suitable containers for recycle, recovery or safe disposal. Absorb spill with inert absorbent material, then place in a container for chemical waste.

D. Storage and Handling

General Handling

Ensure that all relevant regulations regarding explosive atmospheres, and handling and storage facilities of flammable products, are followed.

Other Handling Precautions

Wash hands thoroughly after handling.

Storage

Keep containers tightly closed and properly labelled. Protect from the sunlight5.3. Light hydrocarbon vapours can build up in the headspace of containers. These can cause flammability / explosion hazard.

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:
Respiratory protection is not required.

Hand Protection:
Minimize skin contact.

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

Eye protection:
Minimize eye contact.

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

F. Transport Information

The substance retains UN 1223 transport code is listed as such within the Australian Dangerous Goods (AUS 2018)

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

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HYDROXYPROPYL GUAR

This dossier on hydroxylpropyl guar presents the most critical studies pertinent to the risk assessment of hydroxypropyl guar 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: Hydroxylpropyl Guar

CAS RN: [redacted]

Molecular weight: 200,000 to 300,000 daltons (Glickman, 1969)

Hydroxypropyl guar a propylene glycol ether derivative of guar gum. Guar gum is a resinous material derived from milled endosperm from guar beans of the legume *Cyamopsis tetragonolobus*. Structurally, it is a galactomannan (high molecular weight carbohydrate polymer) consisting of a main chain of D-mannose with a side chain of D-galactose at approximately every second mannose unit. The mannose units are β-(l-4) linked, and the single D-galactose units are joined to the main chain by α-(1-6) linkages.

SYNONYMS: Hydroxypropyl guar; hydroxypropyl guar gum; guar gum, 2-hydroxypropyl ether

II. PHYSICAL AND CHEMICAL PROPERTIES

Hydroxypropyl guar is a white to yellow fine powder that is very slightly soluble in water (Johnson et al., 2015).

III. ENVIRONMENTAL FATE PROPERTIES

No biodegradation studies are available on hydroxypropyl gum. Hydroxypropyl guar is the propylene glycol derivative of a carbohydrate polymer consisting of D-mannose and D-galactose sugars from the guar bean. It is expected to be readily biodegradable.

Hydroxypropyl guar is not expected to bioaccumulate based on its large molecular weight.

IV. HUMAN HEALTH HAZARD ASSESSMENT

As the propylene glycol derivative of guar gum, hydroxypropyl guar would be expected to have similar toxicological properties to guar gum. Thus, the toxicity data on guar gum have been used to read-across to hydroxypropyl guar.

A. Summary

There are no mammalian toxicity data available on hydroxypropyl guar, except for one *in vitro* genotoxicity study; thus data on guar gum have been used to read-across to hydroxypropyl guar. Guar gum is 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 showed minimal toxicity in dietary studies. Unlike guar gum, hydroxylpropyl guar was mutagenic in an Ames test in the presence, but not absence, of metabolic activation. Oral exposure to guar gum did not affect fertility in rats; nor was there any indication of developmental toxicity in rats or mice.

B. Acute Toxicity

There are no acute toxicity studies available for hydroxypropyl guar. The oral LD_{50} for guar gum in rats was reported to be 7,060 mg/kg (Graham et al., 1981). [Kl. score = 2]

C. Irritation

There are no irritation studies available for hydroxypropyl guar. Guar gum is non-irritating to the skin, and minimally irritating to the eyes (McCarty *et al.*, 1990).

D. Sensitization

There are no animal sensitization studies available for either hydroxypropyl guar or guar gum. However, under REACH, some data submitters indicate they consider this substance a respiratory sensitizer.

E. Repeated Dose Toxicity

Oral

There are no repeated dose toxicity studies available for hydroxypropyl guar.

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. 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% 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. The LOAEL for this study is 691 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 is 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; U.S. EPA), 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, 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; U.S. EPA), the NOAELs corresponds 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

Hydroxypropyl guar was not mutagenic to *S. typhiumurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 in the absence of metabolic activation. In the presence of metabolic activation hydroxypropyl guar was mutagenic to S. typhimurium strains TA 98, TA 100, TA 1537, and TA 1538, but not to TA 1535 (Johnson et al., 2015).

In Vivo Studies

There are no studies available for hydroxypropyl guar.

G. Carcinogenicity

There are no studies available for hydroxypropyl guar.

H. Reproductive Toxicity

Oral
There are no studies available for hydroxypropyl guar.

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. 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
There are no studies available for hydroxypropyl guar.

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 fetuses per litter were slightly reduced, but was not statistically significantly different from controls. The authors indicate 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 fetal development or sex distribution, and there was 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 was 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 is 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, 2011).

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 nonneoplastic lesions observed 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, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (13 x 70 x 0.1)/2 = 46 mg/L

B. Cancer

There are no carcinogenicity studies on hydroxypropyl guar. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Hydroxypropyl guar does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

No studies are available on the aquatic or terrestrial toxicity of hydroxypropyl guar. As the hydroxypropyl derivative of guar gum, it would be expected to have similar properties to a non-ionic polymer and exhibit low to potentially moderate acute toxicity to aquatic organisms.

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).

Hydroxypropyl guar is a derivative of 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 molecular weight of hydroxypropyl guar ranges from 200,000 to 300,000 daltons. Thus, guar gum is not expected to meet the criteria for bioaccumulation.

No aquatic toxicity data are available on hydroxypropyl guar. It is not possible to determine whether hydroxypropyl guar meets the toxicity criteria.

The overall conclusion is that hydroxypropyl guar is unlikely to be a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Serious health hazard

B. Labelling

Danger!
According to the classification provided by companies to ECHA in CLP notifications this substance may cause allergy or asthma symptoms or breathing difficulties if inhaled. Some data submitters indicate they consider this substance a respiratory sensitizer.

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 hydroxypropyl guar.

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

Hydroxypropyl guar 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

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IRON GLUCONATE

This dossier on iron gluconate presents the most critical studies pertinent to the risk assessment of iron gluconate 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC):

CAS RN: [redacted]

Molecular formula: $C_{12}H_{22}FeO_{14}\cdot 2H_2O$

Molecular weight: 446.14 g/mol

Synonyms: Iron gluconate; iron digluconate;

SMILES: C(C(C(C(C(C(=O)[O-])O)O)O)O)O.C(C(C(C(C(C(=O)[O-])O)O)O)O)O.[Fe+2]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Iron Gluconate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Light yellow-green solid with a mild burnt sugar.	2	ECHA
Melting point	>120°C (decomposition)	1	ECHA
Density	0.79 g/cm^3 @ 20°C	1	ECHA
Vapor pressure	586.5 Pa @ 25°C	1	ECHA
Partition coefficient (log K_{ow})	-7.7 (QSAR)	2	EPA, 2019
Water solubility	118 g/L @ 25°C	1	ECHA
Auto flammability	No self-ignition was observed.	1	ECHA

Iron gluconate dissociates in aqueous media to

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Iron gluconate is expected to biodegrade readily, and has low potential to bioaccumulate.

B. Biodegradation

No biodegradation studies are available on iron gluconate involving freshwater organisms.

In an OECD 306 test involving seawater, degradation of iron gluconate after 28 days was 79% and 78% at concentrations of 6.0 and 7.5 mg/L, respectively. Iron gluconate was considered ready biodegradability but failed the 10-day window (ECHA) [Kl. score = 2].

In a Ready Biodegradability Closed Bottle test (EU Method C.4-E), degradation of sodium gluconate (CAS No. [redacted] was 67% after 3 days, indicating ready biodegradability (ECHA) [Kl. score =2].

In an OECD 302 B inherent biodegradability Zahn-Wellens/EMPA test, degradation of sodium gluconate (CAS No. [redacted] was 98.9% after 3 days (ECHA) [Kl. score = 2].

Using BIOWIN v4.10 in in EPISUITE™ (EPA, 2019), iron gluconate is expected to be readily biodegradable.

Based on the results of the above studies, iron gluconate is expected to be readily biodegradable.

C. Environmental Distribution

<u>Adsorption/desorption</u>
No experimental data are available for iron gluconate. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value from the molecular connectivity index (MCI) is 18.4 L/kg.

D. Bioaccumulation

There are no bioaccumulation studies on iron gluconate. Using BCFBAF v3.01 in EPISUITE™ (EPA, 2019), an estimated BCF value of 3.162 L/kg was determined for iron gluconate, indicating that it has a low potential for bioaccumulation.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Based on the available data, iron gluconate is not toxic via the oral or dermal exposure routes, and no data exists to evaluate the inhalation risks. Iron Gluconate did not contain any structural alerts for skin or eye irritation. The lack of alerts and the physical-chemical properties indicate that iron gluconate should not be reactive to the skin or the eye. There are no skin sensitisation studies on ferrous gluconate. Results of a study conducted with a structurally similar compound, D-gluconic acid found no sensitization. There is no information on repeated dose toxicity on iron gluconate, but one read-across study, a 28-day repeated dose toxicity study (KL = 1), is available for the oral route of exposure that reported reliable no-effect levels on repeated dose toxicity and reproductive and developmental endpoints. No effect levels for repeated dose toxicity were found at 125 mg/kg-bw, and at 500 mg/kg-bw for reproductive and developmental endpoints. Iron gluconate was deemed not genotoxic by read-across in one study.

B. Acute Toxicity

Based on the available data, iron gluconate is not toxic via the oral or dermal exposure routes, and no data exists to evaluate the inhalation risks.

The acute oral toxicity of iron gluconate was assessed in one study (Kl = 2) with Sprague-Dawley rats; the LD50 was 2237 mg/lg. At doses higher or equal to the LD50, stomach and small intestine were dilated and filled with dark fluid and occasionally blood. Stomach and small intestine mucosa were covered with grey-green granular material. Caecum and large intestine contained black liquid feces. At sub-lethal doses, occasional dilation of upper gastrointestinal tract with fluid. Small hemorrhages were seen in stomach or small intestine. Black liquid farces was reported. A read-across study tested D-gluconic acid in Sprague-Dawley rats (Kl = 2) found a LD50 of greater than 2,000 mg/kg bw via the dermal exposure route.

C. Irritation

Iron Gluconate did not contain any structural alerts for skin or eye irritation. The lack of alerts and the physical-chemical properties indicate that iron gluconate should not be reactive to the skin or the eye.

Iron Gluconate, which can be read across to D-Gluconic acid due to the comparable structures and relevant properties has been tested for skin and eye irritation. Gluconic Acid was applied three times successively at a duration of three minutes, one hour, and four hours, respectively (exposure of one animal) to the skin of New Zealand white rabbits. No dermal response to treatment was observed in any animals throughout the

observation period. One dose consisting of 0.1 mL was applied to the eyes of rabbits with the eyelids held closed for one second to prevent loss of dose. Ocular changes were assessed and recorded immediately, one hour after treatment, 24 hours, 48 and 72 hours after treatment. did not induce colouration of the eye and did not interfere with grading of lesions (Kl = 2). 24 hours after instillation, one animal had severe chemosis with lacrimation and severe redness of the conjunctivae, lesions of iris and cornea on an area greater than one quarter. 72 hours after instillation, only slight chemosis and slight redness of the conjunctivae persisted. No ocular lesion persisted in any animal at the end of the exposure period.

D. Sensitization

There are no skin sensitisation studies on ferrous gluconate. Results of a study conducted with a structurally similar compound, D-gluconic acid, are reported and used for read across (Kl = 2). Groups of four mice were treated with the undiluted test material or the test material at concentrations of 50% or 25% v/v in dimethyl formamide; no sensitization was noted. Based on this result, D-Gluconic Acid is not sensitising. Via read across iron gluconate is not classified as a sensitiser.

E. Repeated Dose Toxicity

There is no information on repeated dose toxicity on iron gluconate, but one read-across study is available for the oral route of exposure that reported reliable no-effect levels; there are no other studies available for the other exposure routes on REACH.

A 28-day repeated dose toxicity study (KL = 1) tested a read-across substance iron dichloride (CAS No. [redacted] (NIER, 2004). Male and female SD rats were dosed with the test substance (0 (Control group), 125, 250 and 500 mg/kg/day) from two weeks before mating. Male SD rates were dosed once a day till two weeks after mating while female SD rats were dosed once a day up to postpartum day 4. A total of 42 doses were provided for male rats while female rates had 42 to 54 dosages depending on mating and delivery of individuals. Clinical signs and mortality were observed and body weight and food and water consumption were measured. In the necropsy, gross examination of organs and tests on corpus luteum graviditatis and implantation rates were conducted. In addition, tests for sensory and motor functions, urinalysis and hematological and blood chemical tests were given and organ weights were measured for five individuals randomly selected from each group. External abnormalities, sex ratio, body weights, CRL (Crown Rump Length) and survival rate were observed on postpartum days 0 and 4.

During the observation period, the main group dosed with the substance showed signs such as melaena (black stool) and salivation but these signs were observed to disappear after dosing in the recovery group. There was no mortality in male SD rats, but three mortalities took place in female individuals at 500 mg/kg. The cause for mortalities was presumably the gastrointestinal damage by the substance. It was found that male

individuals were more sensitive to body weight and food consumption than female counterparts. The change by the test substance was not recognized in mating data, sensory functions, motor functions, urine analysis and blood test. Gastric hemorrhage with blackened liver and black pigmentation of liver discovered in the necropsy findings was presumed to be caused by the test substance, but it was found to improve for the recovery period of two weeks. Weight changes in the liver and adrenal were observed in the absolute and relative organ weights of male individuals at 250 and 500 mg/kg and female individuals at 500 mg/kg. The histopathological test found parenchymal hemosiderosis and hyperplasia of adrenocortical zona fasciculate as well. It was found that the substance had no effect on birth rate, survival rate, body weight and CRL of neonates. As a result of the test, the NOAEL of repeated doses to male and female SD rats were 125 and 250 mg/kg/day, respectively.

F. Genotoxicity

There are few studies for this endpoint on ferrous gluconate. In a bacterial reverse mutation assay (Kl = 2), S. typhimurium TA 1535, 1537, 1538 glucono-delta-lactone was negative both with and without metabolic activation. However, some of the positive controls did not appear to be valid. In a mammalian germ cell study (Kl = 4) (Drosophila SLRL assay), iron gluconate did not contain any structural alerts for mutagenicity. The lack of alert and the physical-chemical properties indicate that iron gluconate should not be reactive to DNA.

From this read across ferrous gluconate is classified as non-hazardous for this endpoint.

G. Reproductive and Developmental Toxicity

There are no toxicity to reproduction studies on iron gluconate. Results of a studies conducted with a structurally similar compounds: Iron Sucrose, Ferric Carboxymaltose and iron (II) chloride are reported and used for read across.

Iron (II) Chloride is a good read across material for evaluating the reproductive toxicity potential of iron gluconate because of similarities in their phys/chem properties and similar systemic exposures absorption, distribution, and elimination properties by the oral route of administration. Via read across Iron Gluconate is not classified as toxic to reproduction.

A 28-day repeated dose toxicity study (KL = 1) tested a read-across substance iron dichloride (CAS No. [redacted] with Sprague-Dawley rats (NIER, 2004). No treatment-related effects were observed on mean live neonates, birth rates, survival rates and sex ratios on days 0 and 4 post-partum. The only abnormalilty found in the external appearance examinations is an acaudate was observed in one neonate at 500 mg/kg. Crown Rump Length (CRL) of female neonates showed a significant decrease at 125 mg/kg on Day 4 post-partum. There were no treatment-related effects on reproductive

functions in parental animals and development of neonates at any doses tested. The NOAEL for reproduction and developmental toxicity was considered to be 500 mg/kg/day.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for iron gluconate 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 lowest NOAEL from these studies is 125 mg/kg-day based on a 28-day repeated dose toxicity study (KL = 1) based on no difference in organ weights, which were observed at higher doses (NIER, 2004). The NOAEL of 125 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 = 125/(10 x 10 x 1 x 10 x 1) = 125/1000 = 0.1 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, 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. 4 mg/L

B. Cancer

Iron gluconate is not a carcinogen, so no cancer reference value or drinking water guideline was developed for carcinogenic endpoints.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Iron gluconate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The substance demonstrates a relatively low level of acute aquatic toxicity. Data from specific tests are shown below.

B. Aquatic Toxicity

Acute Studies

There are no aquatic toxicity studies on iron gluconate using freshwater species. Table 2 lists the results of acute aquatic toxicity studies on iron gluconate using marine species.

Table 2: Acute Aquatic Toxicity Studies on Iron Gluconate (Seawater Species)

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Scophthalmus mamimus	96-hr LC_{50}	>1,000	1	ECHA
Acartia tonsa	48-hr EC_{50}	296.2	1	ECHA
Skeletonema costatum	72-hr EC_{50}	265.7	1	ECHA

Table 3 lists the results of acute aquatic toxicity studies on sodium gluconate (CAS No. [redacted]

Table 3: Acute Aquatic Toxicity Studies on Sodium Gluconate (CAS No. [redacted])

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oryzias latipes	96-hr LC_{50}	>100	2	ECHA
Daphnia magna	48-hr EC_{50}	>1,000	2	ECHA
Desmodesmus subspicatus	72-hr EC_{50}	>1,000	1	ECHA

Chronic Studies
No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

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

PNEC water
Experimental results are available for three trophic levels with seawater, but not freshwater species. Acute $E(L)C_{50}$ values are available for fish (>1,000 mg/L), invertebrates (296 mg/L), and algae (266 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 $E(L)C_{50}$ value of 266 mg/L for algae. The $PNEC_{water}$ is 2.7 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 $PNEC_{soil}$ is 0.7 mg/kg soil dry weight.

The calculations are as follows:

$$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$$
$$= (0.37/1500) \times 1000 \times 2.7$$
$$= 0.7$$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 18.4 \times 0.02$
$= 0.37$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for benzaldehyde based on the molecular connectivity index (MCI) is 18.4 L/kg (EPA, 2018).
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).

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

Based on an estimated BCF of 3.162, iron gluconate does not meet the screening criteria for bioaccumulation.

There are no chronic aquatic toxicity studies on iron gluconate. The acute $E(L)C_{50}$ values are >1 mg/L. Thus, iron gluconate does not meet the screening criteria for toxicity.

The overall conclusion is that iron gluconate is not a PBT substance.

IX. CLASSIFICATION AND LABELING

A. Classification
Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008

B. Labeling
Danger

C. Pictogram

(Pubchem 2020)

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

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.

Ingestion
Rinse mouth with water and then drink plenty of water. Do not induce vomiting. Never give anything by mouth to an unconscious person. Seek medical attention.

B. Fire Fighting Information

Extinguishing Media
Water spray or fog, carbon dioxide, dry powder.

Specific Exposure Hazards
Burning produces harmful and toxic fumes.

Special Protective Equipment for Firefighters
Wear a self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions
No special precautions are necessary. Ensure adequate ventilation.

Environmental Precautions
Do not discharge into drains, sewers, or waterways.

Steps to be Taken if Material is Released or Spilt
For large amounts: dike spillage and pump off the product. For residues: pick up with suitable absorbent material. Dispose of contaminated material as prescribed.

D. Storage and Handling

General Handling
Handle in accordance with good industrial hygiene and safety practice.

Other Handling Precautions

Protect against fire and explosion: prevent electrostatic charge; sources of ignition should be kept well clear, and fire extinguishers should be kept handy.

Storage
Keep container tightly closed and dry. Protect against heat. Store below 25oC.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Occupational exposure standards for the low molecular weight PEGs have not been established.

Engineering Controls
Provide local exhaust ventilation to control vapours and mists.

Personal Protection Equipment
Respiratory Protection:
Respiratory protection in case of vapours/aerosol release. Wear a certified organic vapour/particulate respirator.

Hand Protection:
Chemical resistant protective gloves.

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

Eye protection:
Body protection must be chosen depending on activity and possible exposure. Safety glasses with side-shields.

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
Not restricted or not applicable

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

NICNAS: Listed

XIII. REFERENCES

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METHANOL

This dossier on methanol presents the most critical studies pertinent to the risk assessment of methanol in its use in coal seam or shale 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).

NICNAS has assessed methanol in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to the environment

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. PHYSICO-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.

A. Occupational Exposure Standards

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.

B. 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.

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1,4-DIOXANE-2,5-DIONE, 3,6-DIMETHYL-, (3R-CIS)-, POLYMER WITH (3S-CIS)-3,6-DIMETHYL-1,4-DIOXANE-2,5-DIONE AND TRANS-3,6-DIMETHYL-1,4-DIOXANE-2,5-DIONE
[Polylactide resin]

This dossier on disodium;(9,11-dioxido-5-oxoboranyloxy-2,4,6,8,10,12,13-heptaoxa-1,3,5,7,9,11-hexaborabicyclo[5.5.1]tridecan-3-yl)oxy-oxovorane (designated in this dossier as PLA) 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): disodium;(9,11-dioxido-5-oxoboranyloxy-2,4,6,8,10,12,13-heptaoxa-1,3,5,7,9,11-hexaborabicyclo[5.5.1]tridecan-3-yl)oxy-oxovorane

CAS RN: [redacted]

Molecular formula: (C6H8O4.C6H8O4.C6H8O4)x

Molecular weight: 128,000–152,000 g/mol

Synonyms: Polylactide resin, polymer of lactic acid, PLA

SMILES: None

II. PHYSICAL AND CHEMICAL PROPERTIES

PLA polymers range from amorphous glassy polymer to semi-crystalline and highly crystalline polymers with a glass transition 60–65 °C and a melting temperature range of 130-180 °C.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

No readily available experimental data are available regarding the environmental fate of the substance. However, given the plasticine nature of the polymer and its high molecular weight, bioconcentration, bioaccumulation, and sorption are not expected to be appreciable.

Data from degradation testing according to standard methods are not available. However, there is evidence that PLA can undergo degradation via isolated and variable bacterial populations (Li et. al. 2008) (Tokiwa and Calabia 2006).

Since there are no available data obtained from standard and there is evidence that bacterial degradation may occur, PLA is not considered a persistent substance for the purposes of this dossier.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

No readily available experimental data are available regarding the human health hazards fate of the substance. In solid form, the substance is essentially non-toxic. Polylactic Acid (PLA) when used in medical implants will degrade within the body over time. It is often used in food handling and it is accepted as GRAS (Generally Recognized as Safe) by the Food and Drug Administration (FDA) and suitable for using in food and beverage packaging Conn et. al. (1995).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Given the noted lack of toxicity information and the GRAS status of the substance, toxicological reference values were not developed according to methodology discussed in enHealth (2012).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

The substance does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

However, it should be noted that flowing product can create electrical charge, resulting sparks may ignite dust or cause an explosion in some concentration ranges.

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

No readily available experimental data are available regarding the environmental hazard (aquatic or terrestrial) or fate of the substance.

B. Calculation of PNEC

Given the relative lack available toxicity data and its generally recognized safe status, no PNEC values for water, sediment or soil were derived for the substance.

VIII. PERSISTENCE, BIOACCUMULATION AND TOXICITY (PBT) ASSESSMENT

Sufficient data are not available to apply the methodology for the Persistent, Bioaccumulative and Toxic (PBT) substances assessment based on the Australian and EU Reach Criteria methodology (DEWHA, 2009; ECHA, 2008). However, given the biopolymeric nature of the substance, and its expected environmental lability, it is not expected to be ultimately persistent in the environment. As noted above, the substance is not expected to bioconcentrate or bioaccumulate, nor is it believed to be appreciably toxic.

Lastly, it should be noted that, according to the majority of notifications provided by companies to ECHA in CLP notifications, no hazards have been classified (ECHA).

Therefore, PLA is not considered a PBT substance for this dossier.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified

B. Labelling

None

C. Pictogram

None

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 body with soap and fresh water. Get medical attention.

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
Dust may form an explosive mixture with air, ignited by sparks or sources of ignition. Emits toxic fumes under fire conditions. Depending on conditions, decomposition products may include the following: carbon dioxide, carbon monoxide, aldehydes and ketones.

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 dust, mist, vapors, 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. Clean up promptly by scoop or vacuum. Sweep up and shovel into suitable containers for disposal. 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 excessive heat and light.

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. 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 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

The substance 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

EINECS: Substances inventory is not required.
United States TSCA (Toxic Substances Control Act) inventory: Listed
Canadian DSL (Domestic Substances List) inventory: Listed
Japanese ENCS (Existing & New Chemical Substances) inventory: Listed
Korean ECL (Existing Chemical List) inventory: Listed
People's Republic of China register - CRC-SEPA Administration): Listed
New Zealand Inventory of Chemicals (NZIoC): Listed
Australian AICS Inventory: Listed

XIII. REFERENCES

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POLYETHYLENE GLYCOL

This dossier on polyethylene glycol presents the most critical studies pertinent to the risk assessment polyethylene 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 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).

NICNAS has assessed polyethylene glycol in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to human health.[1]

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Poly(oxy-1,2-ethanediyl),α-hydro-ω-hydroxy- Ethane-1,2-diol, ethoxylated

CAS RN: [redacted]

Molecular formula: $C_{2n}H_{4n+2}O_{n+1}$

Molecular weight: variable (polymer)

Synonyms: Polyethylene glycol; poly(oxyethylene); polyethylene oxide

Polyethylene glycols (PEGs) are water-soluble linear polymers formed by the addition reaction of ethylene oxide to an ethylene glycol equivalent. The general formula for polyethylene glycol is: H-$(OCH_2CH_2)_n$-OH where "n" is the average number of repeating oxyethylene groups.

SMILES: **O{-}CC(n+}** (curly SMILES notation)

II. PHYSICO-CHEMICAL PROPERTIES

Key physical and chemical properties for the substance are shown in Table 1.

Table 1: Overview of the physico-chemical properties of polyethylene glycol

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Pale yellow organic liquid	1	ECHA
Melting Point	No freezing down to -14.08°C @ 97.4 kPa	1	ECHA
Boiling Point	205.7°C @97.8 kPa	1	ECHA
Density	1,116 kg/m^3@ 20°C and 97.6 kPa	1	ECHA
Vapour Pressure	10 Pa @ 20°C	1	ECHA
Partition Coefficient (log K_{ow})	-0.698 @ 30°C and pH of 6.44	1	ECHA

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

Property	Value	Klimisch Score	Reference
Water Solubility	256 g/L at 25°C	1	ECHA
Viscosity	289.87 mPa s @ 20°C (dynamic)	1	ECHA

Polyethylene glycols are water-soluble linear polymers formed by the addition reaction of ethylene oxide to an ethylene glycol equivalent. The general formula for polyethylene glycol is: $H\text{-}(OCH_2CH_2)_n\text{-}OH$ where "n" is the average number of repeating oxyethylene groups.

All of the lower molecular weight polyethylene glycols are liquid at room temperature; polyethylene glycols with higher molecular weights (defined as > 600 g/mol) exist as solids at room temperature.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Polyethylene glycol is readily biodegradable, and it is not expected to bioaccumulate. Polyethylene glycol has low potential to adsorb to soil and sediment.

B. Biodegradation

Polyethylene glycol is readily biodegradable. In an OECD 301D test, there was 75% degradation after 28 days, as determined by oxygen consumption (ECHA) [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).

C. Environmental Distribution

Experimental data are available for polyethylene glycol. In the key study, the soil organic carbon partition coefficient (K_{oc}) in soil and in sewage sludge of test chemical was determined by the Reverse Phase High Performance Liquid Chromatographic method according to OECD Guideline No. 121 for testing of Chemicals. The Log K_{oc} value of test chemical was determined to be 1.8568 dimensionless at 25°C (ECHA) [KI.score=1].

Using KOCWIN in EPISUITE™ (USEPA, 2019), the estimated soil organic carbon partition coefficient (K_{oc}) value from the molecular connectivity index (MCI) and K_{ow} method are 10 and 0.02935 L/kg, respectively (ECHA) [KI.score=2].

Based upon these K_{oc} values, if released to soil, polyethylene 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, polyethylene 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

Using BCFBAF in EPISUITE™, the estimated the estimated BCF for polyethylene glycol is 3.162 L/Kg (ECHA). [KI.score=2]. Based on this BCF value, the substance is not expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Polyethylene glycol is partially absorbed from the small intestine, can undergo metabolism in the body, and both polyethylene glycol and its metabolites are excreted mainly in the urine. Polyethylene glycol has low acute oral, inhalation, and dermal toxicity. It is not irritating to the skin or eyes. Polyethylene glycol is not a skin sensitiser. Polyethylene glycol is not likely to be genotoxic *in vitro* although it did induce chromosome aberrations at doses of 2mM. This substance has low oral and inhalation repeated dose toxicity. There are no available dermal repeated dose toxicity studies available. There are no *in vivo* genotoxicity studies and there are no carcinogenicity studies available. Polyethylene glycol is not considered a reproductive toxicant. However, polyethylene glycol exposure has been shown to have negative teratogenic effects such as foetal body weight, foetal loss and malformation.

B. Toxicokinetics and Metabolism

Low molecular weight polyethylene glycol is partially absorbed in the proximal small intestine following oral administration. About 50-65% of PEG 400 was shown to be absorbed in humans (Shaffer et al., 1950).

Metabolism of polyethylene glycol to acidic metabolites may occur following absorption. PEG and its acidic metabolites appear to be excreted in the urine and bile, with the biliary route playing a major role for the higher molecular weight PEGs (Herold et al., 1982).

C. Acute Toxicity

Oral

The lethal concentration LD_{50} value for acute oral toxicity test was considered to be >2000 mg/kg bw,when female wistar rats were treated with polyethylene glycol via oral gavage according to OECD Guideline 423 (Acute Oral toxicity - Acute Toxic Class Method) (ECHA) [KI.score =1].

Inhalation

No deaths were reported in rats exposed to an aerosol of 2,516 mg/m3 PEG 200 for 6 hours (OECD, 2004).

Dermal

The LD_{50} value was considered to be >2000 mg/kg bw when male and female wistar rats were treated with polyethylene glycol by dermal application (semiocclusive) following 14 days of observation period according to OECD Guideline 402 (Acute Dermal Toxicity) (ECHA) [KI.score=1].

D. Irritation

Skin

An acute dermal Irritation/corrosion study (OECD guideline 404) of polyethylene glycol was conducted using New Zealand White rabbits. The individual mean score at 24, 48 and 72 hours for the test animals were 0.33, 0.33, 0.33 and 0.00, 0.00, 0.00, for erythema and oedema formation, respectively. Hence, polyethylene glycol was regarded as non-irritating to the skin of female New

Zealand White rabbits under the experimental conditions tested and is thus not considered a skin irritant (ECHA) [KI.score=1].

Eye

An acute eye irritation/corrosion study (OECD guideline 405) of polyethylene glycol was conducted using female New Zealand white rabbits. Under the experimental conditions tested, eye irritation and reversibility of effects on the eyes was observed till 72 hours which were recovered on day 7. Hence, polyethylene glycol is not irritating to New Zealand White female rabbit eyes and is thus not considered an eye irritant (ECHA) [KI.score=1].

E. Sensitisation

Polyethylene glycol was considered to be not sensitising on skin of guinea pigs in a guinea pig maximisation test described by Magnusson and Kligman (ECHA) [KI.score=2].

F. Repeated Dose Toxicity

Oral

A 90-day sub chronic oral toxicity study was conducted using male and female Wistar rats exposed to 0, 2000, 4000, 8000, 16000, or 24000 mg/kg bw/day polyethylene glycol via dietary feed. Polyethylene glycol exposure showed no effect upon male and female rats when it was present in the diet at a dose level up to 8000 mg/kg/day (8% concentration) during a 90-day study period. But at 16000 mg/kg/day, the test chemical showed effects on organ weight (liver and kidney heavier than that of control rats);and a decrease in weight gain was observed. Thus, the NOAELs (no observed adverse effect level) for repeated dose oral toxicity was 8000 mg/kg/day whereas the LOAELs (low observed adverse effect level) for subacute repeated dose was 16000 mg/kg/day. (ECHA) [KI.score=2].

Inhalation

A sub-chronic inhalation toxicity study was conducted using male and female Fischer 344 rats exposed to 0, 100, 1000 mg/m^3 polyethylene glycol via whole body inhalation for 13 weeks (6 hours per day for 5 days a week). No pattern of significance could be related to polyethylene glycol exposure for the 13-week or the 30-day postexposure periods. The polyethylene glycol exposure did not product any adverse physiological effects on the rats exposed to the 100 and 1000 mg/m^3 concentrations for the various exposure periods. There were no consistently 'significant changes in rat blood chemistry at the end of the 6- or 13-week exposures or the 30-day postexposure period. It appears that polyethylene glycol produced no positive effects in the rodents at the 100 and 1000 mg/m3 test chemical concentrations over the 13 weeks of exposure used in this study. Thus, it is concluded that the no observed adverse effect concentration (NOAEC) of polyethylene glycol in rats was observed at dose level of 1000 mg/m3 (ECHA) [KI.score =2].

Dermal

No studies were located on polyethylene glycol.

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on polyethylene glycol are presented in Table 2.

Table 2: *In vitro* genotoxicity studies on polyethylene glycol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
In vitro gene mutation study in bacteria (Salmonella typhimurium strains TA100, TA1535, TA1537, and TA98)	-	-	2	ECHA
In vitro cytogenicity/chromosome aberration study in mammalian cells (mammalian cell line/CHEL cells)* did not induce chromosome aberrations at dose level of 2mM	+	+	2	ECHA
In vitro Mammalian cell gene mutation assay (OECD 476) Chinese hamster ovary (CHO) cells	-	-	1	ECHA

*+, positive; -, negative

In Vivo Studies

There are no studies available.

H. Carcinogenicity

No studies were located.

I. Reproductive Toxicity

A reproduction/developmental toxicity screening test (OECD 421) study was conducted using male and female Fischer 344 rats exposed to 0, 5000, 25000, 50000 ppm polyethylene glycol via their drinking water. Reproductive parameters, including number of fertile males and number of gravid females with viable implants, were not affected by test chemical treatment. There were no significant preimplantation losses or dominant lethal effects observed. Based on all the observation, and all the results it was concluded that the NOAEL for polyethylene glycol was found to be 5699 ± 1341 mg/kg (ECHA) [KI.score=4].

A two-year (three-generation reproductive toxicity) study was conducted using male and female Wistar rats exposed to 15, 59, 270, or 1690 mg/kg bw/day polyethylene glycol via their drinking water. The oral administration of polyethylene glycol to rats by drinking water, resulted in no injury to the test animals when administered in the drinking water over a two-year period. The 'No Observed Adverse Effect Level' (NOAEL) for reproductive toxicity was therefore considered to be 1690 mg/kg for the test chemicals (ECHA) [KI.score=2].

A multigeneration reproductive toxicity study was conducted using male and female ICR Swiss mice exposed to 0 and 1% (0 or 1667 mg/kg bw/day) polyethylene glycol via their drinking water. No significant changes in reproductive performance were observed in any of the matings. No adverse

effects were observed when fetuses were analysed for mean litter size, postnatal body weight and pup survival indices. The only significant change observed in both the dominant lethal and teratology screenings was an increase in the ratio of dead fetuses to live fetuses. Thus, based on all the observations and results, NOAEL for the Swiss ICF mice was 1% (1667 mg/kg bw) of the test chemical for the parental generation and the offspring generation (ECHA) [KI.score=2].

J. Developmental Toxicity

Oral

A prenatal developmental toxicity study (OECD Guideline 414) was conducted using Sprague-Dawley rats exposed to polyethylene glycol via an unspecified oral exposure for 20 days. Female rats were orally dosed on gestational days 6-14 or 11-16 with 1.5 -5 ml/animal/day (equivalent to 1500 -5000 ng/kg bw/d). Polyethylene glycol exposure was shown to have negative teratogenic effects as foetal body weight, foetal loss and malformation at dose levels of 1.5 - 5 ml/animal/day (equivalent to 1500 -5000 mg/kg bw/d) in 6-14 or 11-16 days of gestation period. Thus, the LOAEL was reported as 1.5 -5 ml/animal/day (equivalent to 1500 -5000 mg/kg bw), it is regarded that there is no teratogenic effects in the fetuses at concentrations 1.5 -5ml/animal/day (equivalent to 1500 -5000 mg/kg bw/d) when administered orally (ECHA) [KI.score=2].

In a developmental toxicity test, the teratogenic effects of oral polyethylene glycol exposure to female mice were assessed in a one generation in an overall estimation of 6-17 days of gestation. The teratogenic effects on external, visceral and skeletal malformations and body weight of fetuses by polyethylene glycol was observed at dose concentration 0.5 mg/animal/day (equivalent to 500 mg/kg bw/d) in 6-17 days gestation period. The dosage of the test chemical was given orally to mice on a daily basis and resulted in skeletal anomalies and external malformations. Thus, the LOAEL for teratogenicity study is considered to be 500 mg/kg/day (ECHA) [KI.score=2].

Inhalation

No studies were located.

Dermal

No studies were located.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for lower molecular PEGs 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

A two-year (three-generation reproductive toxicity) study was conducted using oral administration of polyethylene glycol to rats by drinking water. This exposure resulted in no injury to the test animals when administered in the drinking water over a two-year period. The NOAEL for reproductive toxicity was therefore considered to be 1690 mg/kg for the test chemicals. This value will be used to determine the oral reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / ($UF_A \times UF_H \times UF_L \times UF_{Sub} \times UF_D$)

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 = 1690/(10 × 10 × 1 × 1 × 1) = 1690/100 = <u>16.9 mg/kg/day</u>

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 = (16.9 × 70 × 0.1)/2 = <u>59.15 mg/L</u>

B. Cancer

There are no carcinogenicity studies on the low molecular weight PEGs. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

The low molecular weight PEGs does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Polyethylene glycol is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

<u>Acute Studies</u>

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

Table 3: Acute aquatic toxicity studies on polyethylene glycol

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Poecilia reticulata	96-hr LC_{50}	>100	2	ECHA
Daphnia magna	48-hr EC_{50}	>100	1	ECHA
Scenedesmus subspicatus	96-hour EC_{50}	>100	2	ECHA

Chronic Studies

Based on the EPISUITE™ ECOSAR version 1.11 predicted model, in 28 days long term fish toxicity (NOEC value) was estimated to be 13,671.586 mg/L on fish for on the basis of mortality effects (ECHA). [Kl.score=2].

The calculated value was further supported by 7-day freshwater study conducted on *Poecilia reticulata* (guppy fish) in semi-static conditions. The median lethal concentration of the test chemical (LC_{50}) was determined as 1150 mg/L (ECHA) [Kl.score=2].

Based on the EPISUITE™ ECOSAR version 1.10 predicted model, in 21 days long term aquatic invertebrate toxicity (NOEC value) was estimated to be 17,475.27 mg/L to Daphnid on the basis of reproductive effects (ECHA) [Kl.score=2].

Data for algae was available for read-across substance diethylene glycol mono-butyl ether (CAS No. [redacted] The effect of the test chemical to algae *Scenedesmus quadricauda* was performed for a period of 8 days. Based on the results obtained, the 8-day EC_{50} value was determined to be 1,000 mg/L (ECHA) [Kl.score=2].

C. Terrestrial Toxicity

No studies were located. These studies don't need to be conducted because direct and indirect exposure of the soil compartment is less as considering its use as binding agents and emulsion stabilizers and even if PEGs are accidentally exposed to the soil compartment, there is likely to be little or no adsorption of chemical in soil compartment as the chemical is not persistent in soil (ECHA).

D. Calculation of PNEC

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

PNEC Water

Experimental results are available for three trophic levels for polyethylene glycol. Acute $E(L)C_{50}$ values are available for fish (>100 mg/L), invertebrates (>100 mg/L), and algae (>100 mg/L). Chronic toxicity data are available fish (1,150 mg/L) and invertebrates (17,475 mg/L) and in algae (1,000 mg/L) based on a read-across substance. On the basis that the data consists of short-term results from three trophic levels and long-term results of three trophic levels, an assessment factor of 10 has been applied to the lowest chronic NOEC of 1,000 mg/L for algae. The $PNEC_{water}$ is 100 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 770 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.99/1280) \times 1000 \times 100$
$= 770$ 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]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.4/1000 \times 2400]$
$= 0.99\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 10 \times 0.04$
$= 0.4$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for polyethylene glycol calculated from EPISUITE™ using the MCI is 10 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 13 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.2/1500) \times 1000 \times 100$
$= 13$ 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]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 10 \times 0.02$
$= 0.2\ m^3/m^3$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for polyethylene glycol calculated from EPISUITE™ using the MCI is 10 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).

Polyethylene glycol has been shown to be readily biodegradable; thus, it does not meet the screening criteria for persistence.

The calculated BCF is 3.162 L/kg. Thus, polyethylene glycol does not meet the screening criteria for bioaccumulation.

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

Therefore, polyethylene glycol is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not 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 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.

Ingestion

Rinse mouth with water and then drink plenty of water. Do not induce vomiting. Never give anything by mouth to an unconscious person. Seek medical attention.

B. Firefighting Information

Extinguishing Media

Water spray or fog, carbon dioxide, dry powder.

Specific Exposure Hazards

Burning produces harmful and toxic fumes.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions

No special precautions are necessary. Ensure adequate ventilation.

Environmental Precautions

For large amounts: dike spillage and pump off the product. For residues: pick up with suitable absorbent material. Dispose of contaminated material as prescribed.

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

Handle in accordance with good industrial hygiene and safety practice.

Other Handling Precautions

Protect against fire and explosion: prevent electrostatic charge; sources of ignition should be kept well clear, and fire extinguishers should be kept handy.

Storage

Keep container tightly closed and dry. Protect against heat. Store below 25°C.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Occupational exposure standards for the low molecular weight PEGs have not been established.

Engineering Controls

Provide local exhaust ventilation to control vapours and mists.

Personal Protection Equipment

Respiratory Protection: Respiratory protection in case of vapours/aerosol release. Wear a certified organic vapour/particulate respirator.

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: 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

The low molecular weight PEGs are 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

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POLYPROPYLENE GLYCOL

This dossier on polypropylene glycol (PPG) presents the most critical studies pertinent to the risk assessment of PPG 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) and on a Cosmetics Ingredient Review (CIR) on PPG (Andersen, 1994). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

NICNAS has assessed PPG in an Inventory Multi-tiered Assessment and Prioritisation (IMAP) Tier 1 assessment and concluded that it poses no unreasonable risk to human health.[1]

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 2-(2-hydroxypropoxy)propan-1-ol

CAS RN: [redacted]

Molecular formula: $C_6H_{14}O_3$

Molecular weight: 134.17 g/mol

Synonyms: Propane-1,2-diol propoxylated; polyoxypropylene; oxirane, methyl-, homopolymer; propylene oxide homopolymer; propylene oxide, propylene glycol polymer; poly[oxy(methyl-1,2-ethanediyl)], alpha.-hydro-.omega.-hydroxy-; alpha-hydro-omega-hydroxypoly(oxy(methyl-1,2-ethanediyl)); alpha-hydro-omega-hydroxypoly(oxypropylene)

PPG is a polymer of propylene oxide, with a minimal of three propylene oxide units.

SMILES: CC(CO)OCC(C)O

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of polypropylene glycol

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Clear, colourless, viscous, organic, liquid	1	ECHA
Melting Point*	< -150°C @ 101.3 kPa	1	ECHA
Boiling Point*	287.6°C @ 101.3 kPa	1	ECHA
Density*	1012 kg/m^3@ 20°C	1	ECHA
Vapour Pressure**	8.39×10^{-2} Pa @ 20°C 1.35×10^{-1} Pa @ 25°C	1	ECHA

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]2C+

Property	Value	Klimisch Score	Reference
Partition Coefficient (log K_{ow})***	<0.3 to 0.9 (measured) @ 23°C	1	ECHA
Water Solubility*	Miscible 47 g/L @ 22°C	1	ECHA
Flash Point*	151°C	1	ECHA
Auto flammability*	305°C	1	ECHA
Viscosity**	78.34 mPa s @ 20°C 27.37 mPa s @ 20°C	1	ECHA
Henry's Law Constant	-	-	-

*Polypropylene glycol (MW 260)

**Polypropylene glycol (MW 250)

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

PPG is an organic substance that biodegrades readily, is not expected to bioaccumulate and has a low potential to adsorb to soil.

B. Biodegradation

PPG has been determined to be readily biodegradable via an OECD Guideline 301 F test. After 28 days, 86.6% of the test substance had been degraded in a manometric respirometry test (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 adsorption/desorption data are available for PPG. However, the estimated soil organic carbon partition coefficient (K_{oc}) values for homologous components of this UVCB substance range from 1 to 10 L/kg for the lowest (least sorptive) and highest (most sorptive) molecular weight homologues. The components of this UVCB substance can be regarded as having low affinity for adsorption to soils and activated sludge biosolids (ECHA).

D. Bioaccumulation

Based on a log K_{ow} of <=3 and relatively high water solubility, PPG is not expected to bioaccumulate.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute oral toxicity of PPG varies from moderately to non-toxic, depending on the molecular (toxicity decreases with increasing molecular weight). These substances are non-toxic by the dermal route. PPG is not a skin and eye irritant, nor is it a skin sensitisers. Repeated dose toxicity studies showed minimal systemic toxicity in rats given oral doses or rabbits given dermal applications of PPG. This substance is not genotoxic. In a screening study, no reproductive or developmental effects were seen in rats dosed orally with a substance that is structurally related PPG.

B. Acute Toxicity

Acute oral toxicity studies on PPG of various molecular weights (300 to 3,900) have indicated LD_{50} values in rats ranging from 500 to >40,000 mg/kg (Andersen, 1994).

In acute dermal toxicity studies, doses of PPG 1025 (20 mL/kg) and PPG 2025 (20 mL/kg) did not cause death to rabbits. Two of five rabbits dosed with 20 mL/kg PPG 425 and one of five dosed with 10 mL/kg PPG 425 died (Andersen, 1994).

No acute inhalation studies on PPG were identified

C. Irritation

Skin irritation was not noted after PPG 425, PPG 1025 or PPG 2025 was applied once to the skin of rabbits or when applied a total of eight times to the same area within 4 hours (Andersen, 1994).

PPGs 425, 1025 and 2025 were classified as harmless agents in rabbits in another ocular irritation study; PPG 1200 induced slight, transient ocular irritation in an albino rabbit (Andersen, 1994).

D. Sensitisation

PPG (MW 260) was considered a non-sensitiser in a mouse local lymph node assay (LLNA) (ECHA) [Kl.score=1]. Neither skin irritation nor sensitisation reactions were observed in 300 human subjects who received continuous and repeated dermal applications of undiluted PPG 2000 (Andersen, 1994).

E. Repeated Dose Toxicity

Oral

PPG 2000 was administered to rats over a period of 100 days. Concentrations of 0.1, 0.3, 1.0 and 3.0% were administered in oral doses of 50 to 1,500 mg/kg-day. There were no adverse effects noted at concentrations of 0.1 to 1.0%. Slight decreases in growth were observed after the administration of 3% PPG 2000. The NOAEL is 1% (500 mg/kg-day) in the diet (Andersen, 1994).

In a 90-day study, PPG 2000 was administered orally to rats in doses ranging from 275 to 501 mg/kg-day. There was no evidence of adverse histopathologic, hematologic or clinical chemistry effects in any of the animals tested. Body weight effects (not specified) were noted at the highest dose tested. The NOAEL is ~500 mg/kg-day (Andersen, 1994).

PPG 750 was administered to rats over a period of 100 days. Concentrations of 0.1 and 1% were administered at doses of 50 and 500 mg/kg-day. PPG 750 (0.1%) did not induce any adverse effects. However, in the group dosed with 1% PPG 750, there was a slight increase in liver and kidney weights; there were no histological changes. Neither of the doses resulted in a central nervous system stimulatory effect. The NOAEL is 500 mg/kg-day (Andersen, 1994).

A rat 28-day oral gavage study was conducted on triethanolamine, propoxylated (CAS No. [redacted] a structurally related substance to PPG. Male and female Wistar rats were dosed with 0, 100, 300 or 1,000 mg/kg-day. There were no treatment-related deaths and no clinical signs of toxicity. Haematological and clinical chemistry parameters measured in the study were similar across all groups. There were no gross necropsy or histopathological changes that were considered to be treatment-related. The NOAEL for this study is 1,000 mg/kg-day (ECHA) [Kl.score=1].

Inhalation

No studies are available.

Dermal

PPG-2000, at doses of 1, 5 or 10 ml/kg, was applied to the skin of rabbits 24 hours/day, 5 days/week for three months. It was reported that there was a slight reduction in growth in the 5 and 10 ml/kg groups; no effects were seen at 1 mL/kg (Andersen, 1994).

F. Genotoxicity

In Vitro Studies

Polypropylene glycol (MW 260) was not mutagenic to *S. typhimurium* strains TA1535, TA1537, TA102, TA98 and TA100 in the absence or presence of metabolic activation (ECHA).

The *in vitro* genotoxicity studies on PPG are presented in Table 2.

Table 2: In vitro genotoxicity studies on polypropylene glycol

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
In vitro mammalian chromosome aberration test: human lymphocytes	-	-	1	ECHA
OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test): human lymphocytes	-	-	1	ECHA
Mammalian cell gene mutation assay: Chinese hamster lung fibroblasts V79	-	-	1	ECHA
OECD Guideline 471 (Bacterial Reverse Mutation Assay): Salmonella typhimurium strains TA1535, TA 1537, TA102, TA98, TA100	-	-	1	ECHA

*+, positive; -, negative

In Vivo Studies

No studies are available.

G. Carcinogenicity

Oral

There are no studies available

Inhalation

There are no studies available

Dermal

There are no studies available

H. Reproductive Toxicity

No studies are available on PPG.

A reproductive and developmental screening toxicity study (OECD 421) was conducted on triethanolamine, propoxylated (CAS No. [redacted] a structurally related substance to PPG. Male and female Wistar rats were dosed by oral gavage with doses of 0, 100, 300 or 1,000 mg/kg-day. Transient salivation was noted in the high-dose parental animals. There were marginal body weight gains in females in all dose groups during the pre-mating period, and a slight body weight loss in the high-dose females during lactation. There were no reproductive or developmental effects that were considered treatment-related. The NOAEL for reproductive and developmental toxicity is ≥1,000 mg/kg-day (ECHA) [Kl.score=1].

I. Developmental Toxicity

PPG is not classifiable as hazardous in respect to its reproductive toxicity. There is sufficient information from a qualitative and quantitative understanding of the toxicological properties of the core substance, the repeating unit and screening studies on the most bioavailable members of the category, such that testing for developmental toxicity is not necessary (ECHA).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for PPG 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

Several rat subchronic toxicity studies conducted on PPG showed an NOAEL of 1% PPG in diet (500 mg/kg-day). In one study, it was reported that there was a slight increase in liver and kidney weights, but no data were provided to determine if the change in organ weights were statistically significant. Nevertheless, these organ weight changes may not be considered adverse since there were no accompanying histopathologic changes. No adverse effects were seen in rats given oral doses of up to 1,000 mg/kg-day for four weeks of a substance that is structurally similar to PPG.

The NOAEL of 500 mg/kg-day from the PPG studies will be used for determining the oral Reference dose (RfD) and the drinking water guidance value.

Oral Reference Dose (oral RfD)

Oral RfD = NOAEL / ($UF_A \times UF_H \times UF_L \times UF_{Sub} \times UF_D$)

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 = 500/(10 × 10 × 1 × 10 × 1) = 500/1,000 = 0.5 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 = (0.5 × 70 × 0.1)/2 = 2 mg/L

B. Cancer

No carcinogenicity studies are available on PPG. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

PPG does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

PPG is low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

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

Table 3: Acute aquatic toxicity studies on polypropylene glycol

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Danio rerio	96-h LC_{50}	>100	1	ECHA
Daphnia magna	48-h EC_{50}	105.8	1	ECHA
Desmodesmus subspicatus	72-h EC_{50}	>100	1	ECHA

Chronic Studies

No studies on PPG are available. Chronic toxicity to invertebrates of the structurally related substance D-Glucitol (Sorbitol), propoxylated (CAS RN [redacted] has been investigated in a reproduction test with *Daphnia magna f*ollowing the OECD guideline 211 using semi-static exposure. No effects were observed at the maximum concentration test (10 mg/l) and the NOEC are reported at 10 mg/l (nominal) for reproduction and mortality (ECHA) [Kl.score=1].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for PPG 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* (105.8 mg/L), and algae (>100 mg/L). A chronic *Daphnia* study has been conducted on D-Glucitol (Sorbitol)(CAS No. [redacted] a structurally similar substance to PPG, with a NOEC of 10 mg/L On the basis of the short-term results from three trophic levels and long-term results from one trophic levels, an assessment factor of 100 has been applied to the lowest reported NOEC value of 10 mg/L for invertebrates. The $PNEC_{water}$ is 0.1 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 0.07 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.896/1280) \times 1000 \times 0.1$
$= 0.07$ 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]
$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 0.2/1000 \times 2400]$
$= 0.896\ m^3/m^3$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 5 \times 0.04$
$= 0.2$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for PPG estimated as the mid-point from a range of values is 5 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 0.0067 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$

$= (0.1/1500) \times 1000 \times 0.1$

$= 0.0067$ 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]

$Kp_{soil} = K_{oc} \times f_{oc}$

$= 5 \times 0.02$

$= 0.1\ m^3/m^3$

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for PPG estimated as the mid-point from a range of values is 5 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).

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

No data are available on bioaccumulation. However, based on the low log K_{ow}, and rapid degradation rate, and significant water solubility, bioaccumulation is not expected.

There are no chronic toxicity studies on PPG. The NOEC values for a structurally related substance [D-Glucitol (Sorbitol), propoxylated (CAS# [redacted] are >0.1 mg/L for invertebrates. The acute $E(L)C_{50}$ values of PPG are >1 mg/L for fish, invertebrates and algae. Thus, PPG does not meet the criteria for toxicity.

The overall conclusion is that PPG is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not 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 5 minutes. Remove contacts, if possible. If symptoms persist, seek 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

If swallowed, seek medical attention. Do not induce vomiting. Never give anything by mouth to an unconscious person.

B. Firefighting Information

Extinguishing Media

Water spray, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Burning produces harmful and toxic fumes. Combustion products may include carbon monoxide, carbon dioxide.

Special Protective Equipment for Firefighters

Wear a self-contained breathing apparatus and protective clothing.

C. Accidental Release Measures

Personal Precautions

Use appropriate protective equipment. Spilled material may cause a slipping hazard.

Environmental Precautions

Prevent from entering sewers, waterways or low areas.

Steps to be Taken if Material is Released or Spilled

Isolate spill and stop leak where safe. Contain spill with sand or other inert materials. Scoop up and remove.

D. Storage And Handling

General Handling

Do not swallow. Wash thoroughly after handling.

Storage

Keep container closed when not in use. Store in a dry place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure limit for propylene glycol.

Engineering Controls

Use in a well-ventilated area. Local exhaust ventilation should be used in areas without good cross ventilation.

Personal Protection Equipment

Respiratory Protection: Not normally needed. But if significant exposures are possible then the following respirator is recommended: organic vapour respirator with a dust/mist filter.

Hand Protection: Chemical protective gloves.

Skin Protection: Normal work coveralls.

Eye protection: Chemical goggles; also wear a face shield if splashing hazard exists.

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

F. Transport Information

PPG 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

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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

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PROPYLENE GLYCOL *n*-PROPYL ETHER

This dossier on propylene glycol *n*-propyl ether presents the most critical studies pertinent to the risk assessment of propylene glycol *n*-propyl ether 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 1-Propoxypropan-2-ol

CAS RN: [redacted]

Molecular formula: $C_6H_{14}O_2$

Molecular weight: 118.18

Synonyms: Propylene glycol *n*-propyl ether; 1-propoxypropan-2-ol; 1-propoxy-2-propanol; 2-propanol, 1-propoxy; propylene glycol propyl ether; propylene glycol-n-monopropyl ether; 2-propanol, propoxy-

SMILES: CCCOCC(C)O

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Propylene Glycol n-Propyl Ether

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colorless organic liquid with an ether-like odor.	2	ECHA
Melting point	ca. -70°C	2	ECHA
Boiling point	149.4°C	2	ECHA
Density	0.885 g/cm^3 @ 20°C	2	ECHA
Vapor pressure	2.85 mm Hg @ 25°C	2	ECHA
Partition coefficient (log K_{ow})	0.621 @ 20°C (calculated)	2	ECHA
Water solubility	Completely miscible @ 30°C	2	ECHA
Flash point	46.4°C	2	ECHA

Property	Value	Klimisch score	Reference
Auto flammability	252°C	2	ECHA
Viscosity	2.389 mPa s @ 25°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

The substance is expected to biodegrade and not expected to bioaccumulate.

B. Biodegradation

Propylene glycol n-propyl ether is readily biodegradable. In an OECD 301 A test, degradation was 91.5% after 28 days (ECHA) [Kl. score = 1].

C. Environmental Distribution

Adsorption/desorption

No experimental data are available for propylene glycol n-propyl ether. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} value from log K_{ow} of 0.621 is 4.944 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 2.375 L/kg.

D. Bioaccumulation

There are no bioaccumulation studies on propylene glycol n-propyl ether. Propylene glycol n-propyl ether is not expected to bioaccumulate based on a log K_{ow} of 0.621 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The substance is not significantly acutely toxic via oral exposure. It is not irritating nor is it considered a sensitizer. Repeat dose toxicity tests do not suggest a high degree of systemic toxicity.

B. Acute Toxicity

The oral LD_{50} of propylene glycol *n*-propyl ether in rats is >2,000 mg/kg (ECHA) [Kl. score = 2]. The inhalation 4-hour LC_{50} of propylene glycol *n*-propyl ether in rats is >1,725 ppm, the highest concentration attainable at room temperature (25°C) (ECHA) [Kl. score = 2].

The dermal LD_{50} of propylene glycol *n*-propyl ether in rabbits is >2,000 mg/kg (ECHA) [Kl. score = 2].

C. Irritation

Application of 0.5 mL propylene glycol *n*-propyl ether to the skin of rabbits for 4 hours under occlusive conditions was not considered irritating. The mean of the 24, 48, and 72 hour scores were: 0.9 for erythema and 0.4 for edema (ECHA) [Kl. score = 2].

Instillation of 0.1 mL into the eyes of rabbits was considered irritating. The mean of the 24, 48, and 72 hour scores were: 0.9 for corneal opacity; 0.7 for iridial lesions; 0.9 for conjunctival redness; and 0.8 for chemosis (ECHA) [Kl. score = 2].

D. Sensitization

Propylene glycol *n*-propyl ether was not considered to be a skin sensitizer in a mouse local lymph node assay (ECHA) [Kl. score = 1].

E. Repeated Dose Toxicity

Oral
No studies are available.

Inhalation
Male and female F344 rats (20/sex/dose) were exposed by inhalation to 0, 30, 100, or 300 ppm propylene glycol n-propyl ether 6 hours/day, 5 days/week for 14 weeks. At the end of the 14-week exposure period, 10 animals/sex/dose were sacrificed; the other 10 animals/sex/dose were given a 3-month recovery period. Clinical signs and the ophthalmic examination showed no treatment-related effects. The 300 ppm females had consistently lower body weight gain, except during the recovery period. Body weights, food and water consumption, and urinalysis were similar across groups. Total leucocyte count was decreased in the 30 and 300 ppm females and was associated with a decrease in lymphocytes in the 300 ppm females. There was no dose-response and the changes were not present following the 3-month recovery period. Organ weights, gross necropsy, and histopathology showed no treatment-related effects. The NOAEC for this study is 300 ppm (ECHA) [Kl. score 1].

Male and female SD rats (20/sex/dose) were exposed by inhalation to 0, 30, 100, or 300 ppm propylene glycol n-propyl ether 6 hours/day, 5 days/week for 14 weeks. At the end of the 14-week exposure period, 10 animals/sex/dose were sacrificed; the other 10 animals/sex/dose were given a 3-month recovery period. Clinical signs and the ophthalmic examination showed no treatment-related effects. The 100 ppm female rats had lower body weight gains for the first two weeks of the study. Body weights, food and water consumption, urinalysis, and hematology parameters were similar across groups. Organ weights, gross necropsy, and histopathology showed no treatment-related effects. The NOAEL for this study is 300 ppm (ECHA) [Kl. score 1].

Dermal
No studies are available.

F. Genotoxicity

In Vitro Studies

The in vitro genotoxicity studies on propylene glycol *n*-propyl ether are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Propylene Glycol *n*-Propyl Ether

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	1	ECHA
Mammalian cell gene mutation (Chinese Hamster Ovary cells)	-	-	1	ECHA
Chromosomal aberration (rat lymphocytes)	-	-	1	ECHA

*+, positive; -, negative

In Vivo Studies

No studies are available.

G. Carcinogenicity

No studies are available.

H. Reproductive/Developmental Toxicity

A reproductive and developmental toxicity screening (OECD 421) study was conducted on propylene glycol n-propyl ether. Male and female Crl:CD(SD) rats were dosed by oral gavage with 0, 100, 300, or 1,000 mg/kg propylene glycol *n*-propyl ether. Transient, excess salivation was noted in many of the 1,000 ppm animals immediately after dosing; this was considered a local response to the dosing material and not toxicologically significant. Absolute and relative liver weights were increased in the male and female rats, with corresponding hepatocellular hypertrophy. Absolute and relative kidney weights were increased in the 1,000 males and females. There were hyaline droplets in the proximal tubules in the 1,000 ppm males, but no histopathologic changes seen in the 1,000 ppm females. At 1,000 mg/kg, there was a slight, treatment-related increase in post-implantation loss (11.26% vs 6.47% in controls), with a slight increase in gestation survival and a very slight decrease in litter size (14.0 vs 14.4 live pups/litter in control; not statistically significant but considered treatment-related). The mean litter size would have been lower (13.4%); one animal had a very large litter of 20 pups. One of the 1,000 mg/kg females had a difficult birth and retained placentae; this was considered an equivocal treatment-related effect. There was no indication of parental, reproductive, or developmental

toxicity at the lower two dose levels. The NOAEL for parental, reproductive, and developmental toxicity is 300 mg/kg-day (ECHA) [Kl. score = 1].

Pregnant female CD (SD) rats were dosed by exposed by inhalation to 0, 100, 750, or 1,500 ppm propylene glycol *n*-propyl ether 6 hours/day on GD 6-15. The 1,500 ppm females had eye irritation, significant reductions in body weight gain during GD 609, and reduced feed consumption during the exposure period. Corneal opacity was grossly observed in one 1,500 ppm dam; histologic examination showed corneal ulceration and associated keratitis, as well as corneal and scleral mineralization and scleral granulomas. The only developmental effect noted was poorly ossified hindlimb phalanges in the 1,500 ppm group. The NOAEL for maternal and developmental toxicity is 750 ppm (ECHA) [Kl. score = 1].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for propylene glycol *n*-propyl ether 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

A reproductive and developmental screening (OECD) study on propylene glycol n-propyl ether has been conducted by the oral route (ECHA). The NOAEL for parental, reproductive, and developmental toxicity is 300 mg/kg-day. This study is inadequate for an oral reference dose.

Two 14-week rat (different strains) inhalation studies have been conducted on propylene glycol n-propyl ether. The NOAEC for both studies is 300 ppm, based on decreased body weight gain in the female rats. The NOAEC of 300 ppm (1,474 mg/m^3) will be used for deriving an oral reference dose and drinking water guidance value for propylene glycol n-propyl ether.

It is assumed that absorption is 100% and the ventilation rate and body weight of a rat is 0.29 m^3/day (0.0121 m^3/hr) and 0.35 kg, respectively.

1,474 mg/m^3 x 0.0121 m^3/hr x 6 hr/day x 1/0.35 kg x 5 days/7 days = 218 mg/kg-day

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) = 3
UF_D (database uncertainty) = 1

Oral RfD = 218/(10 x 10 x 1 x31 x 1) = 218/300 = 0.7 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 = (0.7 x 70 x 0.1)/2 = 2.5 mg/L

B. Cancer

There are no carcinogenicity studies on propylene glycol *n*-propyl ether. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Propylene glycol *n*-propyl ether does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

B. Aquatic Toxicity

Acute Studies
Table 3 lists the results of acute aquatic toxicity studies conducted on propylene glycol n-propyl ether

Table 3: Acute Aquatic Toxicity Studies on Propylene Glycol *n*-Propyl Ether

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-hr LC_{50}	>100	2	ECHA
Daphnia magna	48-hr EC_{50}	>100	2	ECHA

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pseudokirchnierella subcapitata	72-hr EC_{50}	3,440	1	ECHA

Chronic Studies
No data are available.

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

The PNEC calculations for propylene glycol *n*-propyl ether 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 (>100 mg/L), and algae (3,440 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 $E(L)C_{50}$ value of 100 mg/L for fish and *Daphnia*. The $PNEC_{water}$ is 1.0 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 $PNEC_{soil}$ is 0.03 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.05/1500) \times 1000 \times 1.0$
$= 0.03$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 2.38 \times 0.02$
$= 0.05$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for propylene glycol n-propyl ether based on the molecular connectivity index (MCI) is 2.38 L/kg (EPA, 2018).
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).

Propylene glycol *n*-propyl ether is readily biodegradable; thus, it does not meet the screening criteria for persistence.

Based on a calculated log K_{ow} of 0.621, propylene glycol *n*-propyl ether does not meet the screening criteria for bioaccumulation.

There are no chronic aquatic toxicity studies on propylene glycol *n*-propyl ether. The acute $E(L)C_{50}$ values for fish, invertebrates, and algae are >1 mg/L. Thus, propylene glycol n-propyl ether does not meet the screening criteria for toxicity.

The overall conclusion is that propylene glycol *n*-propyl ether is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Flammable Liquid Category 3
Eye irritant Category 2

B. Labelling

Warning

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 5 minutes. Remove contacts, if possible. If symptoms persist, seek 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
If swallowed, seek medical attention. Do not induce vomiting. Never give anything by mouth to an unconscious person.

B. Fire Fighting Information

Extinguishing Media
Water fog, carbon dioxide, foam, dry chemical.
Specific Exposure Hazards
Burning produces harmful and toxic fumes. Combustion products may include: carbon monoxide, carbon dioxide.
Special Protective Equipment for Firefighters
Wear a self-contained breathing apparatus and protective clothing.

C. Accidental Release Measures

Personal Precautions
Use appropriate protective equipment. Spilled material may cause a slipping hazard.
Environmental Precautions
Prevent from entering sewers, waterways, or low areas.
Steps to be Taken if Material is Released or Spilled
Isolate spill and stop leak where safe. Contain spill with sand or other inert materials. Scoop up and remove.

D. Storage and Handling

General Handling
Do not swallow. Wash thoroughly after handling.
Storage
Keep container closed when not in use. Store in a dry place.

B. Fire Fighting Information

Extinguishing Media
Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

Specific Exposure Hazards
Carbon oxides may be generated upon combustion. Substance is incompatible materials with strong oxidizing agents.

Special Protective Equipment for Firefighters

Wear self-contained breathing apparatus for fire fighting if necessary.

C. Accidental Release Measures

Personal Precautions

Environmental Precautions

Steps to be Taken if Material is Released or Spilled
Do not allow release to open drains or surface water. Contain release with appropriate dikiing and barriers. Notify local authorities if substance migrates to public drains or surface water.

D. Storage And Handling

General Handling
Do not swallow. Wash thoroughly after handling.

Storage
Keep container closed when not in use. Store in a dry place.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Workplace Australia has not established an occupational exposure standard for propylene glycol *n*-propyl ether.

Engineering Controls
Use in a well-ventilated area. Local exhaust ventilation should be used in areas without good cross ventilation.

Personal Protection Equipment
Respiratory Protection:
Not normally needed. But if significant exposures are possible then the following respirator is recommended: organic vapour respirator with a dust/mist filter.

Hand Protection:
Chemical protective gloves

Skin Protection:
Normal work coveralls.

Eye protection:
Chemical goggles; also wear a face shield if splashing hazard exists.

Other Precautions:

F. Transport Information

Australian Dangerous Goods

UN1993 (FLAMMABLE LIQUID, N.O.S.)
Class: 3
Packing Group: 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

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.

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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).

I. 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

Silicon dioxide is the IUPAC name for synthetic amorphous silica (SAS) [CAS No. [redacted] it can be produced by a "wet process" or by a "thermal or fumed process." Silica gel and precipitated silica, crystalline-free (CAS No. [redacted] is a SAS prepared by the "wet process." Silica, amorphous, fumed, crystalline-free (CAS No. [redacted] is a SAS prepared by flame hydrolysis.

II. 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

Property	Value	Klimisch score	Reference
Boiling Point	2.2 g/cm^3	2	ECHA
Water Solubility	76 – 128 mg/L* (slightly soluble)	1	ECHA

*Based on dissolved SiO_2.

III. 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 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.

IV. 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 bioavailablity 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 fetal 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 bioavailablity 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 mass median aerodynamic diameter (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 mass median aerodynamic diameter (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. Sensitization

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 $\geq$25,000 ppm females from 12 to 24 months; a dose-related trend was not apparent. The NOAEL is 50,000 ppm. Using 0.05 as the fraction of body weight that rats consume per day as food (U.S. EPA), the NOAEL corresponds to 2,500 mg/kg-day (Takizawa *et al.*, 1988) [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 (Takizawa et al., 1988). [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 $\geq$6 mg/m^3, there were hematological 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 tumors was similar between treated and control animals. The number of animals used in this study was small (Takizawa *et al.*, 1988). [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 tumors was similar between treated and control animals (Takizawa *et al.*, 1988). [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].

V. 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

<u>Oral</u>

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.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Silicon dioxide does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. 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 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.

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).

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.

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

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.

XI. DISPOSAL MANAGEMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

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SODIUM BICARBONATE

This dossier on sodium bicarbonate presents the most critical studies pertinent to the risk assessment of sodium bicarbonate 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).

NICNAS has assessed sodium bicarbonate in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to human health or the environment.[1] In addition, based on an assessment of environmental hazards, NICNAS also identified sodium bicarbonate as a chemical of low concern to the environment (DoEE, 2017). Chemicals of low concern are unlikely to have adverse environmental effects if they are released to the environment from coal seam gas operations.

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Sodium hydrogen carbonate

CAS RN: [redacted]

Molecular formula: $CH_2O_3.Na$

Molecular weight: 84.01 g/mol

Synonyms: Sodium bicarbonate; sodium hydrogen carbonate; baking soda; carbonic acid monosodium salt; sodium hydrogencarbonate; carbonic acid sodium (1:1)

SMILES [Na+].OC([O-])=O

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of sodium bicarbonate

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	White, crystalline, odourless solid	1	ECHA
Melting Point	Decomposes above 50°C (pressure not provided)	1	ECHA
Boiling Point	Not applicable	-	-
Density	2,100-2230 kg/m^3 @ 20°	1	ECHA
Vapor Pressure	Negligible, ionisable inorganic compound	-	ECHA

[1] https://www.industrialchemicals.gov.au/chemical-information/search-assessments?assessmentcasnumber=[redacted]

Property	Value	Klimisch Score	Reference
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	93.4 g/L @ 20°C (pH 8.4)	1	ECHA
Flash Point	Not applicable	-	-
Autoflammability	Not applicable	-	-
Viscosity	Not applicable	-	-
Dissociation constant (pKa)	6.3 (temperature not indicated)	-	NCBI, 2024

III. ENVIRONMENTAL FATE PROPERTIES

Due to its high-water solubility and low vapor pressure, sodium bicarbonate will be found predominantly in the aquatic environment where it dissociates completely to sodium (Na^+) and bicarbonate (HCO_3^-) ions. Both ions are ubiquitous in the environment (UNEP, 1995).

When bicarbonate is dissolved in water, a re-equilibration takes place according to the following equations:

$HCO_3^- \leftrightarrow CO_3^{2-} + H^+$ pKa = 10.33

$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$ pKa = 6.35

Only a small fraction of the dissolved CO_2 is present as H_2CO_3 (carbonic acid); the major part is present as CO_2. The amount of CO_2 in water is in equilibrium with the partial pressure of CO_2 in the atmosphere. The CO_2/ HCO_3^-/ CO_3^{2-} equilibria are the major buffer of the pH of freshwater.

Based on the above equations, CO_2 is the predominant species at a pH smaller than 6.35, while HCO_3^- is the predominant species at a pH in the range of 6.35-10.33 and CO_3^{2-} is the predominant species at a pH higher than 10.33.

Geochemical and biological processes dictate the natural concentration of CO_2/ HCO_3^-/ CO_3^2 in freshwater. For instance, a continuous source of carbonate in freshwater is from the deposition of carbonate ions from the dissolution of minerals. Carbon dioxide comes from the decay of organic matter in aquatic ecosystems. On the other hand, carbon dioxide dissolved in freshwater is utilised by plants in photosynthesis.

The addition of sodium bicarbonate to the aquatic environment could potentially increase the sodium and bicarbonate concentration. However, unlike sodium carbonate, sodium bicarbonate does not increase the pH of the water to high and/or lethal levels. Addition of bicarbonate to water will move the pH towards 8.34 (the mean of the two pKa values from the two above equations) (OECD, 2002).

Na^+ and HCO_3^- ions will not adsorb on particulate matter or surfaces and will not accumulate in living tissues.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Sodium bicarbonate is not expected to be systemically available in the body. Sodium bicarbonate is not acutely toxic by the oral and inhalation routes. Sodium bicarbonate is slightly irritating to the skin and eyes. There are no adequate repeated dose toxicity studies available in animals exposed to sodium bicarbonate. However, it is not expected to be systemically available in the body from oral exposure due to its dissociation in bodily fluids and the neutralisation of the bicarbonate ion in the stomach to CO_2. Sodium bicarbonate was not mutagenic or carcinogenic and is not considered to be genotoxic. There are no reproductive toxicity studies available to evaluate the effects of sodium bicarbonate on mammalian reproduction. However, based on the normal physiological role of sodium and bicarbonate no toxicity on mammalian reproduction is expected. It is not a developmental toxicant.

B. Toxicokinetics/Metabolism

Sodium bicarbonate will dissociate in bodily fluids to sodium (Na^+) and bicarbonate (CO_3^-) ions. The oral uptake of sodium bicarbonate would lead to neutralisation of bicarbonate in the stomach by the gastric acids, resulting in carbon dioxide (CO_2) formation (see equation below). It is unlikely that an oral uptake of sodium bicarbonate would disrupt the acid-base balance of the body because CO_2 formation in the stomach would alleviate the high amounts of bicarbonate that would be present in the stomach from an acute exposure. The equation that describes this reaction is:

$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$

The bicarbonate is the principal extracellular buffer in the blood and interstitial fluids (Ganong, 1995; ECHA).

C. Acute Toxicity

<u>Oral</u>

An acute oral toxicity study was conducted using male and female Crl:CD BR rats exposed to 3,000, 3,500, 4,000 and 4,500 mg/kg bw/day of sodium bicarbonate via oral gavage. The LD_{50} was reported to be >4,000 mg/kg bw/day in males and 3,000 mg/kg bw/day in females (ECHA) [KI.score=1].

An acute oral toxicity study was conducted using male and female Sprague-Dawley rats exposed to sodium bicarbonate. The acute oral LD_{50} was reported to be 4,220–8,290 mg/kg bw/day (ECHA) [KI.score=2].

The LD_{50} studies presented indicate low acute oral toxicity in rats, with LD_{50} values varying from >4,000 mg/kg bw/day up to 7,334 mg/kg bw/day (ECHA; OECD SIDS 2002).

In humans, acute oral ingestion of sodium bicarbonate may result in a ruptured stomach due to excessive gas development. Acute or chronic excessive oral ingestion may cause metabolic alkalosis, cyanosis and hypernatremia. These conditions are reversible and will not cause adverse effects (OECD, 2002).

Inhalation

A whole-body acute inhalation toxicity study was conducted using male and female Sprague-Dawley rats exposed to 4.74 mg/L of sodium bicarbonate for 4.5 hours. The inhalation 4.5-hour LC_{50} in rats was reported to be >4,740 mg/m^3 mg/L air. There was no mortality, and the mass median aerodynamic diameter (MMAD) was 2.8 µm (ECHA) [KI.score=1].

Dermal

There are no studies available.

D. Irritation

Skin

Skin-irritating properties of sodium bicarbonate have been studied in two GLP-compliant studies, performed according to OECD Guideline 404 and EPA Guideline OTS 798.4470. In the first study, 0.3 g of the test substance (0.5 ml bump volume) was applied to the shaved skins of three male rabbits for 4 hours under semi-occlusive conditions. One rabbit had a slight erythema (score 1) 1 hour after the test patch removal, which was resolved at 24 hours examination. Another had slight erythema (score 1) observed 24 hours after the test patch removal, which was resolved at 48 hours examination. The mean erythema score was reported to be 0.1, and the mean oedema score was reported to be 0. All of these effects were found to be fully reversible within 48 hours (ECHA) [KI.score=1].

In the second study, 0.5 g of the sodium bicarbonate, moistened with distilled water prior to application, was applied under semi-occlusive conditions to clipped skins of three male and three female New Zealand white rabbits. The Primary Dermal Irritation Index was reported to be 0.3. The mean of the 24-, 48-, and 72-hour scores for erythema and oedema were 0.06 and 0.00, respectively. In this study, sodium bicarbonate was reported to be slightly irritating to the skin of rabbits (ECHA) [KI.score=1].

Eye

Eye-irritating potential of sodium bicarbonate has been studied in two GLP-compliant studies, performed according to OECD Guideline 405 (Henkel, 1991b) and EPA Guideline EPA OTS 798.4500. In the first study, 0.05–0.07 ml (bump volume) of the test substance were instilled into the eyes of three rabbits, the untreated eyes serving as negative controls. Twenty-four hours post-instillation, the eyes were rinsed thoroughly with tepid water, and the reactions were scored using the Draize system. All rabbits had a slight to moderate conjunctival erythema (scores 1–2) 1 hour after the instillation, which was resolved at 48 hours observation. Two out of three animals also exhibited mild chemosis (score 1), which was resolved at 24 hours observation (ECHA) [KI.score=1].

In the second study, 0.1 g of the test substance was instilled in the eyes of nine rabbits. The treated eyes of three rabbits were irrigated with 30 ml of physiological saline approximately 20–30 seconds after installation of the test substance. The eyes of the remaining six rabbits were not irrigated. The rabbits were observed for four days. No corneal opacity was noted during the study. One washed and one unwashed eye exhibited iritis one hour after installation only. All treated eyes had conjunctivitis. The incidence and severity of irritation decreased with time. All ocular irritation cleared from the washed and unwashed eyes by days 3 and 4, respectively. Based on these results, sodium bicarbonate is considered to be non-irritating to rabbit eye (ECHA) [KI.score=1].

E. Sensitisation

There are no studies available. However, the weight of evidence suggests that sodium bicarbonate does not have sensitising properties based on the physiological role of both its constituent ions. In addition to this, the sensitising effects of sodium bicarbonate have never been reported despite the long-term historical and wide dispersive (e.g., human food, pharmaceutical, cosmetics, and detergents) (ECHA).

F. Repeated Dose Toxicity

There are no acceptable repeat dose studies available. However, in humans, there is a long history of sodium bicarbonate use as an antacid in doses up to 4 grams without adverse effects of long-term use, although it is recommended not to use high doses of pure sodium bicarbonate instead of antacids (Gosselin, 1976; McEvoy, 1994; as cited in ECHA).

Sodium bicarbonate is recognised as 'GRAS' in food with no other limitation than current good manufacturing practice (FDA, 1983). In addition, sodium bicarbonate is an important extracellular buffer in vertebrates and is therefore readily regulated in the body. Therefore, additional testing for repeated dose toxicity is not deemed necessary (ECHA).

G. Genotoxicity

In Vitro Studies

The results of the *in vitro* genotoxicity studies on sodium bicarbonate are presented below in Table 2.

Table 2: *In vitro* genotoxicity studies on sodium bicarbonate

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	Ishidate et al., 1984; OECD, 2002
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	2	De Flora et al., 1984; OECD, 2002
Chromosomal aberration (Chinese hamster fibroblasts)	-	-	2	Ishidate et al., 1984; OECD, 2002
Bacterial reverse mutation assay (Ames test)	-	-	2	ECHA
In vitro mammalian chromosomal aberration test	-	-	2	ECHA
In vitro gene mutation study in bacteria (Ames) (E. coli WP2, WP67, CM871)	-	-	2	ECHA
Bacterial reverse mutation assay (Salmonella typhimurium TA 92, TA 94, TA98, TA100, TA1535, TA1537)	NA	-	2	ECHA

*+, positive; -, negative
** NA, not applicable

In Vivo Studies

There are no studies available.

H. Carcinogenicity

Male F344 rats were administered sodium bicarbonate in combination with o-phenylphenol (OPP-Na) (only one group received 0.64% sodium bicarbonate alone) in their feed for 104 weeks. The survival rate was 84% and 73% for the treated and control animals, respectively. There was no significant difference in the incidence of bladder tumours between the treated and control groups. No carcinogenic effects were found in this study when sodium bicarbonate only. A NOAEL was not established for this study (OECD, 2002; ECHA) [Kl.score= 2].

I. Reproductive Toxicity

There are no studies are available. However, based on the normal physiological role of sodium and bicarbonate no toxicity on mammalian reproduction is expected (ECHA).

J. Developmental Toxicity

Pregnant female Wistar rats were given by oral gavage 0, 3.4, 15.8, 73.3 or 340 mg/kg sodium bicarbonate on gestational days 6 to 15. There was no maternal or developmental toxicity, with the NOAEL being 340 mg/kg-day, the highest dose tested (ECHA) [Kl.score=2].

Pregnant female CD-1 mice were given by oral gavage 0, 5.8, 27, 125 or 580 mg/kg sodium bicarbonate on gestational days 6 to 15. There was no maternal or developmental toxicity, with the NOAEL being ≥580 mg/kg-day, the highest dose tested (ECHA) [Kl.score=2].

Pregnant female Dutch rabbits were given by oral gavage 0, 3.3, 15.3, 71.2 or 330 mg/kg sodium bicarbonate on gestational days 6 to 18. There was no maternal or developmental toxicity, with the NOAEL being ≥330 mg/kg-day, the highest dose tested (ECHA) [Kl.score=2].

Sodium bicarbonate will usually not reach the foetus when the exposure to sodium bicarbonate is sufficiently low, as it does not become systemically available (ECHA).

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

There are no adequate repeated dose toxicity studies conducted on sodium bicarbonate by any route of exposure. A limited carcinogenicity study showed no increase in bladder tumours in rats given sodium bicarbonate in their diet. Developmental toxicity studies conducted by the oral route in three animals species showed no developmental effects at the highest doses tested. Sodium bicarbonate dissociates to sodium and bicarbonate ions in bodily fluids, and 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.

Sodium bicarbonate is used in many countries (e.g., U.S. and EU) as a food additive. It is regarded as a ‘Generally Recognised as Safe’ (GRAS) substance in food with no limitation other than current good manufacturing practice (OECD, 2002).

Thus, a toxicological reference value was not derived for sodium bicarbonate.

The Australian drinking water guideline values for sodium (180 mg/L, aesthetic) and pH of 6.5 to 8.5 may be applicable (ADWG, 2011).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium bicarbonate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium bicarbonate is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies on sodium bicarbonate.

Table 3: Acute aquatic toxicity studies on sodium bicarbonate

Test Species	Endpoint	Results (g/L)	Klimisch Score	Reference
Oncorhynchus mykiss	96-hour LC_{50}	7,700	2	OECD, 2002
Lepomis macrochirus	96-hour LC_{50}	7,100	1	OECD, 2002; ECHA
Daphnia magna	48-hour EC_{50}	4,100	1	OECD, 2002; ECHA
Daphnia magna	48-hour EC_{50}	>1,000	2	OECD, 2002
Ceriodaphnia dubia	48-hour EC_{50}	1,020	2	OECD, 2002

Chronic Studies

Table 4 lists the results of chronic aquatic toxicity studies conducted on sodium bicarbonate.

Table 4: Chronic aquatic toxicity studies on sodium bicarbonate

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Pimephales promelas	30-day NOEC	400	2	ECHA
Daphnia magna	21-day NOEC	>576	2	ECHA

C. Terrestrial Toxicity

The 48-hour LC_{50} and NOEC from an acute honeybee test on sodium bicarbonate was >24 and 24 µg/bee, respectively (OECD, 2002).

D. Calculation of PNEC

The acute $E(L)C_{50}$ values are available for fish (7100 mg/L) and invertebrates (1000 mg/L). NOECs from chronic studies are available for fish (400 mg/L) and invertebrates (>576 mg/L). Both sodium and bicarbonate ions are ubiquitous in the environment. UNEP (1995) reported that the 10^{th} and 90^{th} percentiles of bicarbonate ion present in 77 rivers were 20 and 195 mg/L, respectively; for sodium, the 10^{th} and 90^{th} percentiles in 75 rivers were 1.5 and 68 mg/L, respectively.

OECD (2002) concluded:

> Because the natural pH, bicarbonate and also the sodium concentration (and their fluctuations in time) varies significantly between aquatic ecosystems, it is not considered useful to derive a generic PNEC. To assess the potential environmental effect of a sodium bicarbonate discharge, the increase in sodium, bicarbonate and pH should be compared with the natural values and their fluctuations and based on this comparison it should be assessed if the anthropogenic addition is acceptable.

Based on the information above, PNEC values for water, sediment, and soil were not derived for sodium bicarbonate.

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).

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

Sodium and bicarbonate ions are essential to all living organisms and their intracellular and extracellular concentrations are actively regulated. Therefore, sodium bicarbonate is not expected to bioaccumulate, and it does not meet the screening criteria for bioaccumulation.

The NOEC for sodium bicarbonate from a chronic *Daphnia* study is >0.1 mg/L. The acute $E(L)C_{50}$ values for sodium bicarbonate are >1 mg/L in fish and invertebrates. Thus, sodium bicarbonate does not meet the screening criteria for toxicity.

The overall conclusion is that sodium bicarbonate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictogram

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 15 minutes and get medical attention if irritation persists.

Skin Contact

Wash with soap and water. Get medical attention if irritation persists.

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. Slowly dilute with one to two glasses of water or milk and seek medical attention. Never give anything by mouth to an unconscious person.

B. Firefighting Information

Extinguishing Media

Water fog, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards

Decomposition in fire may produce toxic gases. Combustion products include carbon dioxide and carbon 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. 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 up and remove.

D. Storage and Handling

General Handling

Avoid contact with eyes, skin or clothing. Avoid creating or inhaling dust.

Storage

Store away from acids. Store in a cool, dry location. Product has a shelf life of 36 months.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia does not have an occupational exposure standard for sodium bicarbonate.

Engineering Controls

Use in a well-ventilated area. Localised ventilation should be used to control dust levels.

Personal Protection Equipment

If engineering controls and work practices cannot prevent excessive exposures, the selection and proper use of personal protective equipment should be determined by an industrial hygienist or other qualified professional based on the specific application of this product.

Respiratory Protection: Dust/mist respirator. (N95, P2/P3)

Hand Protection: Normal work gloves.

Skin Protection: Normal work coveralls.

Eye protection: Dust proof coveralls.

Other Precautions: Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Sodium bicarbonate 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

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SODIUM BISULFITE

This dossier on sodium bisulfite presents the most critical studies pertinent to the risk assessment of sodium bisulfite used 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 mainly 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 hydrogen sulfite

CAS RN: [redacted]

Molecular formula: $NaHSO_3$

Molecular weight: 104.1

Synonyms: Sodium bisulfite; sodium hydrogen sulfite; sodium hydrogensulfite; monosodium sulfite; sodium sulfhydrate; hydrogen sodium sulfite; sulfurous acid, monosodium salt

SMILES: OS(=O)[O].[Na]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Physico-chemical Properties of Sodium Bisulfite

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, crystalline, solid	-	HSDB
Melting Point	Decomposes	-	HSDB
Density	1.348 g/cm^3	1	ECHA
Vapor Pressure	Not applicable	-	-
Partition Coefficient (log K_{ow})	Not applicable	-	-

Property	Value	Klimisch score	Reference
Water Solubility	Very soluble	2	ECHA

Sodium bisulfite is a weak acid with a pK_a of 6.97. Its conjugate base is the sulfite ion (SO_3^{2-}).

$NaHSO_3 \leftrightarrow Na^+ + HSO_3^-$

$HSO_3^- \leftrightarrow H^+ + SO_3^{2-}$

At neutral pH, a mixture of 50% sulfite (SO_3^{2-}) and 50% bisulfite (HSO_3^{2-}) is present.

In surface waters, sulfite is oxidized to sulfate either catalytically by air oxygen or by microbial action (OECD, 2008). The presence of cations like iron, copper or manganese in the environment accelerates the oxidation rate significantly.

Dissociation of sodium bisulfite in aqueous solutions can also liberate sulfur dioxide (SO_2), which is a gas.

III. ENVIRONMENTAL FATE PROPERTIES

At environmental pHs, sodium bisulfite dissociates in water to form sodium (Na^+) ions, bisulfite ions (HSO_3^-), sulfite (SO_2^{3-}) ions, and sulfur dioxide (SO_2) which is a gas.

Sodium bisulfite is not expected to bioaccumulate in the environment because of its dissociation to ionic species and a gas. Furthermore, sulfite will oxidize to sulfate, which is ubiquitous in the environment.

Sodium bisulfite and its dissociated species are expected to have a low potential to adsorb to soil and sediment.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Limited toxicity data are available on sodium bisulfite; therefore, structural analogues have been used to read-across to sodium bisulfite. Sodium sulfite has low acute toxicity by the oral, inhalation, and dermal routes. Sodium sulfite is minimally irritating to the skin and slightly irritating to the eyes. Sodium sulfite is not a skin sensitizer. No systemic toxicity was seen in rats when given sodium metabisulfite in their diet over a lifetime. There were, however, indications of stomach lesions as a result of localized

irritation from the ingestion of sodium metabisulfite. Sodium bisulfite is not expected to be genotoxic. No reproductive or developmental toxicity was observed in any of the animal studies on sodium bisulfite or its structural analogues.

B. Acute Toxicity

No acute toxicity studies are available for sodium bisulfite.

The oral LD_{50} value in rats for sodium sulfite is 2,610 mg/kg (ECHA) [Kl. score = 2]. The oral LD_{50} values in rats for sodium metabisulfite are 1,420 mg/kg (males), 1,630 mg/kg (females), and 1,540 mg/kg (combined sexes) (ECHA) [Kl. score = 2].

The 4-hour inhalation LC_{50} in rats for sodium sulfite is >5.5 mg/L (ECHA). [Kl. score = 2]

The dermal LD_{50} in rats for sodium sulfite is >2,000 mg/kg (ECHA). [Kl. score = 2]

C. Irritation

No studies are available on sodium bisulfite.

Application of 0.5 mL of sodium sulfite to the skin of rabbits for 4 hours under occlusive conditions was minimally irritating. The mean of the 24, 48, and 72 scores were: 0.5 for erythema and 0.0 for edema (ECHA). [Kl. score = 2]

Instillation of 0.1 mL of sodium sulfite (with 0.5% cobalt sulfate) into the eyes of rabbits produced slight irritation. The mean of the 24, 48, and 72 hour scores are as follows: 0.5 for conjunctival redness; 0.5 for conjunctival chemosis; 0.0 for corneal lesions; and 0.0 for iridial lesions (ECHA). [Kl. score = 2]

D. Sensitization

No studies are available on sodium bisulfite.

Sodium bisulfite was not considered a skin sensitizer in a mouse local lymph node assay (ECHA). [K. score = 1]

E. Repeated Dose Toxicity

<u>Oral</u>
No studies are available on sodium bisulfite.

A study is available on sodium metabisulfite. Sodium metabisulfite dissociates in water to form sodium (Na^+) ions, disulfite ($S_2O_5^{2-}$) ions, and sulfur dioxide (SO_2). The disulfite

ions can form bisulfite (HSO_3^-) and sulfite ions (SO_2^{3-}); at neutral pH, a mixture of 50% sulfite (SO_3^{2-}) and 50% bisulfite (HSO_3^{2-}) is present.

Male and female Wistar rats were fed in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulfite for up to two years and over three generations. The diet was enriched with thiamine to prevent thiamine deficiency as a result of sulfite-induced destruction of this vitamin. During storage up to the time of consumption, the losses of sulfite from the feed containing sodium metabisulfite at levels of 0.125, 0.25, 0.5, 1.0, and 2.0% averaged 22, 14,12, 8, and 4.5%, respectively, while the decrease in thiamine was 2.7, 1.7, 8.3, 14.5, and 15.4%, respectively. Addition of thiamine to the diet prevented thiamine deficiency in rats at all dose levels based on measurements of thiamine levels in the urine and liver. The general condition of the rats was good during the first 72 weeks in the F_0 generation, as well as the other two generations. After 72 weeks, there was a rapid increase in mortality in all groups. Survival in the treated groups were generally higher than the controls, except for the 2% F_1 males; no deaths occurred in the 2% F_2 females. A marginal reduction in body weight gain was observed in the 2% dose group (both sexes) in the F_1 and F_2 generations. Feed consumption was similar between treated and control groups. There were no changes in hematology and clinical chemistry parameters and urinalysis that were considered toxicologically significant. The $\geq$1% dietary groups had occult blood in their feces. Relative kidney weights were increased in the 2% F_2 females, but there were no pathological changes noted in the kidneys from this group. Hyperplastic changes in the fore- and glandular stomachs were noted in the $\geq$1% groups in all three generations. Some slight alterations were also noted in stomachs of the 0.5% F_2 rats. The NOAEL for systemic toxicity is 1.91% in the diet. This was estimated to be 955 mg/kg-day based on a rat body weight of 400 g and a daily feed intake of 20 g. The histopathologic effects on the stomach and the occult blood in feces are considered to be the result of localized irritation (a site-of-contact effect) from the ingestion of sodium metabisulfite (Til et al., 1972; ECHA). [Kl. score = 2]

Inhalation

No studies on sodium bisulfite were located.

Dermal

No studies on sodium bisulfite were located.

G. Genotoxicity

In Vitro Studies

No *in vitro* genotoxicity studies were located for sodium bisulfite. Table 2 presents the findings from *in vitro* genotoxicity studies conducted on structural analogues of sodium bisulfite.

Table 2: *In Vitro* Genotoxicity Studies on Structural Analogues to Sodium Bisulfite

Test System	Test Substance	Results*		Klimisch Score	Reference
		-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	Sodium metabisulfite	-	-	2	ECHA
Bacterial reverse mutation (*S. typhimurium* strains)	Potassium metabisulfite	-	-	2	ECHA
Bacterial reverse mutation (*S. typhimurium* strains)	Potassium metabisulfite	-	-	2	ECHA
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	Sodium metabisulfite	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	Sodium metabisulfite	-	-	2	ECHA
Chromosomal aberration (human lymphocytes)	Sodium metabisulfite	-	-	1	ECHA

*+, positive; -, negative

In Vivo Studies

Sodium bisulfite did not show a mutagenic response in a rat dominant lethal assay when given in feed at doses of 0, 4.5, 15, or 45 mg/kg-day (ECHA). [Kl. score = 2]

Sodium sulfite was not genotoxic in a bone marrow micronucleus test in rats. Male NMRI rats were given a single subcutaneous injection of 0, 250, 500, or 1,000 mg/kg sodium sulfite (ECHA). [Kl. score = 1]

H. Carcinogenicity

No studies are available on sodium bisulfite.

Male and female Wistar rats were fed in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulfite for up to two years and over three generations. There was no increased incidence of tumors in the treated groups compared to the controls (Til et al., 1972). [Kl. score = 2]

Male and female ICR/JCL mice were given in their drinking water 0, 1, or 2% potassium metabisulfite for two years. There was no increased incidence of tumors in the treated groups compared to the controls (Tanaka et al., 1979). [Kl. score = 2]

No inhalation or dermal carcinogenicity studies were located.

I. Reproductive Toxicity

No studies are available on sodium bisulfite.

Male and female Wistar rats were fed in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulfite for up to two years and over three generations. The diet was enriched with thiamine to prevent thiamine deficiency as a result of sulfite-induced destruction of this vitamin. During storage up to the time of consumption, the losses of sulfite from the feed containing sodium metabisulfite at levels of 0.125, 0.25, 0.5, 1.0, and 2.0% averaged 22, 14,12, 8, and 4.5%, respectively, while the decrease in thiamine was 2.7, 1.7, 8.3, 14.5, and 15.4%, respectively. Addition of thiamine to the diet prevented thiamine deficiency in rats at all dose levels based on measurements of thiamine levels in the urine and liver. The effects other than reproductive and developmental toxicity are discussed above in the Repeated Dose Toxicity section. There were no treatment-related effects on female fertility, the number of young per litter, or birth weight or mortality of the offspring. The number of F_{2a} pups was significantly reduced in the $\geq$0.5% groups during the first breeding cycle, but there was no dose-response and the reduction did not occur during the second breeding cycle. Slight growth retardation was observed in the F_1 and F_2 generation rats both before and after weaning. The NOAEL for reproductive toxicity is 1.91% in the diet. This was estimated to be 955 mg/kg-day based on a rat body weight of 400 g and a daily feed intake of 20 g (Til et al., 1972; ECHA). [Kl. score = 2]

Male and female rats were given sodium metabisulfite in their drinking water for up to 2.5 years and in three successive generations. The doses were 375 and 750 ppm as sulfur dioxide (SO_2). There was no evidence of systemic toxicity in either dose group. The number of offspring of either the F_1 and F_2 generation and the proportion surviving to the end of lactation were similar between treated and control groups. The NOAEL for reproductive toxicity is 750 ppm (as SO_2) in drinking water. Assuming an average rat body weight of 400 g and a daily water intake of 28 mL, 750 ppm (as SO_2) corresponds to 53 mg/kg-day sodium metabisulfite (Lockett and Natoff, 1960; ECHA). [Kl. score = 2]

J. Developmental Toxicity

Pregnant female Wistar rats were dosed by oral gavage with up to 110 mg/kg-day sodium bisulfite during GD 6-15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity for this study is 110 mg/kg-day (ECHA). [Kl. score = 2]

Pregnant female CD-1 mice were dosed by oral gavage with up to 150 mg/kg-day sodium bisulfite during GD 6-15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity for this study is 150 mg/kg-day (ECHA). [Kl. score = 2]

Pregnant female Dutch-belted were dosed by oral gavage with up to 100 mg/kg-day sodium bisulfite during GD 6-18. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity for this study is 100 mg/kg-day (ECHA). [Kl. score = 2]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for sodium metabisulfite 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>

No repeated dose toxicity studies have been conducted on sodium bisulfite. In a study conducted on sodium metabisulfite, there was no evidence of systemic toxicity in rats fed up to 2% for two years (Til et al., 1972). The NOAEL for this study is 2% or 955 mg/kg-day.

Using the molecular weights of sodium metabisulfite (190.1 g/mol) and sodium bisulfite (104.1 g/mol), the NOAEL of 955 mg/kg-day for sodium metabisulfite is converted to 523 mg/kg-day for sodium bisulfite. The NOAEL of 523 mg/kg-day will be used for determining the oral reference dose (RfD) and the drinking water guidance value for sodium bisulfite.

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 = 523/(10 x 10 x 1 x 1 x 1) = 523/100 = 5 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 = (5 x 70 x 0.1)/2 = 18 mg/L

The Australian drinking water guidance value for sodium is 180 mg/L based on aesthetics (ADWG, 2011).

B. Cancer

There are no carcinogenicity studies on sodium bisulfite. No carcinogenic effects were reported for sodium metabisulfite in rat and mouse chronic studies. As there is inadequate evidence for the carcinogenicity in humans of sulfur dioxide, sulfites, bisulfites and metabisulfites (PubChem 2020) a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium bisulfite does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

No aquatic toxicity studies have been conducted on sodium bisulfite. Other inorganic sulfite compounds show low to moderate toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

No acute aquatic studies are available on sodium bisulfite; however, studies are available on other inorganic sulfite compounds. The studies on these inorganic sulfite compounds can used to read-across to sodium bisulfite since sulfite ions are formed in water upon dissociation of sodium bisulfite. Table 3 lists the results of acute aquatic toxicity studies on the structural analogues of sodium bisulfite.

Table 3: Acute Aquatic Toxicity Studies on the Structural Analogues of Sodium Bisulfite

Test Species	Test Substance	Endpoint	Results (mg/L)	Klimisch score	Reference
Leuciscus idus	Potassium sulfite	96-hr LC_{50}	316	2	ECHA
Salmo gairdneri	Sodium pyrosulfite	96-hr LC_{50}	147-215 (177.8*)	2	ECHA
Brachydanio rerio	Potassium metabisulfite	96-hr LC_{50}	464-1,000 (681.2*)	1	ECHA
Daphnia magna	Sodium disulfite	48-hr EC_{50}	88.8	2	ECHA
S. subspicatus	Sodium disulfite	96-hr EC_{50} 72-hr EC_{10}	43.9 33.3	2	ECHA

*Geometric mean.

Chronic Studies

No chronic studies are available on sodium bisulfite; however, studies are available on sodium sulfite. Table 4 lists the results of chronic aquatic toxicity studies conducted on sodium sulfite.

Table 4: Chronic Aquatic Toxicity Studies on Sodium Sulfite (CAS No. [redacted])

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Danio rerio	34-d NOEC	>316	1	ECHA
Daphnia magna	21-d NOEC	>10	2	ECHA

B. Terrestrial Toxicity

No studies were located.

C. Calculation of PNEC

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

PNEC water

No studies have been conducted on sodium bisulfite; however, the results from studies conducted on other inorganic sulphite compounds can be used to read-across to sodium bisulfite. Hence, experimental results are available for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (177.8 mg/L for sodium pyrosulfite), invertebrates (88.8 mg/L for sodium sulfite), and algae (43.9 mg/L for sodium disulfite).

Results from chronic studies on sodium sulfite are also available for all three trophic levels, with the lowest NOEC being 10 mg/L for invertebrates. Using the molecular weights of sodium sulfite (126 g/mol) and sodium bisulfite (104.1 g/mol, the NOEC of 10 mg/L for sodium sulfite is converted to 8.3 mg/L. On the basis that the data consist 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 8.3 mg/L for invertebrates. The $PNEC_{water}$ is 0.8 mg/L.

PNEC sediment

No experimental toxicity data on sediment organisms are available. Sodium bisulfite 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 bisulfite. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. Based on its properties, no adsorption of sodium bisulfite 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. Sodium bisulfite 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 bisulfite. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on its properties, no adsorption of sodium bisulfite to 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).

Sodium bisulfite is an inorganic compound that dissociates completely to ionic species and sulfur dioxide gas. Biodegradation is not applicable to these compounds. For the purposes of this PBT assessment, the persistent criterion is not considered applicable to sodium bisulfite or its dissociated compounds.

Sodium bisulfite is not expected to bioaccumulate because its dissociated species are inorganic ions and a gas.

There are no aquatic toxicity data on sodium bisulfite. The lowest NOEC from chronic aquatic toxicity studies on sodium sulfite, a structural analogue of sodium bisulfite, is >0.1 mg/L. Thus, sodium bisulfite is not expected to meet the criteria for toxicity.

The overall conclusion is that sodium bisulfite is not a PBT substance.

IX. CLASSIFICATION AND LABELING

A. Classification

Aquatic Acute Category 3
Harmful if swallowed

B. Labelling

Warning

C. Pictogram

(Pubmed 2020)

X. HANDLING AND SAFETY INFORMATION (OCCUPATIONAL LIMITS AND TRANSPORTATION REQUIREMENTS) [for a solution of sodium bisulfite]

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
When contacted by water, sodium bisulfite releases sulfur dioxide (SO_2), a poisonous gas. In the case of fire, the following may be liberated: Sulfur oxides and sulfur dioxide.

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
Pick up with absorbent material. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling
No special measures necessary provided product is used correctly.

Other Handling Precautions
Avoid eye and skin contact.

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 sodium bisulfite in Australia is 5 mg/m^3 as an 8-hr TWA.

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

Sodium bisulfite 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

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SODIUM CARBONATE

This dossier on sodium carbonate presents the most critical studies pertinent to the risk assessment of sodium carbonate 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 sodium carbonate (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): disodium carbonate

CAS RN: [redacted]

Molecular formula: $CH_2O_3.2Na$

Molecular weight: 106

Synonyms: sodium carbonate; disodium carbonate; carbonic acid, disodium salt; bisodium carbonate; soda ash, calcined soda

SMILES: C(=O)([O-])[O-].[Na+].[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-Chemical Properties of Sodium Carbonate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Solid; white powder	1	ECHA
Melting Point	851°C	2	ECHA
Boiling Point	No data	-	-
Density	>2.52 and <2.53 (20°C)	1	ECHA
Vapour Pressure	No data	-	-
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	404 g/L* [soluble]	2	ECHA
pH	ca 11.5**	2	ECHA
Flammability	No	1	ECHA

*GLP-compliant study. The water solubility was overestimated, possibly due to the high temperature (during dissolution) or due to gel formation.

**pH value from water solubility test.

Aqueous solutions are strongly alkaline. At 25°C, the pH of 1, 5 and 10 wt% sodium carbonate solutions are 11.37, 11.58, and 11.70, respectively (Eggeman, 2001).

III. ENVIRONMENTAL FATE PROPERTIES

Due to its high water solubility and low vapour pressure, sodium carbonate will be found predominantly in the aquatic environment where it dissociates completely to sodium (Na^+) and carbonate (CO_3^{2-}) ions. Both ions are ubiquitous in the environment (UNEP, 1995).

Addition of sodium carbonate to an aquatic ecosystem will result in an increase in alkalinity and a tendency to increase the pH. The carbonate ions will react with water, forming bicarbonate (HCO_3^-) and hydroxide (OH^-) ions until an equilibrium is reached. A re-equilibration takes place when carbonate (CO_3^{2-}) is dissolved in water according to the following equations:

$HCO_3^- \leftrightarrow CO_3^{2-} + H^+$ pKa=10.33

$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$ pKa = 6.35

Only a small fraction of the dissolved CO_2 is present as H_2CO_3 (carbonic acid), the major part is present as CO_2. The amount of CO_2 in water is in equilibrium with the partial pressure of CO_2 in the atmosphere. The CO_2/ HCO_3^-/ CO_3^{2-} equilibria are the major buffer of the pH of freshwater.

Based on the above equations, CO_2 is the predominant species at a pH smaller than 6.35, while HCO_3^- is the predominant species at a pH in the range of 6.35-10.33 and CO_3^{2-} is the predominant species at a pH higher than 10.33.

A release of sodium carbonate into the aquatic environment from the use of sodium carbonate could potentially increase the sodium concentration and the pH in the aquatic environment. Table 2 shows the concentration of sodium carbonate needed to increase the pH to values of 9.0, 10.0, and 11.0.

Table 2: Sodium Carbonate 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
0 mg/L HCO_3^- (distilled water)	11.1 (0.6)	16 (6.1)	603 (61)
20 mg/L HCO_3^- (10^{th} percentile of 77 rivers)	2.7 (21)	32 (26)	766 (81)
106 mg/L HCO_3^- (mean value of 77 rivers)	9.7 (107)	102 (112)	1467 (167)
195 mg/L HCO_3^- (90^{th} percentile of 77 rivers)	17 (196)	175 (201)	2192 (256)

*The initial pH of a bicarbonate solution with a concentration of 20-195 mg/L is 8.3 (calculated).

**The final concentration of bicarbonate is given in parentheses.

Na^+ and CO_3^{2-} ions will not adsorb on particulate matter or surfaces and will not accumulate in living tissues (OECD 2002b).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

There are limited toxicity data on sodium carbonate. It has a low order of acute toxicity by the oral, dermal, and inhalation routes. It is not a skin irritant, but it is an eye irritant. Sodium carbonate is not expected to be systemically available in the body from oral exposure due to its dissociation in bodily fluids and the neutralisation of the carbonate ion in the stomach. No developmental toxicity was seen in studies with rats, mice, or rabbits.

B. Toxicokinetics and Metabolism

Sodium carbonate will dissociate in bodily fluids into sodium (Na^+) and carbonate (CO_3^{2-}) ions. The oral uptake of sodium carbonate would lead to neutralisation of carbonate in the stomach by the gastric acids which would lead to bicarbonate and/or carbon dioxide (CO_2) formation. It is unlikely that an oral uptake of sodium carbonate would disrupt the acid-base balance of the body because CO_2 formation in the stomach would alleviate the high amounts of carbonate that would be present in the stomach from an acute exposure. However, excessively large doses may be corrosive to the gastro-intestinal tract. The equation that describes the bicarbonate dissociation reaction is:

$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$

C. Acute Toxicity

An acute oral LD_{50} of sodium carbonate monohydrate in rats is 2,800 mg/kg, and the acute dermal LD_{50} in rabbits is >2,000 mg/kg (OECD, 2002a,b; ECHA). [Kl. scores = 1]

An acute inhalation toxicity study was conducted on an aerosol of sodium combustion products, which contain predominantly sodium carbonate. The 2-hour inhalation LC_{50} values for this aerosol to guinea pigs, mice and rats were 800, 1,200 and 2,300 mg/m^3, respectively. The median aerodynamic diameter of the aerosol was 0.77 $\pm$ 2.1μm (OECD, 2002a, b; ECHA). [Kl. score = 1]

D. Irritation

As reviewed in the OECD-SIDS documents (OECD, 2002a,b), skin irritation studies in laboratory animals and human volunteers with sodium carbonate either as a 50% solution or as a solid showed slight to no skin irritation.

Sodium carbonate is an eye irritant (OECD, 2002a,b; ECHA). A dose of 0.1 ml sodium carbonate monohydrate was irritating to the eyes of rabbits and, in another study, 0.1 ml of sodium carbonate (anhydrous) was highly irritating to rabbit eyes. However, 0.1 g sodium carbonate (anhydrous) was found not to be an eye irritant. [Kl scores of 1, 2, 1, respectively]

E. Sensitisation

No studies were identified.

F. Repeated Dose Toxicity

No studies were identified by the oral, inhalation or dermal routes.

G. Genotoxicity

In Vitro Studies

Sodium carbonate did not induce primary DNA damage in an *E. coli* chromotest (Olivier and Marzin, 1987; OECD, 2002a, b). [Kl. score = 3]

In Vivo Studies

No studies were identified.

H. Carcinogenicity

No studies were identified.

I. Reproductive Toxicity

No studies were identified.

J. Developmental Toxicity

Pregnant rats were dosed by oral gavage with 0, 2.45, 11.4, 52.9 or 245 mg/kg sodium carbonate on gestational days 6 to 15. No maternal or developmental toxicity was observed. The NOAEL for maternal and developmental toxicity is 245 mg/kg-day, the highest dose tested (OECD, 2002a, b). [Kl. score = 2]

Pregnant mice were given doses of sodium carbonate (3.4 to 340 mg/kg) by oral gavage on gestational days 6 to 15. No maternal or developmental toxicity was observed. The NOAEL for maternal and developmental toxicity is 340 mg/kg-day, the highest dose tested (OECD, 2002a, b). [Kl. score = 2]

Pregnant rabbits were dosed by oral gavage with 0, 1.79, 8.31, or 179 mg/kg sodium carbonate on gestational days 6 to 15. No maternal or developmental toxicity was observed. The NOAEL for maternal and developmental toxicity is 179 mg/kg-day, the highest dose tested (OECD, 2002a, b). [Kl. score = 2]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

There are no repeated dose toxicity studies conducted on sodium carbonate by any route of exposure. Developmental toxicity studies conducted by the oral route in three animal species showed no developmental effects at the highest doses tested. Sodium carbonate dissociates to sodium and carbonate ions in bodily fluids, and 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.

Sodium carbonate is used in many countries (e.g., U.S. and EU) as a food additive. It is regarded as a Generally Recognized as Safe (GRAS) substance in food with no limitation other than current good manufacturing practice (OECD, 2002a, b).

Therefore, a toxicological reference value was not derived for sodium carbonate.

The Australian drinking water guideline values for sodium (180 ppm, aesthetic) and pH may be applicable (ADWG, 2011).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium carbonate does not exhibit the following physico-chemical properties:

- Flammability
- Explosivity
- Oxidising potential.

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium carbonate is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

The results of the aquatic toxicity studies conducted on sodium carbonate are presented in Table 3.

Table 3: Aquatic Toxicity Studies on Sodium Carbonate (OECD, 2002a,b)

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Bluegill sunfish	96-h LC_{50}	300	2	OECD, 2002a, b
Mosquitofish	96-h LC_{50}	740	2	OECD, 2002a, b
Bluefill sunfish	24-h LC_{50}	385	4	OECD, 2002a, b
Molly	50-h LC_{50}	297	4	OECD, 2002a, b
Ceriodaphnia dubia	48-h EC_{50}	200 - 227	2	OECD, 2002a, b

There are other studies conducted on invertebrates, but the results of these studies were not included in Table 3 because of the low reliability of the data (OECD, 2002a, b). No studies on algae were identified (OECD, 2002a, b).

C. Terrestrial Toxicity

No studies were identified.

D. Calculation of PNEC

The OECD-SIDS SIAR on sodium carbonate states the following regarding the aquatic toxicity studies on sodium carbonate (OECD, 2002b):

> "In general, the available toxicity studies with sodium carbonate were not conducted according to current standard guidelines. 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 sodium carbonate. In general, mortality of the test organisms was found at concentrations higher than 100 mg/l but for *Amphipoda*, salmon and trout lethal effects were already observed at 67-80 mg/l although these studies had a low reliability. The main factor explaining the acute aquatic toxicity of sodium carbonate is most likely the increase of the pH."

"Because the natural pH, bicarbonate and also the sodium concentration (and their fluctuations in time) varies significantly between aquatic ecosystems, it is not considered useful to derive a generic PNEC or $PNEC_{added}$."

Based on the information above, PNEC values for freshwater, sediment, and soil were not derived for sodium carbonate.

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 carbonate is an organic salt that dissociates completely to sodium and carbonate ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; both sodium and carbonate 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 carbonate ions are essential to all living organisms and their intracellular and extracellular concentrations are actively regulated. Thus, sodium carbonate is not expected to bioaccumulate.

No chronic aquatic toxicity data exist on sodium carbonate; however, the acute $EC(L)_{50}$s are >1 mg/L in fish, invertebrates and algae. Therefore, sodium carbonate does not meet the screening criteria for toxicity.

The overall conclusion is that sodium carbonate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Eye Irritant Category 2

B. Labelling

Warning

C. Pictograms

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. Never give anything by mouth to an unconscious person. If symptoms persist, get medical attention.

B. Firefighting Information

Extinguishing Media
Water fog, carbon dioxide, foam, dry chemical.

Specific Exposure Hazards
Decomposition in fire may produce toxic gases.

Special Protective Equipment for Fire fighters
Full protective clothing and approved self-contained breathing apparatus.

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 up and remove.

D. Storage and Handling

General Handling
Avoid contact with eyes and skin. Avoid creating or inhaling dust.

Storage
Store away from acids. Store in a cool, dry location.

E. Exposure Controls/Personal Protection

Occupational Exposure Standards
Workplace Australia has not established an occupational exposure limit for sodium carbonate.

Engineering Controls
Use in a well ventilated area. Localised ventilation should be used to control dust levels.

Personal Protection Equipment
Respiratory Protection: In case of insufficient ventilation, wear suitable respiratory equipment. Dust/mist respirator.

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 Carbonate 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.

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SODIUM DIACETATE

This dossier on sodium diacetate presents the most critical studies pertinent to the risk assessment of sodium diacetate 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 hydrogen di(acetate)

CAS RN: [redacted]

Molecular formula: $C_4H_7NaO_4$

Molecular weight: 142.09 g/mol

Synonyms: Sodium diacetate; sodium hydrogen di(acetate); sodium hydrogen diacetate; acetic acid, sodium salt (2:1); sodium acid acetate; sodium acetate, acid; sodium hydrogen acetate; sodium acetate (1:2); acetic acid, dimer, sodium salt

SMILES: CC(=O)O.CC(=O)[O-].[Na+]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of sodium diacetate

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	White crystalline powder with the odour of acetic acid	2	ECHA
Melting Point	>150°C @ 101.3 kPa (decomposes)	2	ECHA
Boiling Point	Not applicable		ECHA
Density	1405 kg/m^3@ 20°C	1	ECHA
Vapour Pressure	7.16 × 10^{-7}Pa @ 25°C (calculated)	2	ECHA
Partition Coefficient (log K_{ow})	-3.72 (temperature not provided) C	2	EPA, 2019
Water Solubility	1,000 g/L (temperature not provided)	2	ECHA
Flash Point	Study not applicable for solids		ECHA
Auto flammability	Study not applicable for solids		ECHA
Viscosity	Study not applicable for solids		ECHA
Henry's Law Constant	Not available		

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Sodium diacetate is readily biodegradable, and it is not expected to bioaccumulate.

B. Biodegradation

No studies are available on sodium diacetate.

Read-across substance sodium acetate (CAS RN [redacted] is readily biodegradable. In a Dissolved Organic Carbon (DOC) Die-Away test, degradation for sodium acetate was 86% after 7 days and 99% after 28 days (ECHA) [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).

C. Environmental Distribution

No experimental data are available for sodium diacetate. Using KOCWIN in EPISUITE™ (EPA, 2019), the estimated K_{oc} values from log K_{ow} of -3.72 is 0.0125 L/kg (acetic acid). The estimated K_{oc} value from the molecular connectivity index (MCI) is 1.0 L/kg (acetic acid).

D. Bioaccumulation

There are no bioaccumulation studies on sodium diacetate. Bioaccumulation of sodium diacetate is not expected to occur because the substance dissociates completely in aqueous media to acetate and its sodium ion. Both ions are ubiquitous in the environment. Acetate is naturally found in eukaryotic and prokaryotic cells and is involved in their biochemical pathways. Sodium diacetate is not expected to bioaccumulate based on a log K_{ow} of -3.72 (ECHA).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The substance is of low oral, inhalation, and dermal acute toxicity. It is not irritating to the skin but displays severe eye irritation. It is not expected to be a skin sensitiser, it is not genotoxic or carcinogenic. It has low oral repeat dose toxicity. It is not a reproductive or developmental toxicant.

B. Acute Toxicity

<u>Oral</u>

The oral LD_{50} in rats is 5,600 mg/kg (ECHA) [KI.score=2].

<u>Inhalation</u>

No acute inhalation studies are available on sodium diacetate. However, the calculated LC_{50} for sodium diacetate was reported as 18929 mg/L based on read across of analogues with similar molecular weights (ECHA) [KI.score=2].

Dermal

The dermal LD_{50} in rats is >2,000 mg/kg (ECHA) [Kl.score=2].

C. Irritation

Skin

Application of 0.5 g sodium diacetate to the skin of rabbits for 4 hours under unspecified conditions was non-irritating (ECHA) [Kl.score=1].

Eye

Instillation of 0.1 g sodium diacetate into the eyes of rabbits was severely irritating. Conjunctival redness was not fully reversible after 21 days (ECHA) [Kl.score=1].

D. Sensitisation

No studies are available for sodium diacetate. However, read across approaches were employed using citric acid (CAS RN [redacted] as a surrogate chemical. Based on read across approaches, sodium acetate is not considered as a skin sensitiser for human skin (ECHA) [Kl.score=2].

E. Repeated Dose Toxicity

No data are available on repeat dose toxicity studies for this substance. However, the analogue citric acid, sodium salt which shares the same functional group with sodium diacetate, also has comparable values for the relevant molecular properties for the repeated dose toxicity endpoint. Therefore, read across approaches were employed to calculate a NOAEL for sodium acetate. An oral repeated dose toxicity study was conducted using rats exposed to citric acid via their feed for one year. No additional study details were provided. The NOAEL for sodium acetate was calculated to be ≥ 50 mg/kg bw/day (ECHA) [Kl.score=2].

F. Genotoxicity

In Vitro Studies

No studies are available on sodium diacetate. The *in vitro* genotoxicity studies on sodium acetate are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Sodium Acetate

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains TA92, TA1535, TA 100, TA 1537, TA 94, TA98)	NC	-	2	ECHA
Chromosomal aberration (Chinese hamster fibroblast CHL cells)	-	NC	2	ECHA

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

In Vivo Studies

No studies are available on sodium diacetate or sodium acetate. However, sodium diacetate was not considered mutagenic to male mice based on read across from an *in vivo* study evaluating DNA-replication in male mice treated with sodium acetate. Sodium acetate exposure did not produce an inhibitory effect on DNA-replication in male mice. No further study details were provided. Thus, sodium diacetate is not considered to be mutagenic (ECHA) [Kl.score=2].

A bone marrow micronucleus study has been conducted on acetic anhydride (which hydrolyses to acetic acid). Male and female SD rats were exposed by inhalation to 0, 1, 5, or 20 ppm acetic anhydride, 6 hours/day, 5 days/week for 13 weeks. The incidence of micronucleated immature erythrocytes was not increased at any exposure concentration (ECHA) [Kl.score=1].

G. Carcinogenicity

No studies are available.

H. Reproductive Toxicity

No studies are available on sodium diacetate. Based on the experimental results obtained with the analogue citric acid on rats daily treated by feed for several months (NOAEL for reproductive effects = 600 mg/kg bw/day; LOAEL > 600 mg/kg bw/day for the same effects), and the molecular weights, the read-across approach was applied and the NOAEL with the substance sodium diacetate is calculated to be 665.5 mg/kg bw/day, and LOAEL higher than 665.5 mg/kg bw/day for reproductive effects. Read across from experimental results on rats and mice treated with citric acid and citric acid, sodium salt. No toxicity to reproduction was observed in any case (ECHA) [Kl.score=2].

I. Developmental Toxicity

Oral

Pregnant female Wistar rats were dosed by oral gavage with 0 or various concentrations up to 1,600 mg/kg apple cider vinegar (5% acetic acid) on gestational days 6 to 15. There were no maternal or developmental toxicity at any dose level. The NOAEL for maternal and developmental toxicity is 1,600 mg/kg-day (ECHA) [Kl.score=2].

Pregnant female CD-1 mice were dosed by oral gavage with 0, 16, 74.3, 345, or 1,600 mg/kg apple cider vinegar (5% acetic acid) on gestational days 6 to 15. There were no treatment-related effects on maternal or fetal survival, or on soft or skeletal tissues. There was no effect on the fetal development in the presence of slight maternal toxicity (reduced body weight gain) at 345 mg/kg. At 1,600 mg/kg, there was an increase in the number of litters containing a dead fetus and some reductions in ossification. The NOAELs for maternal and developmental toxicity are 74.3 and 345 mg/kg-day, respectively (ECHA) [Kl.score=2].

Pregnant female Dutch-belted rabbits were dosed by oral gavage with 0, 16, 74.3, 345, or 1,600 mg/kg apple cider vinegar (5% acetic acid) on gestational days 6 to 18. There were no treatment-related effects on maternal or fetal survival, or on soft or skeletal tissues. There was a reduction in the pregnancy rate in the high-dose group; and a dose-dependent decrease in maternal body weights at $\geq$74.3 mg/kg. Some deaths or abortions occurred in all treated groups and some litter losses were reported at $\geq$345 mg/kg. Maternal effects were much more noticeable than the effects on fetal development. These findings have been considered a consequence of the bactericidal properties of orally administered acetic acid within the gastrointestinal tract of female rabbits, and

not a direct effect on embryonic implantation and development of acetic acid (EU, 2008). It is likely that this accounts for the apparent increased sensitivity of this species to oral administration of acetic acid. The NOAEL for developmental toxicity is 1,600 mg/kg-day; a NOAEL for maternal toxicity was not identified (ECHA) [KI.score=2].

Inhalation

No studies are available.

Dermal

No studies are available.

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for sodium diacetate 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

An oral reference dose was not derived for sodium diacetate.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has maintained a group acceptable daily intake (ADI) of “not limited” for related substance acetic acid and its potassium and sodium salts (JECFA).

The Australian drinking water guidance value for sodium (180 mg/L [aesthetics]) and pH (6.5 to 8.5) may be applicable (ADWG, 2011).

B. Cancer

No carcinogenicity studies are available. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium diacetate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Acute aquatic toxicity studies on analogs of sodium diacetate suggest a relatively low level of toxicity. Data on these studies are shown below.

B. Aquatic Toxicity

Acute Studies

There are no studies on sodium diacetate. Table 3 lists the results of acute aquatic toxicity studies read-across from sodium acetate and potassium acetate. Read-across is justified since all three substances dissociate to the acetate anion and their respective cations (Na^+ or K^+). The toxicity of these substances is expected to be driven by the acetate ion, with the cations having a minor role.

Table 3 lists the results of acute aquatic toxicity studies conducted on sodium acetate and potassium acetate.

Table 3: Acute aquatic toxicity studies on sodium acetate and potassium acetate

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Brachydanio rerio	96-hr LC_{50}	>100 173*	1	ECHA
Daphnia magna	48-hr EC_{50}	>1,000 1,730*	2	ECHA
Daphnia magna	48-hr EC_{50}	>459.5 665*	2	ECHA
Skeletonema costatum	72-hr EC_{50}	>500 724*	2	ECHA

*Values converted to sodium diacetate using the molecular weights of sodium acetate (82.03 g/mol), potassium acetate (98.15 g/mol), and sodium diacetate (142.09 g/mol).

Chronic Studies

No studies are available.

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for sodium diacetate 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 (173 mg/L), invertebrates (665 mg/L), and algae (724 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 $E(L)C_{50}$ value of 173 mg/L for fish. The $PNEC_{water}$ is 1.7 mg/L.

PNEC Sediment

There are no toxicity data for sediment-dwelling organisms. Therefore, the $PNEC_{sed}$ was calculated using the equilibrium partitioning method. This is considered a conservative estimate since the substance dissociates completely in water. The $PNEC_{sed}$ is 1.1 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.82/1280) \times 1000 \times 1.7$
$= 1.1$ 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]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 1.0 \times 0.04$
$= 0.04$ L/kg

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for sodium diacetate calculated from EPISUITE™ using the MCI is 1.0 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. This is considered a conservative estimate since the substance is ionizable (ECHA). The $PNEC_{soil}$ is 0.02 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.02/1500) \times 1000 \times 1.7$
$= 0.02$ 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]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 1.0 \times 0.02$
$= 0.02\ m^3/m^3$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for sodium diacetate calculated from EPISUITE™ using the MCI is 1.0 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).

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

Bioaccumulation of sodium diacetate is not expected to occur because the substance dissociates completely in aqueous media to acetate and its sodium ion. Both ions are ubiquitous in the environment. Acetate is naturally found in eukaryotic and prokaryotic cells and is involved in their biochemical pathways. Based on a measured log K_{ow} of -3.72, sodium diacetate does not meet the screening criteria for bioaccumulation.

There are no chronic aquatic chronic toxicity data for sodium diacetate (or its surrogates). The acute $E(L)C_{50}$ values for sodium acetate and potassium acetate (read-across to sodium diacetate) are >1 mg/L. Thus, sodium diacetate does not meet the screening criteria for toxicity.

The overall conclusion is that sodium diacetate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H318 Eye damage Category 1

B. Labelling

Danger

C. Pictogram

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 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.

Ingestion

Rinse mouth with water and then drink plenty of water. Do not induce vomiting. Never give anything by mouth to an unconscious person. Seek medical attention.

B. Firefighting Information

Extinguishing Media

Water spray or fog, carbon dioxide, dry powder.

Specific Exposure Hazards

Burning may produce harmful and toxic fumes.

Special Protective Equipment for Firefighters

Wear a self-contained breathing apparatus if exposed to vapours, fumes or combustion products.

C. Accidental Release Measures

Personal Precautions

No special precautions are necessary. Ensure adequate ventilation.

Environmental Precautions

Do not discharge into drains, sewers, or waterways.

Steps to be Taken if Material is Released or Spilled

For large amounts: dike spillage and pump off the product. For residues: pick up with suitable absorbent material. Dispose of contaminated material as prescribed.

D. Storage and Handling

General Handling

Handle in accordance with good industrial hygiene and safety practice.

Other Handling Precautions

Protect against fire and explosion: prevent electrostatic charge; sources of ignition should be kept well clear, and fire extinguishers should be kept handy

Storage

Keep container tightly closed and dry. Protect against heat. The most favourable course of action is to use an alternative chemical product with less inherent propensity for occupational exposure or environmental contamination. Recycle any unused portion of the material for its approved use or return it to the manufacturer or supplier. Ultimate disposal of the chemical must consider: the material's impact on air quality; potential migration in soil or water; effects on animal, aquatic, and plant life; and conformance with environmental and public health regulations.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

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

Engineering Controls

Provide local exhaust ventilation to control vapours and mists.

Personal Protection Equipment

Respiratory Protection: Respiratory protection in case of vapours/aerosol release. Wear a certified organic vapour/particulate respirator.

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: 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

Sodium diacetate 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

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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

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SODIUM IODIDE

This dossier on sodium iodide presents the most critical studies pertinent to the risk assessment of sodium iodide 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 iodide

CAS RN: [redacted]

Molecular formula: NaI

Molecular weight: 149.89 g/mol

Synonyms: Ioduril, Sodium iodide (NaI), sodiumiodide, Sodium monoiodide, Soiodin, Iodure de sodium, Natriumjodid, Natriumiodid

SMILES: [Na+].[I-]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of sodium iodide

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	White colourless odorless crystalline inorganic solid	1	ECHA
Melting Point	651°C @ 97.5 kPa	1	ECHA
Boiling Point	1,304°C @ 96.57 kPa	2	ECHA
Density	3,700 kg/m^3@ 25°C	1	ECHA
Vapour Pressure	133.32 Pa @ 767°C	2	ECHA
Partition Coefficient (log K_{ow})	-1.301 @ 25°C	1	ECHA
Water Solubility	837 g/L @ 25°C	1	ECHA
Flash Point	Not applicable because the substance is a solid	-	ECHA
Auto flammability	There is no evidence of this substance self-heating. This substance is not considered auto flammable in nature	-	ECHA
Viscosity	Not applicable because this substance is a solid	-	ECHA
Henry's Law Constant	Not available	-	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Sodium iodide dissociates in aqueous media to sodium (Na^+) and iodide (I^-) ions. Biodegradation is not applicable to inorganic compounds. There are no bioaccumulation studies on sodium iodide. The low Log K_{ow} (-1.301) suggests sodium iodide will not bioaccumulate to a substantial degree (ECHA) [Kl.score=1]. Further, both ions are essential to living. Sodium (Na^+) ions are essential to all living organisms, and its intracellular and extracellular concentrations are actively regulated (Ganong, 1995). Iodine is essential for thyroid hormone synthesis in vertebrate species. Ingested iodine is converted to iodide (I^-) and absorbed. The minimum daily iodine intake that will maintain normal thyroid function is 150 mg in adult humans (Ganong, 1995).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Sodium iodide is not considered acutely toxic by any route of exposure, but any potential toxicity would be limited to the oral route as the size of iodide crystals precludes inhalation or dermal exposure. Likewise, it is not considered irritating to skin or eyes and has a history of therapeutic use that has not found evidence of sensitivity except in certain hypersensitive individuals. Iodide is not a sensitizing agent. Although evidence exists for toxicity via repeated doses that can disrupt thyroid hormones, iodine is an essential nutrient and lack of intake is associated with sub-clinical hypothyroidism. Iodide is not genotoxic, mutagenic or carcinogenic. Iodide is not toxic to reproductive endpoints or embryonically toxic, but developmental toxicity was showed under concentration of 0.1% in diet. However, this value is much higher than the temporary most tolerated dose of 1.0 mg iodine/day, set by the FAO/WHO Joint Expert Meeting on Food Additives.

The following sections detail the available and relevant literature on the toxicity of iodide. The information described below was obtained from NICNAS IMAP if available and the ECHA database. Please refer to those information sources for the studies referenced therein.

B. Acute Toxicity

Sodium iodide is not considered acutely toxic by any route of exposure. The potential acute toxicity of sodium iodide is limited to the ingestion pathway as the crystal size precludes both dermal and inhalation exposure. The most relevant study on vertebrates by oral route is a company study (Hausner et al., 1980) [Kl.score=2]. In the test, the effects of iodide were studied in male and female Wistar rats. Ten male and ten female in each dose and control groups were administrated with potassium iodide for 14 days at dose of 0 (control), 2000, 2500, 2800 3200, 3600 and 4000 mg/kg body weight mg/kg bw respectively. This study calculated a 24 hour and 7–14 days of LD50 to rats (male/female) of 3118 and 2779 mg/kg bw, respectively under test conditions.

C. Irritation

Based on existing information, iodide does not meet the skin or eyes irritation/corrosion criteria under the Regulation (EC) No. 1272/2008 nor Directive 67/548/EEC. Iodide has no effect to the human skin. Iodine has been used for dermal application in human as disinfectant (as Iodine and Povidine Iodine) for long time. The mechanism of disinfecting is oxidizing bactericide by iodine; meanwhile the iodine is reduced to iodide. It can be assumed that following application of iodine on

skin, there is iodide exposure to the epidermis. Further, in a human assay, potassium iodide in concentrations ranging from 5% to 20% in petrolatum was applied to skin with negative reactions.

There are no recent acceptable studies evaluating iodide effects on eye irritation, but iodide has been evaluated, and the results are negative for irritation. Although there is some exceptional case showing the iodide can have different degrees of impact on eyes, most reports gave negative results. Testing of potassium iodide on rabbit eyes by injection of 3% solution into the cornea has caused only slight reaction. In a report of large-scale intravenous injections given to patients with eye diseases, some individuals hypersensitive to iodide displayed watery rhinitis, lacrimation, edema of the eyelids and conjunctival hyperemia. Rarely, superimposed infection may cause more serious disturbances, and in one instance hypopyon was observed in the anterior chambers. Serious involvement of the eyes in iodism is uncommon, but in two patients severe keratoconjunctivitis was reported and in one of these there were hemorrhagic iritis and vitreous opacities. The eyes recovered when iodides were discontinued. The ordinary signs and symptoms of iodism clear up promptly when iodides are stopped.

D. Sensitisation

Based on the properties of sodium iodide, it does not meet classification criteria of skin and respiration sensitisation under Regulation (EC) No. 1272/2008 or Directive 67/548/EEC. The lack of sensitization to sodium iodide is thought to be driven by the large crystal size preventing inhalation and epidermal penetration.

E. Repeated Dose Toxicity

Oral

The most likely route for human exposure is via ingestion, so the dermal and inhalation route are irrelevant in the repeated toxicity assessment.

Boyages et al. (1989) compared thyroid status in groups of children 7–15 years of age who resided in two areas of China where drinking-water iodide concentrations were either 462.5 µg/l (n = 120) or 54 µg/l (n =51). Urinary iodine concentrations were 1236 µg/g creatinine in the high-iodine group and 428 µg/g creatinine in the low-iodine group. Although the subjects were all euthyroid, with normal values for serum thyroid hormones and TSH concentrations, TSH concentrations were significantly higher ($P < 0.05$) in the high-iodine group. The high-iodine group had a 65% prevalence of goiter and a 15% prevalence of Grade 2 goiter compared with 15% for goiter and 0% for Grade 2 goiter in the low-iodine group. To transform the measured urinary iodine levels into estimates of iodine intakes, steady state baseline dietary intakes of iodide were assumed to be equivalent to the reported 24-h urinary iodine excretion rates. Assuming a body weight of 40 kg and lean body mass of 85% of body weight, the urinary iodine/creatinine ratios reported by Boyages et al. (1989) can be converted to approximate equivalent intake rates of 1150 µg/day (0.029 mg/kg body weight per day) and 400 µg/day (0.01 mg/kg body weight per day) for the high- and low-iodine groups, respectively. Thus, the NOAEL for this study is 0.01 mg/kg body weight per day.

Supporting studies indicate that the NOAEL from the Boyages et al. (1989) study would be applicable for both acute and chronic-duration exposure of elderly adults, who may represent another sensitive subpopulation (Chow et al., 1991; Szabolcs et al., 1997). In the Chow et al. (1991) study, 30 healthy 60 to 75-year-old females received daily doses of 500 µg iodine per day for 14 or 28 days. Serum concentrations of free T4 were significantly decreased, and serum TSH concentrations were significantly elevated. On average, the magnitude of the changes did not produce clinically significant depression in thyroid hormone levels; however, five subjects had serum TSH

concentrations that exceeded 5 mU/l. The pre-existing dietary iodine intake was approximately 72–100 µg/day, based on urinary iodide measurements. Therefore, the total iodide intake was approximately 600 µg/day (0.0087 mg/kg body weight per day, based on a mean weight of 69 kg for women 19–64 years of age in the British National Diet and Nutrition Survey; British Nutrition Foundation, 2004). Szabolcs et al. (1997) studied elderly nursing home residents who had received long-term exposure to iodine in one of three regions where the intakes were estimated to be approximately 117, 163 or 834 µg/day (0.0017, 0.0023 or 0.012 mg/kg body weight per day for low, moderate or high intake, respectively). The prevalence of clinical hypothyroidism was 0.8%, 1.5% and 7.6% in the low-, moderate- and high-iodine groups, respectively. Serum TSH concentrations were elevated as free T4 levels were reduced (P = 0.006).

In a study by Paul et al. (1988), healthy euthyroid adults (nine males, nine females) who had no history of thyroid disease or detectable antithyroid antibodies received daily oral doses of 250, 500 or 1500 µg iodine (as sodium iodide) per day for 14 days. Based on 24-h urinary excretion of iodide prior to the iodide supplement, the background iodine intake was estimated to be approximately 200 µg/day; thus, the total iodide intake was approximately 450, 700 or 1700 µg/day (approximately 0.0064, 0.01 or 0.024 mg/kg body weight per day, assuming a 70-kg body weight). Subjects who received 1700 µg/day (0.024 mg/kg body weight per day) had significantly depressed (5–10%) serum concentrations of total T4, free T4 and total T3 compared with pretreatment levels, and serum TSH concentrations were significantly elevated (47%) compared with pretreatment values. Hormone levels were within the normal range during treatment. In this same study, nine females received daily doses of 250 or 500 µg iodine per day for 14 days (total intake was approximately 450 or 700 µg/day; 0.0064 or 0.010 mg/kg body weight per day), and there were no significant changes in serum hormone concentrations.

In a comparable quality study by Gardner et al. (1988), 10 healthy adult euthyroid males received daily oral doses of 500, 1500 or 4500 µg iodine (as sodium iodide) per day for 14 days. Based on 24-h urinary excretion of iodide of 256–319 µg/day prior to the iodide supplement, the total estimated intakes were 800, 1800 or 4800 µg/day, or approximately 0.011, 0.026 or 0.069 mg/kg body weight per day. In this study, there were no effects on serum thyroid hormone or thyroid stimulating hormone (TSH) concentrations at the 800 µg/day intake (0.011 mg/kg body weight per day); however, intakes of 1800 or 4800 µg iodine per day (0.026 or 0.069 mg/kg body weight per day) produced small (10%), but significant, transient decreases in serum thyroid hormone concentrations and an increase (48%) in serum TSH concentration, relative to the pretreatment values.

From the Boyages et al. (1989) study, supported by the studies of Gardner et al. (1988), Paul et al. (1988) and others, a TDI of 0.01 mg/kg body weight, based upon reversible subclinical hypothyroidism, can be established by dividing the NOAEL of 0.01 mg/kg body weight per day by an uncertainty factor of 1.

However, iodine is also an essential trace element for synthesis of thyroid hormones. In healthy adults, sub-clinical hypothyroidism is associated with intakes of 1.7 to 1.8 mg/day, and for children with intakes of 1.15 mg/day (EFSA 2006, FSANZ 2008). Chronic iodine intakes of approximately 1 mg/day, however, appear to be well tolerated by healthy adults. This is consistent with the provisional maximum tolerated daily intake of 1 mg/day established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 1989), and the nutrient reference value and tolerable upper intake level of 1.1 mg/day respectively recommended by the NHMRC (2006) and Food Standards Australia New Zealand (FSANZ 2008) for iodine intake by adults in Australia and New Zealand. This value has been used as the basis for calculating the drinking water guideline described in Section V.

Inhalation

There are no studies available.

Dermal

There are no studies available.

F. Genotoxicity

In Vitro Studies

The mutagenic potential for iodide (in potassium iodide) was studied using the L5178Y mouse (TK+/-) lymphoma assay (Kessler et al., 1980). The established mutagens ethylmethanesulphonate (EMS) and dimethylnitrosamine (DMN) were highly active in this assay, whereas iodide was inactive. Using the BALB/c 3T3 transformation assay well assessed the transformational capacities of these same agents and the positive mutagen N-ethyl-N-nitro-N-nitrosoguanidine. All concentrations of the iodide tested were inactive in this assay.

Another study (Poul & Sanders, 2004) on genotoxic effects of potassium iodide was conducted *in vitro* using the alkaline comet assay at concentration of 0.625, 1.25, 2.5, 5 and 10 mM. Additionally, in the test cell viability was also measured using the Trypan blue exclusion method and expressed as proportion of total cells. The test results showed that potassium iodide did not induce DNA damage or cytotoxicity in the alkaline comet assay for doses up to 10 mM.

In the same study, the chromosome damage effects of potassium iodide were evaluated *in vitro* using cytokinesis-block micronucleus test at concentration of 0.625, 1.25, 2.5, 5 and 10 mM. Additionally, in the test cytotoxicity was also measured by the binucleated (BN) cell ratio between treated and control slides. The test results showed that potassium iodide did not induce chromosome damage or cytotoxicity in the alkaline comet assay for doses up to 10 mM.

In Vivo Studies

In an *in vivo* chromosome aberration test on embryonic hepatocytes, Stable iodine of 10 mg/kg is administered to the rats 7 days after fertilization. Then the embryonic liver was homogenized and the cells in metaphase were stained and checked under metaphase. The chromosome aberration cells were counted respectively for the concentration group and control group. The chromosome aberration rate in the concentration group was compared with that in the control group. The result showed there was no significant difference between iodide dosed group with the control group.

Based on the available studies summarized above, iodide has neither genetic toxicity nor cytotoxicity to mammalian cells.

G. Carcinogenicity

Oral

There are no studies available.

Inhalation

There are no studies available.

Dermal

There are no studies available.

H. Reproductive Toxicity and Developmental Toxicity

Iodide is not considered to meet the reproductive/developmental criteria under the Regulation (EC) No. 1272/2008 nor Directive 67/548/EEC. Several studies have evaluated reproductive and developmental effects.

A study [Kl.score=2] was conducted with rats to determine the effects of intake of the test chemical. Females were bred to normal males, wherein the test chemical was added to the diet during the latter portion of gestation and the females were permitted to litter normally. The effect of the treatment on gestation period, lactation and survival of the young was observed. Gestation time for rats was not affected but prolonged parturition was observed. In fetal parameters, average mortality was slightly greater for young fed with the test chemical while the weaning weight was significantly less than that of controls. Female rats re-bred after removal of dietary intake of the test chemical gave birth and nursed litters normally. The study resulted in a LOAEL of 150 mg/kg bw.

The effect of the test chemical on the reproductive performance of female minks was investigated [Kl.score=2]. Female mink were administered with 0, 10, 100 or 1000 ppm of the test chemical, in diet for 18 days, from breeding through lactation. Gestation periods of the test chemical-treated mink were shorter than the controls. Kit birth weights were not significantly different from the controls. The average number of kits whelped per female mated in the control group was 5.0. Only 2.1 kits per female mated were whelped by the mink fed 100 ppm supplemental test chemical, and none of the females that received the 1000 ppm supplemental test chemical diet whelped. Body weights of kits whelped and nursed by the females that received the 100 ppm supplemental test chemical diet were significantly lighter at 4 weeks of age. No detrimental effects were observed on litter size or kit survival in the group fed 10 ppm supplemental test chemical, and hence the NOAEL for reproductive toxicity in female minks is determined to be 10 ppm of the test chemical in the diet.

Iodide was administered in diet to male and female Sprague-Dawley rats before and during breeding, to females only during gestation and lactation, at levels of 0, about 23, 45 and 90 mg/kg bw (0, 0.025, 0.05 or 0.1% [w/w]). Dams in a positive control group were given 4 mg/kg i.p. of the anti-mitotic/cytotoxic drug 5-azacytidine on day 17 of gestation. The LOAEL value for the test chemical in rats is found to be about 90 mg/kg/day (0.1%). At this dose level, the test chemical did not produce any significant reduction in parental body weight or food consumption, though it significantly reduced litter size and increased offspring mortality. The LOAEL value for the test chemical is found to be about 45 mg/kg/day (0.05%) for the F_1 generation based on the effect of decreased pre-weaning body weights in the offspring, delay in auditory startle and delayed olfactory orientation from the home-cage scent. Overall, the data in this experiment [Kl.score=2] support the view that the test chemical at doses of up to 0.1% in the diet of growing rats produces evidence of developmental toxicity.

In a one-generation (experiment I) and fertility (experiment II) reproductive study [Kl.score=2], pregnant female Wistar rats were given fluid orally on a regular basis at dose levels of 0.1% (w/v) or 1% (w/v) of the test chemical. Treatment with 1% (w/v) solution led to reduced body weight and fluid intake, enlarged adrenal glands and the level of implantation was reduced. No change in food or fluid intake was seen for rats treated with 0.1% (w/v) solution. In addition, the 0.1% (w/v) of the test chemical solution-treated rats showed a high rate of implantation. Since 0.1% (w/v) of the test chemical is regarded as a high value intake, and it is concluded that the test chemical has no effect

on reproductive toxicity when orally administered. Neither has it provided any further information about the possible functional significance of the test chemical endometrial concentration in female rats during early pregnancy.

In conclusion, iodide is not toxic to reproductive endpoints or embryonically toxic, but developmental toxicity was showed under concentration of 0.1% in diet. However, this value is much higher than the temporary most tolerated dose of 1.0 mg iodine/day, set by the FAO/WHO Joint Expert Meeting on Food Additives

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

An oral RfD for sodium iodide was not derived because there is an existing Australian drinking water guidance value of 0.5 mg/L for iodide (health) and 180 mg/L for sodium (aesthetics). The substance is not carcinogenic, so a cancer reference value was not developed.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium iodide does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium iodide is of low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

The acute aquatic toxicity studies conducted on the substance suggest a wide range of toxicity that is species dependent. The results of the studies are shown below.

Acute Studies

Table 2 lists the results of acute aquatic toxicity studies conducted on sodium iodide.

Table 2: Acute aquatic toxicity studies on sodium iodide

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Danio rerio	96-hr LC_{50}	>100	2	ECHA
Oncorhynchus mykiss	96-hr LC_{50}	3780	2	ECHA
Daphnia magna	48-hr EC_{50}	0.17	2	ECHA
Pseudokirchneriella subcapitata	72-hr EC_{50}	>37.26 (growth)	1	ECHA

Chronic Studies

The 35-day NOEC in Danio rerio based on hatchability and larvae survival was found to be > 10 mg/L (ECHA) [Kl.score=1].

The 21-day NOEC in a Daphnia reproduction test is 0.153 mg/L (ECHA) [Kl.score=1].

On the basis of growth rate, the 72-hour NOEC to green algae *Pseudokirchneriella subcapitata* was also > 37.26 mg/L (ECHA) [Kl.score=1].

C. Terrestrial Toxicity

No studies are available and do not need to be conducted because direct and indirect exposure of the soil compartment is unlikely and the chemical is readily biodegradable and not persistent in soil (ECHA).

D. Calculation of PNEC

The PNEC calculations for sodium iodide 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 (0.17 mg/L) and algae (37.3 mg/L). Results from chronic studies are available for fish (>10 mg/L), invertebrates (0.153 mg/L) and algae (>37.26 mg/L). On the basis that the data consist of short-term studies for three trophic levels and long-term results studies for three trophic levels, an assessment factor of 10 has been applied to the lowest reported NOEC value of 0.153 mg/L for *Daphnia*. The $PNEC_{water}$ is 0.0153 mg/L.

PNEC Sediment

There are no toxicity data for sediment-dwelling organisms. The environmental distribution of sodium iodide is dominated by its water solubility. Sorption of sodium iodide 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 iodide. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sediment}$. As a result, 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 iodide is dominated by its water solubility. Sorption of sodium iodide 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 iodide. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. As a result, 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 (IChEMS, 2022; ECHA, 2023).

Sodium iodide dissociates completely to sodium and iodide ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions. For the purposes of this PBT assessment, the persistence criteria is not considered applicable. The low Log K_{ow} (-1.301) suggests sodium iodide will not bioaccumulate to a substantial degree. In addition, sodium ions are essential to all living organisms and its intracellular and extracellular concentrations are actively regulated. The iodide ion

is essential for thyroid function in all vertebrates. Thus, sodium iodide does not meet the screening criteria for bioaccumulation. The lowest NOEC value on sodium iodide is >0.1 mg/L for fish, invertebrates and algae. Thus, sodium iodide does not meet the screening criteria for toxicity.

Therefore, sodium iodide is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H315: Skin irritation (Category 2)

H319: Eye irritation (Category 2A)

H400: Acute aquatic toxicity (Category 1)

B. Labelling

Warning

C. Pictogram

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

Immediately flush eyes with plenty of water for at least 15 minutes, lifting lower and upper eyelids occasionally. Remove contact lenses, if present and easy to do. Continue rinsing. Get medical attention immediately.

Skin Contact

Wipe off excess material from skin then immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Get medical attention. Wash clothing before reuse. Thoroughly clean shoes before reuse.

Inhalation

Remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give Oxygen. Get medical attention.

Ingestion

Induce vomiting immediately as directed by medical personnel. Never give anything by mouth to an unconscious person. Get medical attention.

B. Firefighting Information

Extinguishing Media

Sodium iodide is not considered a fire hazard. Use any means suitable for extinguishing surrounding fire.

Specific Exposure Hazards

Non-combustible, substance itself does not burn but may decompose upon heating to produce corrosive and/or toxic fumes.

Special Protective Equipment for Firefighters

As in any fire, wear self-contained breathing apparatus and full protective gear.

C. Accidental Release Measures

Personal Precautions

Use personal protective equipment. Ensure adequate ventilation. Avoid dust formation. Avoid contact with skin, eyes and clothing. Isolate hazard area. Keep unnecessary and unprotected personnel from entering.

Environmental Precautions

Do not flush into surface water or sanitary sewer system. Do not allow material to contaminate groundwater system. Prevent product from entering drains. Local authorities should be advised if significant spillages cannot be contained.

Substance may decompose upon heating to produce corrosive and/or toxic fumes. Do not allow runoff from firefighting to enter drains or water courses.

Steps to be Taken if Material is Released or Spilled

Pick up and place in a suitable container for reclamation or disposal, using a method that does not generate dust.

D. Storage and Handling

General Handling

Wear personal protective equipment. Ensure adequate ventilation. Avoid dust formation. Avoid contact with skin, eyes and clothing. Do not breathe dust. Do not ingest. Containers of this material may be hazardous when empty since they retain product residues (dust, solids). Observe all warnings and precautions listed for the product.

Other Handling Precautions

Protect from light.

Storage

Keep in a tightly closed container, stored in a cool, dry, ventilated area. Protect against physical damage. Isolate from incompatible substances.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

None established.

Engineering Controls

Ensure adequate ventilation, especially in confined areas. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protection Equipment

Respiratory Protection: When workers are facing exposure to dust or mist, they must use appropriate certified respirators. To protect the wearer, respiratory protective equipment must be the correct fit and be used and maintained properly.

Hand Protection: Wear protective gloves; inspect gloves before use.

Skin Protection: Wear clean body-covering clothing.

Eye protection: Use chemical safety goggles. Maintain eye wash fountain and quick-drench facilities in work area.

Other Precautions: None noted.

F. Transport Information

UN Number UN3077

Hazard class 9

XI. DISPOSAL MANAGMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

XIII. REFERENCES

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SODIUM PERBORATE TETRAHYDRATE

This dossier on sodium perborate tetrahydrate presents the most critical studies pertinent to the risk assessment of sodium perborate tetrahydrate 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).

NICNAS has assessed sodium perborate tetrahydrate in an IMAP Tier 1 assessment and concluded that it poses no unreasonable risk to the environment.[1] NICNAS concluded that it is a reactive substance which rapidly converts into species of low ecotoxicological concern. This chemical, and its degradant species, are not expected to pose an unreasonable risk to the environment provided that ANZECC water quality guidelines for physical and chemical stressors are not exceeded.

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): sodium perborate tetrahydrate

CAS RN: [redacted]

Molecular formula: $NaBO_3 \bullet 4H_2O$

$[NaBO_2(OH)_2 \bullet 3H_2O]_2$ (presented as the dimer)

Molecular weight: 153.9 g/mol

Synonyms: sodium peroxoborate tetrahydrate; perboric acid, sodium salt, tetrahydrate

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of sodium perborate tetrahydrate

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	White, odorless, crystalline powder	4	EC, 2007
Melting Point	65°C @ 101.3 kPa	-	EC, 2007
Boiling Point	Decomposes	-	EC, 2007
Density	0.65–0.9 (relative density)	-	EC, 2007
Vapour Pressure	Negligible	-	-
Partition Coefficient (log K_{ow})	Not applicable, substance is inorganic	-	-
Water Solubility	23 g/L @ 20°	-	EC, 2007
Flash Point	Not available	-	-

[1] https://services.industrialchemicals.gov.au/assessment-detail/?id=d785433e-f36b-1410-8c14-0026b2c59b62

Property	Value	Klimisch Score	Reference
Auto flammability	Not available	-	-
Viscosity	Not available	-	-
Henry's Law Constant	Not available	-	-

The molecular crystalline structure of sodium perborate tetrahydrate consists of dimeric $[(HO)_2(BOO)]$-units which forms symmetric cyclic hexagonal anions with two peroxo bridges each. In its crystalline form the substances are stable under dry conditions (EC, 2007).
In aqueous solutions at room temperature, an equilibrium occurs between sodium perborate and hydrogen peroxide (H_2O_2)/sodium metaborate ($NaBO_2$):

$NaBO_2(OH)_2 \bullet 3H_2O]2 \rightarrow 2NaBO_2 + 2H_2O_2 + 6H_2O$

At low concentrations (about <2 g/L), the equilibrium is largely on the side of the hydrolysis products; at high concentrations (about >12 g/L), the un-dissociated molecule is present in aqueous solutions. The hydrogen peroxide can be removed from the equilibrium by degradation to active oxygen, leading to an irreversible shift of the equilibrium to the degradation products sodium metaborate and water. This reaction is the basis of the bleaching effect of sodium perborate in the washing process (EC, 2007).

Sodium metaborate is the salt of a strong base (sodium hydroxide) and a weak acid (boric acid). So, sodium metaborate is expected to be present in aqueous solutions at environmental temperature and pH mainly as the weakly dissociated boric acid.

$NaBO_2 + 2H_2O \rightarrow Na^+ + OH^- + H_3BO_3$

H_3BO_3 (Boric acid) $\rightarrow [B(OH)^4]^-$ (borate) $+ H^+$

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 sodium perborate tetrahydrate to B-equivalents is 0.07.

Sodium perborate tetrahydrate has been identified as a Substance of Very High Concern and recommended for inclusion in Annex XIV (the Authorisation List) of the REACH legislation in the European Union based on its toxicity for reproduction (Article 57c). The chemical is on the "Candidate List" and is not on the "Authorisation List". The chemical is not currently identified as being of environmental concern (NICNAS, 2019).

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Boron is almost exclusively found in the environment as boron-oxygen 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).

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." A BCF of <0.1 was reported in Chinook salmon fed boron-supplemented diets for 60 to 90 days (Hamilton & Wiedmeyer, 1990).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Sodium perborate tetrahydrate exhibits low acute toxicity by the oral and dermal routes, and slight-to-moderate acute toxicity by the inhalation route. It is not a skin irritant or sensitiser, but it is severely irritating to the eye. Toxicity studies on boric acid, borax (disodium tetraborate decahydrate), and boron oxide have been used to read-across to sodium perborate tetrahydrate. This is justified because, in aqueous media at physiological pH, all inorganic borate compounds 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, and malformations and variations. Repeated inhalation exposure resulted in slight irritation to the respiratory tract, but no systemic toxicity. Based on read-across substances, sodium perborate tetrahydrate is not genotoxic nor carcinogenic.

B. Acute Toxicity

The oral LD_{50} values of sodium perborate tetrahydrate in rats are 2,567 and 2,800 mg/kg (ECHA) [Kl.score= 1 and 2, respectively].

The 4-hour inhalation LC_{50} of sodium perborate tetrahydrate (as a dust) in rats is 1.17 mg/L. The MMAD ranged from 3.3 to 4.2 µm (ECHA) [Kl.score=2].

There are no acute dermal toxicity studies on sodium perborate tetrahydrate. The dermal LD_{50} of sodium perborate monohydrate in rabbits is >2,000 mg/kg (ECHA) [Kl.score=1].

C. Irritation

Application of 0.5 g. sodium perborate tetrahydrate to the skin of rabbits for 4 hours under occlusive conditions was not irritating (ECHA) [Kl.score=2].

Instillation of 0.1 mL sodium perborate tetrahydrate to the eyes of rabbits was considered corrosive (ECHA) [Kl.score=2]. Another study showed that sodium perborate tetrahydrate was severely irritating to the eyes of rabbits (ECHA) [Kl.score=2].

D. Sensitisation

No studies are available on sodium perborate tetrahydrate. In the mouse local lymph node assay (LLNA), sodium perborate monohydrate was not considered a skin sensitizer (ECHA) [Kl.score=1].

E. Repeated Dose Toxicity

Oral

Male and female Bor:WISW (SPFCpb) rats were dosed by oral gavage with 0 or 1,000 mg/kg sodium perborate tetrahydrate for 28 days. Clinical signs in the treated rats mainly consisted of salivation. There was no mortality. The treated males showed a 15% reduction in body weight gain and up to 15% reduction in feed consumption. There was possible treatment-related reduction in total cholinesterase and protein (both sexes) and albumin (males). Relative liver weights were slightly increased in the females. Histopathologic changes were reduction of parenchyma in the spleen (males), slight acathosis and hyperkeratosis in the forestomach (both sexes), and hyperplasia of the fundic mucosa (both sexes). There were no testicular effects in the treated males. The LOAEL for this study is 1,000 mg/kg-day; a NOAEL was not established (ECHA) [Kl.score=2].

Male and female SD rats were given doses of 0, 52.5, 175, 525, 1,750 or 5,250 ppm B equivalent in their diet boric acid 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 (EPA, 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 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) [Kl.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 equivalent 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 (EPA, 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 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 of the 1,750 ppm males. Four 525 ppm males had partial testicular atrophy. Spermatogenic arrest was found in one 525 ppm male. NOAEL for this study is 175 ppm boron or 8.8 mg B/kg-day (Weir and Fisher, 1972) [Kl.score=2].

Male and female B6CF11 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 (EPA, 2004). There was mortality (8/10 males; 6/10, females) in the 20,000 ppm, 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 hematopoiesis 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) [Kl.score=2].

Male and female SD rats were given in their diet boric acid at doses of 0, 117, 350 or 1,170 ppm boric acid in their diet 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 (EPA, 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 of 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 &Fisher, 1972) [Kl.score=2].

Male and female B6C3F1 mice were given in their diet 0, 2,500 or 5,000 ppm boric acid in their feed for 103 weeks (NTP, 1987). These dose levels were equivalent to 0, 275 or 550 mg/kg-day boric acid or 0, 48 or 96 mg B/kg-day (EPA, 2004). There was reduced survival in the male mice, which was significantly different from the controls in the 2,500 ppm mice after week 63 and in the 5,000 ppm mice after week 84. The survival rates by the end of the study were 82, 60 and 44% in the 0, 2,500, and 5,000 ppm males, respectively, and 66, 66 and 74% in the 0, 2,500, and 5,000 ppm females, respectively. Mean body weights were 10-17% lower in the 5,000 ppm animals after 32 (males) or 52 (females) weeks compared to the controls. There was testicular atrophy and interstitial cell hyperplasia in the testes of the 5,000 ppm males. A dose-related increase in the incidences of splenic lymphoid depletion in male mice was also observed. NTP considered this lesion to be associated with stress and debilitation, and it is reflected in the increased mortality in these groups of male mice. A NOAEL was not reported in this study but the authors note that there is no evidence of carcinogenicity of boric acid at doses of 2,500 or 5,000 ppm for male and female B6C3F1 mice (NTP, 1987) [Kl.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 localized effects (irritation) is 175 mg/m^3 (ECHA) [Kl.score=2].

Dermal

There are no studies available.

F. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on sodium borate tetrahydrate (or sodium perborate) are presented in Table 2. The in vitro genotoxicity studies on boric acid are shown in Table 3.

Table 2: *In vitro* genotoxicity studies on sodium perborate tetrahydrate (or sodium perborate)

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (S. typhimurium TA102 and TA2638; and E. coli WP2/pKM101 and WP2 uvrA/pKM101)	+**	NT	2	Watanabe et al. (1998)
Bacterial reverse mutation (S. typhimurium strains)	(-)TA98 (+) TA100, TA102	(-) TA98 (-) TA100, TA102	2	Seiler (1989)
Chromosomal aberrations (Chinese Hamster Ovary cells)	+	-	2	Seiler (1989)

*+, positive; -, negative; NA, not applicable; NS, not specified; NT, not tested.
**Two independent laboratories.

Table 3: *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.

The genotoxic potential of sodium perborate in the absence of metabolic activation may be due to the generation of hydrogen peroxide. If so, the results from the *in vitro* tests may not be relevant *in vivo* because hydrogen peroxide is readily reduced by catalase. Boric acid, the other dissociated product from sodium perborate tetrahydrate (or sodium perborate) did not show any genotoxic potential in any of the *in vitro* tests.

In Vivo Studies

No studies are available on sodium perborate tetrahydrate.

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) [Kl.score=1].

G. Carcinogenicity

Oral

No studies have been conducted on sodium perborate tetrahydrate.

Male and female SD rats were given disodium tetraborate decahydrate (borax) or boric acid at doses of 0, 117, 350, or 1,170 ppm as Boron equivalents (approximately 0, 5.9, 17.5, or 58.5 mg B/kg-day) in their diet 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; EPA, 2004).

Male and female B6C3F_1 mice were given 0, 2,500, or 5,000 ppm boric acid in their diet 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].

Inhalation

There are no studies available.

Dermal

There are no studies available.

H. Reproductive Toxicity

A three-generation reproductive toxicity study was conducted in albino rats (strain not specified) 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, 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 albino rats (strain not specified) with disodium tetraborate decahydrate. 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, 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. Estrous 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].

I. Developmental Toxicity

Oral

Pregnant female Crl:CD(SD)BR rats were dosed by oral gavage with 0, 100, 300, or 1,000 mg/kg sodium perborate tetrahydrate during gestational days 6 to 15. Maternal body weight gain and feed consumption were significantly reduced in the >300 mg/kg dose groups. A dose-related increase was seen in resorptions, placental weights, and fetal body weights in the 300 and 1,000 mg/kg dose groups. Malformations (mainly related to the skeletal and to the cardiovascular system) were increased in the 1,000 mg/kg dose group. The NOAEL for maternal and developmental toxicity is 100 mg/kg-day (ECHA) [Kl.score=1].

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 dams 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 fetal 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 in their feed 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, fetal 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 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 0, 0.1, 0.2 or 0.4% boric acid in their diet 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) [Kl.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 fetuses 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) [Kl.score=1].

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 disodium perborate tetrahydrate 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

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). 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 disodium tetraborate decahydrate and/or boric acid. Thus, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium perborate tetrahydrate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium perborate tetrahydrate has low chronic aquatic toxicity.

B. Aquatic Toxicity

In ecotoxicological tests for boron, the exposure concentrations are expressed as boron equivalents (i.e., mg B/L). This is because sodium perborate tetrahydrate and similar perborates 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

Table 4 lists the results of acute aquatic toxicity studies conducted on sodium perborate tetrahydrate.

Table 4: Acute aquatic toxicity studies on sodium perborate tetrahydrate

Test Species	Endpoint	Results (mg B/L)	Klimisch Score	Reference
Brachydanio rerio	96hr LC_{50}	5.5	-	EC, 2007
Daphnia magna	48hr EC_{50}	2.1		EC, 2007
Selenastrum capricomutum	72hr EC_{50}	0.36		EC, 2007

Chronic Studies

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 5 below. 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 5: 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 RN [redacted] or borax, $Na_2B_4O_710H_2O$ (CAS RN [redacted] in freshwater.

In the chronic toxicity data set, fish sensitivity to boron ranged from the least sensitive species in the dataset (*Melanotaenia splendida*, LC10 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 (Warne et al. 2018), in this instance, a reliable NOEC of 2.8 mg/L was the most sensitive toxicity value for *P. subcapitata* (ANZG, 2021).

C. 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, 2017). 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).

D. Calculation of PNEC

The PNEC calculations for sodium perborate tetrahydrate follow the methodology discussed in DEWHA (2009).

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

No experimental toxicity data on sediment organisms are available. Sodium perborate tetrahydrate dissociates completely in water and its environmental distribution is dominated by its high-water solubility. Due to the high water solubility of boron and its low partitioning to sediment, sediment toxicity testing for boron is particularly challenging. 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, especially those subject to chemical dissociation, such as sodium perborate tetrahydrate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. Based on its properties, no adsorption of sodium perborate tetrahydrate to sediment is to be expected, and 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 (IChEMS, 2022; ECHA, 2023).

Sodium perborate tetrahydrate 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 to sodium perborate tetrahydrate and thus does not meet the screening criteria for persistence.

A BCF of <0.1 has been reported for borates in fish. This data suggests that sodium perborate tetrahydrate does not bioaccumulate in the aquatic environment. Thus, sodium perborate tetrahydrate does not meet the criteria for bioaccumulation.

The NOECs from the chronic aquatic toxicity studies on sodium perborate tetrahydrate and/or boron are > 0.1 mg/L. Thus, sodium perborate tetrahydrate does not meet the criteria for toxicity.

The overall conclusion is that sodium perborate tetrahydrate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

H331 Acute Toxicity Category 4 [Inhalation]
H318 Eye Damage Category 1
H360 Reproductive Toxicant Category 1B
H335STOT 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

Please refer to the product SDS for additional information and 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.

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. Firefighting 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 appropriate protective equipment. Avoid dust formation. Ensure adequate ventilation. Do not breathe dust. Wear respiratory protection if ventilation is inadequate. Avoid contact with skin, eye, 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

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. 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. Localized 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 perborate tetrahydrate 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.

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SODIUM PERSULFATE

This dossier on sodium persulfate presents the most critical studies pertinent to the risk assessment of sodium persulfate 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): Disodium [(sulfonatoperoxy)sulfonyl]oxidanide

CAS RN: [redacted]

Molecular formula: $O_8S_2.2Na$

Molecular weight: 238.1

Synonyms: Sodium persulfate; disodium persulfate; sodium peroxodisulfate; disodium [(sulfonatoperoxy)sulfonyl]oxidanide

SMILES: [O-]S(=O)(=O)OOS(=O)(=O)[O-].[Na+].[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Sodium Persulfate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, crystalline, odorless solid	1	ECHA
Melting point	Decomposes at 180°C before melting point is reached.	1	ECHA
Density	1.68 g/cm^3	1	ECHA
Vapor pressure	Negligible	2	ECHA
Partition coefficient (log K_{ow})	Not applicable	-	-
Water solubility	Very soluble	2	ECHA
Oxidizing properties	Strong oxidizer	4	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

Sodium persulfate dissociates in aqueous media to the sodium cation (Na^+) and persulfate anion ($S_2O_8^{2-}$) (OECD 2005a; ECHA). The persulfate anion will readily hydrolyze (decompose) into sulfate ions.

The rates of hydrolysis are expected to be similar for sodium persulfate, potassium persulfate, and ammonium persulfate. The rates of decomposition (hydrolysis) was measured at 50°C at various pHs. The half-lives increased from 20 hours at pH 1 to 210 hours at pH 10 (Koltoff and Miller, 1951).

Biodegradation is not applicable to inorganic compounds. Sodium persulfate is not expected to bioaccumulate; it will dissociate (and decompose) to ions that are ubiquitous in the environment. Sodium persulfate is not expected to absorb to soil or sediment because of its dissociation properties, instability (hydrolysis), and high water solubility.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Sodium persulfate exhibits moderate acute toxicity by the oral route, and low acute toxicity by the inhalation and dermal routes. In humans, sodium persulfate has the potential for skin irritation; it is also a skin sensitizer to guinea pigs and humans. Human exposure to persulfates (including sodium persulfate) have been linked to a variety of skin and respiratory complaints indicative of sensitization. The complaints consist of immediate and delayed contact hypersensitivity, contact urticarial, rhinitis, bronchitis, and asthma. Repeated oral exposure to sodium persulfate resulted in irritation to the gastrointestinal tract; and respiratory irritation was seen in rats repeatedly exposed by inhalation to ammonium persulfate. Sodium persulfate is not genotoxic. A dermal carcinogenicity study showed no carcinogenic effects in mice. In a screening study, there was no reproductive or developmental toxicity in rats given oral gavage doses of ammonium persulfate.

B. Acute Toxicity

The oral LD_{50} in male rats is 895 mg/kg (ECHA) [Kl. score = 2].

The 4-hour inhalation LC_{50} of sodium persulfate dust is >5.1 mg/L. The mass median aerodynamic diameter (MMAD) ranged from 4.28 to 5.35 µm. The fraction of particles $\leq$1 µm in MMAD ranged from 0 to 5.6%. The fraction of particles $\leq$10 µm in MMAD ranged from 76.5 to 81.2% (ECHA) [Kl. score = 1].

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

C. Irritation

Application of 0.5 mL of sodium persulfate (aqueous solution) to the skin of rabbits for 4 hours under occlusive conditions was not irritating (ECHA) [Kl. score = 1]. In another study, application of sodium persulfate to the skin of rabbits was not irritating (ECHA) [Kl. score = 2].

Instillation of sodium persulfate into the eyes of rabbits was slightly irritating. Slight conjunctival effects were noted in five of six animals; all observed effects were completely reversible within 24 hours (ECHA) [Kl. score = 2].

Studies in humans indicate that persulfates have the potential for skin irritation (NICNAS, 2001). Calnan and Schuster (1963) reported skin irritation in a human patch test with 5% ammonium persulfate. Jordan (1998) reported that a mixture with 17.5% persulfates (ammonium, potassium, and sodium) induced skin irritation in human subjects from patches applied under occlusive conditions.

D. Sensitization

Sodium persulfate was a skin sensitizer when tested in a guinea pig maximization test. The concentration of sodium persulfate used in the induction and challenge phases was 0.1% in physiological saline (ECHA) [Kl. score = 1]. Sodium persulfate was not a skin sensitizer to guinea pigs in a Buehler test (dermal application only). The concentration of sodium persulfate used for the induction and challenge phase was 0.3 g (ECHA) [Kl. score = 1].

Sodium persulfate was considered a strong skin sensitizer in a mouse local lymph node assay (ECHA) [Kl. score = 1].

Human exposure to persulfates has been linked to a variety of skin and respiratory complaints indicative of sensitization. The complaints consist of immediate and delayed contact hypersensitivity, contact urticarial, rhinitis, bronchitis, and asthma (NICNAS, 2001).

E. Repeated Dose Toxicity

Oral

Male and female CR strain rats were fed in their diet 0, 300, 1,000 or 3,000 ppm sodium persulfate for 90-days. On day 48 of the study, the dietary concentration of the group receiving 1,000 ppm was increased to 5,000 ppm for the remainder of the study. Body weights was decreased in the two highest dose groups during the last six weeks of treatment. There were no treatment-related effects on urinalysis, clinical chemistry or hematology parameters. Histopathological findings were limited to the 3,000 ppm group only and consisted of necrosis and atrophy of the gastrointestinal tract epithelial lining. The absence of the gastrointestinal lesions in the group receiving 1,000 ppm for 8 weeks, followed by 5000 ppm for 5 weeks, indicates that the lesions are related both to concentration in diet (dose) and length of exposure. A clear NOAEL for this study is 300 ppm, which is estimated to be 22 mg/kg-day. Another NOAEL may be the 1,000 ppm dietary group for an 8-week exposure period. (ECHA; OECD, 2005a,b). [Kl. score = 2]

Inhalation

No studies are available on sodium persulfate.

Male and female SD rats were exposed (whole-body) by inhalation to 0, 5, 10.3, or 25 mg/m^3 ammonium persulfate dust, 6 hours/day, 5 days/week for 13 weeks. Additional groups of animals were exposed for 13 weeks, followed by either a 4- or 13-week recovery period. The MMAD was 2.5, 2.7, and 2.5 µm for the 5, 10, and 25 mg/m^3 groups, respectively. No deaths occurred during the study that were considered to be exposure-related. The 25 mg/m^3 animals showed increased respiration rates, as well as a few of the 25 mg/m^3 animals. This clinical sign disappeared during the first few weeks of the recovery period. Body weights of the 25 mg/m^3 animals were significantly lower during most of the exposure period; by the end of the recovery period the body weights were comparable to the controls. Lung weights were increased in the 25 mg/m^3 animals at the end of the 13-week exposure period but were similar to controls after 6 weeks in the recovery period. Histopathologic changes indicative of irritation was seen in the trachea and bronchi/bronchioles in the 25 mg/m^3 animals; these lesions were not seen after 6 weeks in the recovery period. The NOAEL for this study is 10.3 mg/m^3 (ECHA). [Kl. score = 1]

Dermal

No studies are available.

F. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on sodium persulfate are presented below in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Sodium Persulfate

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	1	ECHA
Unscheduled DNA synthesis (rat hepatocytes)	NA	-	1	ECHA

*+, positive; -, negative; NA, not applicable

In vivo Studies

Sodium persulfate did not induce micronuclei in the bone marrow cells of male and female mice given a single intraperitoneal injection of 0, 85, 169, or 338 mg/kg sodium persulfate (ECHA) [Kl. score = 2].

G. Carcinogenicity

No studies are available on sodium persulfate.

A 51-week dermal study in female SENCAR mice exposed to 0.2 ml of a 200 mg/mL solution of ammonium persulfate showed that ammonium persulfate is neither a tumor promoter nor a complete carcinogen when applied to the skin (OECD, 2005a,b; ECHA). [Kl. score = 2]

H. Reproductive and Developmental Toxicity

No studies are available on sodium persulfate.

A reproductive and developmental toxicity screening study (OECD 421) has been conducted on ammonium persulfate. Male and female Crl:CD (SD)GS BR rats were fed in their diet 0, 40, 100, or 250 mg/kg ammonium persulfate. In the parental animals, there was no treatment-related mortality, clinical signs, body or organ weight changes, or effects seen in gross necropsy. There were no effects on reproductive performance, fertility, fetal anomalies, fetal viability, spermatogenesis, spermatogenic cycle. The NOAEL for reproductive and developmental toxicity and parental toxicity is 250 mg/kg-day, the highest dose tested (ECHA). [Kl. score = 1]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

Toxicological reference values were not derived. Sodium persulfate dissociates in water to sodium and persulfate ions. The persulfate ions will further hydrolyze to sulfate ions.

The Australian drinking water guideline value for sodium is 180 mg/L based on aesthetics (ADWG, 2011).

The Australian drinking water guideline value for sulfate 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 sulfate of 250 mg/L based on aesthetics; it is the taste threshold (ADWG, 2011).

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium persulfate is an oxidizing solid.

Sodium persulfate does not exhibit the following physico-chemical properties:
- Explosivity
- Flammability

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium persulfate has a low toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies
Table 3 lists the results of acute aquatic toxicity studies on sodium persulfate.

Table 3: Acute Aquatic Toxicity Studies on Sodium Persulfate

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Oncorhynchus mykiss	96-h LC_{50}	163	1	ECHA
Daphnia magna	48-h EC_{50}	133	1	ECHA
Selenastrum capricornutum	72-h EC_{50}	116	1	ECHA

Chronic Studies
No data are available.

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

The PNEC calculations for sodium persulfate 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 (163 mg/L), *Daphnia* (133 mg/L), and algae (116 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 effect concentration of 116 mg/L for algae. The $PNEC_{water}$ is 1.2 mg/L.

PNEC sediment

No experimental toxicity data on sediment organisms are available. Sodium persulfate 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 persulfate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sediment}$. Based on the its properties, no adsorption of sodium persulfate 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 terrestrial organisms are available. The environmental distribution of sodium persulfate is dominated by its water solubility. Sorption of sodium persulfate should probably be regarded as a reversible situation, *i.e.*, the substance is not tightly nor permanently bound. K_{oc} and K_{ow} parameters do not readily apply to inorganics, such as sodium persulfate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on the its properties, sodium persulfate 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 persulfate is an inorganic compound that dissociates completely to sodium and persulfate ions in aqueous solutions. Persulfate ions are further hydrolysed to sulphate

ions. Biodegradation is not applicable to these compounds. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to sodium persulfate or its dissociated compounds.

Sodium persulfate is an inorganic compound that dissociates completely in water to ionic compounds that are ubiquitous in the environment. Thus, sodium persulfate is not expected to bioaccumulate.

There are no chronic aquatic toxicity data on sodium persulfate. The acute $E(L)C_{50}$ values for fish, invertebrates, and algae are >1 mg/L. Thus, sodium persulfate does not meet the screening criteria for toxicity.

Therefore, sodium persulfate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Oxidizing Solid Category 3
Acute Toxicity Category 4 [Oral]
Skin Irritant Category 2
Eye Irritant Category 2
Skin Sensitizer Category 1
Respiratory Sensitization Category 1
STOT SE Category 3 [Respiratory Irritation]

B. Labelling

Danger

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 and then drink plenty 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: sulfur 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.

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

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.

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 sodium persulfate 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. Localized 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. Remove and wash contaminated clothing before re-use. Contaminated work clothing should not be allowed out of the workplace.

F. Transport Information

UN1505 SODIUM PERSULPHATE
Class: 5.1
Packing Group: 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

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SODIUM POLYACRYLATE (CAS NO. [redacted]
2-PROPENOIC ACID, HOMOPOLYMER, AMMONIUM SALT (CAS NO. [redacted]

This group contains a sodium salt and ammonium salt of polyacrylic acid homopolymers. They are expected to have similar environmental concerns and have consequently been assessed as a group. Information provided in this dossier is based on sodium polyacrylate (CAS No. [redacted]

This dossier on sodium polyacrylate and similar polymers presents the most critical studies pertinent to the risk assessment of these polymers in their use in coal seam or shale 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).

NICNAS has assessed sodium polyacrylate in an IMAP Tier 1 assessment and considers it a polymer of low concern[1] .

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): 1-Propenoic acid, homopolymer, sodium salt

CAS RN: [redacted]

Molecular formula: $(C_3H_4O_2)$ x-.x-Na

Molecular weight: 94.0447 g/mol (monomer); Variable (polymer)

Synonyms: 2-Propenoic acid, homopolymer, sodium salt; polyacrylic acid, sodium salt, sodium polyacrylate; acrylic acid, polymers, sodium salt; poly (acrylic acid), sodium salt; polyacrylate sodium salt

SMILES: Not available

Chemical Name (IUPAC): 2-Propenoic acid, homopolymer, ammonium salt

CAS RN: [redacted]

Molecular formula: $(C_3\text{-}H_4\text{-}O_2)$x-.x-$H_3$-N

Molecular weight: 89.0933 g/mol (monomer); Variable (polymer)

Synonyms: 2-Propenoic acid, homopolymer, ammonium salt;2-Propenoic acid, homopolymer, sodium salt; ammonium polyacrylate; poly(acrylic acid),ammonium salt; ammonium acrylate

SMILES: Not available; C=CC(=O)[O-].[Na]

[1] https://www.nicnas.gov.au/chemical-information/imap-assessments/how-chemicals-are-assessed/Low-concern-polymers.

II. PHYSICO-CHEMICAL PROPERTIES

Sodium polyacrylates are polymers that range in molecular weight (MW) from 1,000 to 78,000 g/mol (HERA, 2014). The sodium polyacrylates mostly used in detergents have a typical molecular weight of approximately 4,500 g/mol (HERA, 2014). For sodium polyacrylate (MW 4,500), the melting point is >150oC, where it decomposes; and the water solubility is >400 g/L (HERA, 2014).

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Sodium polyacrylates are not readily biodegradable. Due to their high molecular weights, sodium polyacrylates are not expected to bioaccumulate. In addition, these water-soluble polymers can form insoluble calcium salts in natural waters, suggesting that bioaccumulation is unlikely.

B. Partitioning

Abiotic degradation mechanisms like photolytic and hydrolytic processes do not significantly influence the environmental fate of sodium polyacrylates (HERA, 2014).

C. Biodegradation

Sodium polyacrylates are not readily biodegradable but are partly accessible to ultimate biodegradation particularly under long incubation conditions. Sodium polyacrylates with MW of <2,000 g/mol are partly biodegradable under the conditions of soil and sediment inoculation. Test results with activated sludge inoculum indicate different elimination degrees, apparently due to adsorption and precipitation processes. The removal degrees of different sodium polyacrylates show no clear relationship between elimination extent and molecular weight (HERA, 2014).

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

Adsorption onto solids and precipitation are the principal mechanisms of abiotic elimination for this type of polymer, the degree of elimination differs and is strongly influenced by test concentration and water hardness (HERA, 2014).

E. Bioaccumulation

No experimental studies are available on sodium polyacrylates. Estimated bioconcentration factors based on octanol-water coefficients are not appropriate since the molecular weights of these polymers are higher than the molecular weight range for the QSAR models. Due to their high molecular weights, sodium polyacrylates are not expected to bioaccumulate. In addition, these water-soluble polymers can form insoluble calcium salts in natural waters, suggesting that bioaccumulation is unlikely (HERA, 2014).

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of sodium polyacrylates are very low by the oral and dermal routes. These polymers are not irritating to the skin and eyes; nor are they skin sensitisers. No systemic toxicity was observed in rats given high oral doses of a sodium polyacrylate for four weeks; pulmonary irritation was seen in rats that inhaled an aerosol or dust of a sodium polyacrylate for 13 weeks, but there was no systemic toxicity. No developmental toxicity was seen in rats when given high oral doses of sodium polyacrylates. Sodium polyacrylates are not genotoxic or mutagenic.

B. Acute Toxicity

Oral

Acute oral toxicity studies have been conducted in rats on sodium polyacrylates with molecular weights (MW) of 1,000 to 78,000. The oral LD50 values are >5,000 or >10,000 mg/kg (the highest doses tested), except for one study on a 3,500 MW sodium polyacrylate, which was reported to be >1,000 mg/kg (the attainable limit dose of a 10% aqueous solution) (HERA, 2014). [Kl. scores = 2].

Inhalation

There are no acute inhalation studies available.

Dermal

The dermal LD50 values in rabbits for sodium polyacrylates with MW of 1,000 or 4,500 are >5,000 mg/kg (HERA, 2014). [Kl. scores = 2].

C. Irritation

According to (HERA, 2014) sodium polyacrylates with MW of 1,000 to 78,000 are not irritating to the skin or eyes [Kl. scores = 2]. However, as per ECHA current classification, the substance 2-Propenoic acid, homopolymer, sodium is considered a skin and eye irritant. Thus, this classification will be retained for purposes of this dossier.

D. Sensitisation

Sodium polyacrylates with MW of 4,500 or 78,000 were not dermal sensitisers in the guinea pig maximisation test (HERA, 2014). [Kl. scores = 2 and 4, respectively].

E. Repeated Dose Toxicity

Oral

Male rats were fed diets containing 0 or 2.5% sodium polyacrylate (MW 2,500) for four weeks. Body weight, body weight gain, and appearance of the animals were similar between treated and control animals. In the fourth week of the study, a small, but significant, decrease in total weight of bone minerals was detected and confirmed by radiographic and histological examination. There was a significant reduction in the concentration of magnesium in the bones and plasma of the treated animals. Calcium loss was slight and not statistically significant. Urinary excretion of sodium and phosphorus was markedly increased, calcium only slightly increased. The authors of the study

interpreted the finding as a metabolic imbalance rather than systemic toxicity. Sodium excretion could have been increased by the high intake of the sodium-neutralised test substance. The NOAEL for the study was considered to be 2.5% sodium polyacrylate in the diet, which was estimated to be 1,136 mg/kg-day (HERA, 2014). [Kl. score = 2].

Inhalation

Male and female rats were exposed by inhalation to 0, 0.2, 1.0, or 5.0 mg/m3 sodium polyacrylate (MW 4,500) as an aerosol for 6 hours/day, 5 days/week for 13 weeks. Additional groups of animals were exposed for 13 weeks followed by a 91-day recovery period. There were no treatment-related effects on body weights, organ weights, feed and water consumption, clinical observations, and blood chemistry. In the histopathologic examination, the lungs of the mid- and high-dose animals showed signs of mild pulmonary irritation increases in polymorphonuclear granulocytes or alveolar macrophages, pneumocyte hyperplasia, alveolar wall thickening and focal alveolitis. The lung effects were reversible and were not seen in the recovery group animals. The NOEC for systemic effects in this study was considered to be 5 mg/m3, and the NOEC for localised irritation is 0.2 mg/m3 (HERA, 2014). [Kl. score = 2].

Dermal

There are no studies available.

F. Genotoxicity

In vitro Studies

The results of the *in vitro* studies on sodium polyacrylates are presented below in Table 1. All the studies show that sodium polyacrylates are not mutagenic or genotoxic.

The *in vitro* genotoxicity studies on sodium polyacrylates are presented in Table 1.

Table 1: *In vitro* Genotoxicity Studies on Sodium Polyacrylates (HERA, 2014)

Mean MW	Test System	Results*	Klimisch Score	Reference
2,000	Bacterial reverse mutation	-	2	HERA (2014)
2,000	Mouse lymphoma	-	2	HERA (2014)
2,000	Unscheduled DNA synthesis	-	2	HERA (2014)
4,500	Bacterial reverse mutation	-	2	HERA (2014)
4,500	Mouse lymphoma	-	2	HERA (2014)
4,500	Unscheduled DNA synthesis	-	2	HERA (2014)
4,500	Cytogenetic (CHO cells)	-	2	HERA (2014)
4,500	Bacterial reverse mutation	-	2	HERA (2014)
4,500	Mammalian cell gene mutation	-	2	HERA (2014)
4,500	Unscheduled DNA synthesis	-	2	HERA (2014)

*+, positive; -, negative

In vivo Studies

There was no increase in micronuclei in polychromatic erythrocytes from the bone marrow of mice given a single oral gavage dose of 13,850 mg/kg sodium polyacrylate with a MW of 2,000 (HERA, 2014).

G. Carcinogenicity

Oral

There are no studies available.

Inhalation

There are no studies available.

Dermal

There are no studies available.

H. Reproductive Toxicity

There are no studies available.

I. Developmental Toxicity

Oral

Pregnant female rats were dosed by oral gavage with 0, 500, 1,000, or 3,000 mg/kg sodium polyacrylate (MW 4,500) on GD 6 to 15. At 3,000 mg/kg, the dams had soft or liquid stools during the treatment period. There was no maternal or developmental toxicity observed in this study. The NOAEL for maternal and developmental toxicity is 3,000 mg/kg-day (HERA, 2014). [Kl. score = 2]

Pregnant female rats were dosed by oral gavage with 0, 125, 375, or 1,125 mg/kg sodium polyacrylate (MW 90,000 as a 77.5% aq. solution) during GD 6 to 13. Some of the dams were sacrificed on GD 13 and the remaining on GD 19. One mid-dose dam and 6 high-dose dams died during the study; of these, three of the high-dose deaths were treatment-related and the remaining were considered the result of gavage errors. There was a transient decrease in feed consumption in the high-dose dams during GD 7-9, but not other indications of maternal toxicity. There was no developmental toxicity. The NOAELs for maternal and developmental toxicity are 375 and 1,125 mg/kg-day (HERA, 2014). [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 sodium polyacrylate 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

A 4-week dietary study showed no systemic toxicity in rats given 2.5% sodium polyacrylate (MW 2,500) in their feed. The estimated dose is 1,136 mg/kg-day. Two pre-natal developmental toxicity studies showed no effects at the highest dose tested: 3,000 and 1,125 mg/kg-day for sodium polyacrylates with MW of 4,500 and 90,000, respectively. The NOAEL of 1,136 mg/kg-day from the 4-week dietary study 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 = 1,136/ (1 x 10 x 1 x 1 x 1) = 1,136/1,000 = 1.1 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, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)
Drinking water guidance value = (1.1 x 70 x 0.1)/2 = 3.85 mg/L

B. Cancer

No carcinogenicity studies have been conducted on sodium polyacrylates. Therefore, a cancer reference value was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium polyacrylates does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium polyacrylates are 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 sodium polyacrylates.

Table 2: Acute Aquatic Toxicity Studies on Sodium Polyacrylates

Mean MW	Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
1,000	*Brachydanio rerio*	96-hour LC_{50}	>200	1	HERA, 2014
1,000	*Salmo gairdneri*	96-hour LC_{50}	>1,000	1	HERA, 2014
1,200	*Leuciscus idus*	96-hour LC_{50}	>500	1	HERA, 2014
2,000	*Brachydanio rerio*	96-hour LC_{50}	>200	1	HERA, 2014
2,500	*Leuciscus idus*	96-hour LC_{50}	>500	1	HERA, 2014
4,500	*Lepomis macrochirus*	96-hour LC_{50}	>1,000	1	HERA, 2014
4,500	*Lepomis macrochirus*	96-hour LC_{50}	>1,000	1	HERA, 2014
8,000	*Leuciscus idus*	96-hour LC_{50}	>500	1	HERA, 2014
10,000	*Lepomis macrochirus*	96-hour LC_{50}	>1,000	1	HERA, 2014
15,000	*Leuciscus idus*	96-hour LC_{50}	>10,000	1	HERA, 2014
78,000	*Brachydanio rerio*	96-hour LC_{50}	>400	2	HERA, 2014
1,000	*Daphnia magna*	48-hour EC_{50}	>200	1	HERA, 2014
1,000	*Daphnia magna*	48-hour EC_{50}	>1,000	1	HERA, 2014
2,000	*Daphnia magna*	48-hour EC_{50}	>200	1	HERA, 2014
4,500	*Daphnia magna*	48-hour EC_{50}	>200	1	HERA, 2014
4,500	*Daphnia magna*	48-hour EC_{50}	>1,000	1	HERA, 2014
78,000	*Daphnia magna*	24-hour EC_{50}	276	2	HERA, 2014

Mean MW	Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
8,000	*Selenastrum capricornutum*	72-hour EC_{50}	40	1	HERA, 2014
78,000	*Scenedesmus subspicatus*	96-hour EC_{50}	44	2	HERA, 2014

Chronic Studies

Table 3 lists the results of chronic aquatic toxicity studies conducted on sodium polyacrylates.

Table 3: Chronic Aquatic Toxicity Studies on Sodium Polyacrylates (HERA, 2014)

Mean MW	Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
4,500	*Pimephales promelas*	32-day NOEC	56	2	HERA, 2014
4,500	*Brachydanio rerio*	28-day NOEC	>450	1	HERA, 2014
78,000	*Brachydanio rerio*	14-day NOEC	>400	2	HERA, 2014
4,500	*Daphnia magna*	21-day NOEC	450	1	HERA, 2014
4,500	*Daphnia magna*	21-day NOEC	58	1	HERA, 2014
4,500	*Daphnia magna*	21-day NOEC	12	2	HERA, 2014
78,000	*Daphnia magna*	21-day NOEC	100	2	HERA, 2014
4,500	*Scenedesmus subspicatus*	96-hour NOEC	180	2	HERA, 2014
78,000	*Scenedesmus subspicatus*	96-hour NOEC	32.8	2	HERA, 2014

There is considerable variability in the chronic aquatic toxicity results for Daphnia magna for sodium polyacrylates with the same molecular weight of 4,500. This was discussed in HERA (2014) and was explained by the solubility of sodium polyacrylates in water. In distilled water, the solubility of sodium polyacrylates with the molecular weight of 4,500 is >400 mg/L; however, under test conditions water solubility will decrease due to the presence of Ca++ and Mg++ (as measured by water hardness). In a study by BASF (reviewed in HERA, 2014), the water solubility of sodium polyacrylate (MW 4,500) was determined with radiolabelled compounds in a test system with a calcium concentration of 70 mg/L, which corresponds to the mean water hardness to the media used in an OECD TG 202 test. Under these conditions, the water solubility of sodium polyacrylate was 1.3 mg/L after 24 hours. So, one explanation for the variability of the chronic Daphnia studies may be due to differences in water hardness.

C. Toxicity to Sediment Organisms

The 96-hour EC0 to Chironomus riparius (larvae) is >4,500 mg/kg sediment dry weight (HERA, 2014).

D. Terrestrial Toxicity

Table 4 lists the results of terrestrial toxicity studies on sodium polyacrylates polymers.

Table 4: Terrestrial Toxicity Studies on Sodium Polyacrylates (HERA, 2014)

Mean MW	Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
4,500	*Eisenia foetida foetida*	14-day EC_0	1,000	1	HERA, 2014
78,000	*Eisenia foetida andrei*	14-day EC_0	1,000	2	HERA, 2014
78,000	*Brassica rapa*	21-day NOEC	1,000	2	HERA, 2014
4,500	Nitrogen transformation*	28-day EC_{10}	>2,500	1	HERA, 2014
4,500	Carbon transformation*	28-day EC_{10}	>2,500	1	HERA, 2014

*Soil organisms

E. Calculation of PNEC

The PNEC calculations for sodium polyacrylate 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 (>200mg/L), *Daphnia* (>200 mg/L), and algae (40 mg/L). NOEC values from long-term studies are available for fish (56 mg/L), invertebrates (12 mg/L) and algae (32.8 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 NOEC value of 12 mg/L for invertebrates. 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 $PNEC_{water}$ is 1.2 mg/L.

PNEC Sediment

Experimental results are available for one trophic level. There were no visual signs of toxicity to Chironomus riparius (larvae) at the highest concentration tested (>4,500 mg/kg sediment dry weight) (HERA) 2014). The EC_0 is considered to be above 4,500 mg/kg and an assessment factor cannot apply. Thus, the equilibrium partitioning method will be used to determine the $PNEC_{sed}$. The HERA (2014) risk assessment calculated a $PNEC_{sed}$ of 130 mg/kg sediment wet weight using the default of 0.05 as the weight fraction of organic carbon in sediment according to the EU Technical Guidance Document (TGD) (EU 2003).

PNEC Soil

Experimental results are available for three trophic levels. An acute LC_{50} value is available for earthworms (1,000 mg/kg soil dry weight). A 21-day NOEC for Brassica rapa was reported to be 1,000 mg/kg soil dry weight. Results from two long-term studies are available for soil microorganisms, with the NOECs for nitrogen and carbon transformation being >2,500 mg/kg soil dry weight. On the basis that the data consists of short-term tests, as well as one long-term test from

one trophic level, an assessment factor of 100 has been applied to the lowest reported long-term NOEC of >2,500 mg/kg soil dry weight. The $PNEC_{soil}$ is 25 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, 2017).

Sodium polyacrylates are not readily biodegradable, thus does not meet the screening criteria for persistence.

The sodium polyacrylates are expected to have high molecular weights and are not expected to be bioavailable. Thus, these polymers do not meet the criteria for bioaccumulation.

Chronic NOECs for fish, daphnia and algae are available for sodium polyacrylates, and the NOEC values are >0.1 mg/L. Thus, sodium polyacrylates do not meet the screening criteria for toxicity.

The overall conclusion is that sodium polyacrylates are not PBT substances.

IX. CLASSIFICATION AND LABELLING

A. Classification

Aquatic Acute Toxicity Category 3

B. Labelling

Warning

According to the classification provided by companies to ECHA in CLP notifications this substance causes serious eye irritation and causes skin irritation.

A. Pictogram

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.

<u>Eye Contact</u>

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. 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.

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

The are no workplace exposure standards for sodium polyacrylates in Australia.

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 polyacrylate 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

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 January 2022. Available: https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines

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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.

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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.

SODIUM SULPHITE

This dossier on sodium sulphite presents the most critical studies pertinent to the risk assessment of sodium sulphite 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 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 sulphite

CAS RN: [redacted]

Molecular formula: Na_2SO_3

Molecular weight: 126.04

Synonyms: Sodium sulphite, disodium sulphite, sodium bisulphite anhydrous, sodium sulfite

SMILES: [O-]S(=O)[O-].[Na+].[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Sodium Sulphite

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	White, crystalline solid	2	ECHA
Melting Point	911°C	2	ECHA
Boiling Point	No data	-	-
Density	2.63 g/cm^3 @ 20°C	2	ECHA
Partition Coefficient (log K_{ow})	Not applicable	-	-
Water Solubility	307 g/L @ 25°C	2	ECHA
Auto flammability	Not applicable	-	-

Sodium sulphite readily dissociates in aqueous media to the sodium (Na^+) and sulphite (SO_3^{2-}) ions. At neutral pH, a mixture of 50% sulphite (SO_3^{2-}) and 50% bisulphite (HSO_3^{2-}) is present.

In surface waters, sulphite is oxidized to sulfate either catalytically by air oxygen or by microbial action. The presence of cations like iron, copper or manganese in the environment accelerates the oxidation rate significantly.

III. ENVIRONMENTAL FATE PROPERTIES

At environmental pHs, sodium sulphite dissociates in water to form sodium (Na^+) ions, sulphite (SO_2^{3-}) ions, and bisulphite ions (HSO_3^-). In acidic solutions, sulfur dioxide (SO_2) gas may be formed.

Sodium sulphite is not expected to bioaccumulate in the environment because of its dissociation to ionic species and a gas. Furthermore, sulphite will oxidize to sulfate, which is ubiquitous in the environment.

Sodium sulphite and its dissociated species are expected to have a low potential to adsorb to soil and sediment.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

Sodium sulphite has low acute toxicity by the oral, inhalation and dermal routes. It is not irritating to the skin or eyes; it is not a skin sensitizer. No systemic toxicity was seen in rats when given sodium metabisulphite (which dissociates to the sulphite ion) in their diet over a lifetime. There were, however, indications of stomach lesions as a result of localized irritation from the ingestion of sodium metabisulphite. Genetic toxicity studies were negative. Lifetime oral feeding studies on sodium metabisulphite in rats and mice showed no evidence of carcinogenicity. No reproductive or developmental toxicity was observed in any of the animal studies on sodium metabisulphite.

B. Pharmacokinetics and Metabolism

Sodium sulphite is rapidly absorbed from the gastro-intestinal tract. Sulfate is the main metabolite formed by the action of sulphite oxidase in many tissues. Tissue accumulation of sulphite-derived S is highest in stomach, skin and hair, intestine and kidney. Excretion is rapid, mainly in the urine (OECD, 2008).

C. Acute Toxicity

The oral LD_{50} of sodium sulphite in rats is approximately 2,610 mg/kg (ECHA) [Kl. score = 2].

The 4-hour inhalation LC_{50} in rats by nose-only exposure is >5.5 mg/L. The mass median aerodynamic diameter (MMAD) was 3.0 μm, with 90.7% of the dust being respirable (ECHA) [Kl. score = 2].

The acute dermal LD_{50} in rats is >2,000 mg/kg (ECHA) [Kl. score = 1].

D. Irritation

Application of 0.5 g sodium sulphite to the skin of rabbits for 4 hours under semi-occlusive conditions was non-irritating. The 24, 48, and 72 hour erythema and edema scores were 0.00 at all time points (ECHA) [Kl. score = 2].

Instillation of 162 mg sodium sulphite (equivalent to 0.1 mL bulk volume) into the eyes of rabbits was not irritating. The mean of the 24, 48, and 72 hour scores were: 0.00 for corneal lesions; 0.00 for iridial lesions; 0.9 for conjunctival redness; and 0.5 for chemosis (ECHA) [Kl. score = 2].

E. Sensitization

Sodium sulphite was not considered to be a skin sensitizer in a mouse local lymph node assay (ECHA) [Kl. score = 1].

F. Repeated Dose Toxicity

Oral

There are no studies available on sodium sulphite.

Male and female Wistar rats were given in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulphite for up to two years and over three generations. The diet was enriched with thiamine to prevent thiamine deficiency as a result of sulphite-induced destruction of this vitamin. During storage up to the time of consumption, the losses of sulphite from the feed containing sodium metabisulphite at levels of 0.125, 0.25, 0.5, 1.0, and 2.0% averaged 22, 14,12, 8, and 4.5%, respectively, while the decrease in thiamine was 2.7, 1.7, 8.3, 14.5, and 15.4%, respectively. Addition of thiamine to the diet prevented thiamine deficiency in rats at all dose levels based on measurements of thiamine levels in the urine and liver. The general condition of the rats was good during the first 72 weeks in the F_0 generation, as well as the other two generations. After 72 weeks, there was a rapid increase in mortality in all groups. Survival in the treated groups were generally higher than the controls, except for the 2% F_1 males; no deaths occurred in the 2% F_2 females. A marginal reduction in body weight gain was observed in the 2% dose group (both sexes) in the F_1 and F_2 generations. Feed consumption was similar between treated and control groups. There were no changes in hematology and clinical chemistry parameters and urinalysis that were considered toxicologically significant. The $\geq$1% dietary groups had occult blood in their feces. Relative kidney weights were increased in the 2% F_2 females, but there were no pathological changes noted in the kidneys from this group. Hyperplastic changes in the fore- and glandular stomachs were noted in the $\geq$1% groups in all three generations. Some slight alterations were also noted in stomachs of the 0.5% F_2 rats. The NOAEL for systemic toxicity is 1.91% in the diet. This was estimated to be 955 mg/kg-day based on a rat body weight of 400 g and a daily feed intake of 20 g. The histopathologic effects on the stomach and the occult blood in feces are considered to be the result of localized irritation (a site-of-contact effect) from the ingestion of sodium metabisulphite (Til et al., 1972; ECHA). [Kl. score = 2]

Inhalation

No studies are available.

Dermal
No studies are available.

G. Genotoxicity

In Vitro Studies

The in vitro genotoxicity studies conducted on sodium sulphite and sodium metasulphite are presented in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Sodium Sulphite and Sodium Metabisulphite

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)*	-	-	1	ECHA

*+, positive; -, negative
**Sodium metasulphite

In Vivo Studies

Sodium sulphite was not negative in a rat dominant lethal mutation assay. Male rats were fed in their diet 0, 4.5, 15, or 45 mg/kg-day sodium sulphite (ECHA) [Kl. score = 2].

Male and female NMRI mice were given a single oral gavage dose of 0, 250, 500, or 1,000 mg/kg sodium sulphite. There were no increases in chromosomal aberrations in the bone marrow cells of treated rats compared to the those in the control animals (ECHA) [Kl. score = 1].

H. Carcinogenicity

Oral
There are no carcinogenicity studies available sodium sulphite.

Male and female Wistar rats were fed in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulphite for up to two years and over three generations. There was no increased incidence of tumors in the treated groups compared to the controls (Til et al., 1972). [Kl. score = 2]

Male and female ICR/JCL mice were given 0, 1 or 2% potassium metabisulphite in drinking water for 104 weeks. There were no increased incidences of tumors in the treated mice compared to controls (Taneka et al., 1994; ECHA) [Kl. score = 2].

I. Reproductive Toxicity

Male and female Wistar rats were fed in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulphite for up to two years and over three generations. The diet was enriched with thiamine to prevent thiamine deficiency as a result of sulphite-induced destruction of this vitamin. During storage up to the time of consumption, the losses of sulphite from the feed containing sodium metabisulphite at levels of 0.125, 0.25, 0.5, 1.0, and 2.0% averaged 22, 14,12, 8, and 4.5%, respectively, while the decrease in thiamine was 2.7, 1.7, 8.3, 14.5, and 15.4%, respectively. Addition of thiamine to the diet prevented thiamine deficiency in rats at all dose levels based on measurements of thiamine levels in the urine and liver. The effects other than reproductive and developmental toxicity are discussed above in the Repeated Dose Toxicity section. There were no treatment-related effects on female fertility, the number of young per litter, or birth weight or mortality of the offspring. The number of F_{2a} pups was significantly reduced in the $\geq$0.5% groups during the first breeding cycle, but there was no dose-response and the reduction did not occur during the second breeding cycle. Slight growth retardation was observed in the F_1 and F_2 generation rats both before and after weaning. The NOAEL for reproductive toxicity is 1.91% in the diet. This was estimated to be 955 mg/kg-day based on a rat body weight of 400 g and a daily feed intake of 20 g (Til et al., 1972; ECHA). [Kl. score = 2]

Male and female rats were given sodium metabisulphite in their drinking water for up to 2.5 years and in three successive generations. The doses were 375 and 750 ppm as sulfur dioxide (SO_2). There was no evidence of systemic toxicity in either dose group. The number of offspring of either the F_1 and F_2 generation and the proportion surviving to the end of lactation were similar between treated and control groups. The NOAEL for reproductive toxicity is 750 ppm (as SO_2) in drinking water. Assuming an average rat body weight of 400 g and a daily water intake of 28 mL, 750 ppm (as SO_2) corresponds to 53 mg/kg-day sodium metabisulphite (Lockett and Natoff, 1960; ECHA). [Kl. score = 2]

J. Developmental Toxicity

Pregnant female Wistar rats were fed in the diet 0, 0.32, 0.63, 1.25, 2.5, or 5% sodium sulphite ($Na_2SO_3 \bullet 7H_2O$) during GD 8 to 20. Maternal body weight gain and feed consumption were reduced in the 5% dose group. There was some evidence of reduced body weight gain in all treated groups, but there was no dose-response relationship and these effects were not observed in the live birth component of the study. The live birth component showed no treatment-related changes in the pups at three weeks after birth. There was no evidence of teratogenicity. The NOAELs for maternal and developmental toxicity are 2.5% and 5% in the diet, respectively. The calculated daily doses are approximately 850 and 1,450 mg/kg-day, respectively (ECHA). [Kl. score = 2]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for sodium sulphite 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 was no evidence of systemic toxicity in a two-year rat dietary study on sodium metabisulphite (Til et al., 1972), the highest dose being 2% sodium in feed (estimated to be 955 mg/kg-day). The NOAEL of 955 mg/kg-day from this study will be used for determining the oral reference dose (RfD) and the drinking water guidance value.

Conversion of dose from sodium metabisulphite to sodium sulphite:

Molecular weight of sodium metabisulphite: 190.1 g/mol
Molecular weight of sodium sulphite: 126.04 g/mol

NOAEL = 955 x 126.04/190.1 = 633 mg/kg-day (as sodium sulphite)

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 = 633/(10 x 10 x 1 x 1 x 1) = 633/100 = 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, 2011)
Proportion of water consumed = 10% (ADWG, 2011)
Volume of water consumed = 2L (ADWG, 2011)

Drinking water guidance value = (6.3 x 70 x 0.1)/2 = 22 mg/L

B. Cancer

No carcinogenic effects were reported for sodium metabisulphite in rat and mouse chronic studies. Thus, a cancer reference value for sodium sulphite was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium sulphite does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Sodium sulphite is of moderate acute toxicity, but low chronic toxicity, concern to aquatic life.

B. Aquatic Toxicity

Acute Studies

Table 3 lists the results of acute aquatic toxicity studies conducted on sodium sulphite and sodium disulphite.

Table 3: Acute Aquatic Toxicity Studies on Sodium Sulphite and Sodium Disulphite

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Golden orfe	96-hr LC_{50}	316	2	ECHA
Daphnia magna	48-hr EC_{50}	89* (59)	2	ECHA
Desmodesmus subspicatus	72-hr EC_{50}	43.8* (29)	2	ECHA

*Test substance: sodium disulphite

Chronic Studies

Table 4 lists the results of chronic aquatic toxicity studies conducted on sodium sulphite and sodium disulphite.

Table 4: Chronic Aquatic Toxicity Studies on Sodium Sulphite and Sodium Disulphite

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Zebrafish	34-d NOEC	>316	1	ECHA
Daphnia magna	21-d NOEC	>10* (6.6)	1	ECHA
Desmodesmus subspicatus	EC_{10}	33.3* (22)	2	ECHA

*Test substance: sodium disulphite; adjusted concentration for sodium sulphite in parentheses.

C. Terrestrial Toxicity

No data are available.

D. Calculation of PNEC

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

The PNEC calculations for sodium metabisulphite 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 (316 mg/L), *Daphnia* (59 mg/L), and algae (29 mg/L). Results from chronic studies are also available for all three trophic levels, with the lowest NOEC or EC_{10} being 6.6 mg/L for invertebrates. 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 6.6 mg/L for invertebrates. The $PNEC_{water}$ is 0.7 mg/L.

PNEC sediment

No experimental toxicity data on sediment organisms are available. Sodium sulphite 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 sulphite. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sed}$. Based on the its properties, no adsorption of sodium sulphite 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. Sodium sulphite 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 sulphite. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on the its properties, no adsorption of sodium sulphite to 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).

Sodium sulphite is an inorganic compound that dissociates completely to sodium ions, sulphite and bisulphite ions, and sulfur dioxide in aqueous solutions. Biodegradation is not applicable to these compounds. For the purposes of this PBT assessment, the persistent criteria are not considered applicable to sodium sulphite or its dissociated compounds.

Sodium sulphite is an inorganic compound that dissociates completely in water to ionic compounds and a gas. Thus, it is not expected to bioaccumulate.

Chronic aquatic toxicity data on sodium sulphite and sodium disulfate; the NOECs are >0.1 mg/L. Thus, sodium sulphite is not expected to meet the criteria for toxicity.

Therefore, sodium sulphite is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Aquatic Acute Toxicity Category 3

B. Labelling

No signal word.

C. Pictogram

None

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
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
When contacted by water, sodium metabisulphite releases sulfur dioxide (SO_2), a poisonous gas. In the case of fire, the following may be liberated: Sulfur oxides and sulfur dioxide.

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. When contacted by water, sodium metabisulphite releases sulfur dioxide (SO_2), a poisonous gas.

Steps to be Taken if Material is Released or Spilled
Scoop up and remove.

D. Storage And Handling

General Handling
When sodium metabisulphite gets wet or moist, it liberates sulfur dioxide (SO_2), a poisonous gas. Use proper protective equipment and exposure controls to prevent exposure to this toxic gas.

Other Handling Precautions
Avoid eye and skin contact. Avoid creating or inhaling dust. Keep away from acids and oxidizing agents.

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

A workplace exposure standard is not available in Australia for sodium sulphite. However, the workplace exposure standards for sodium metabisulphite (disulphite) and sodium bisulphite in Australia is 5 mg/m^3 as an 8-hr TWA.

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

Sodium sulphite 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

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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.

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SODIUM THIOSULFATE

This dossier on sodium thiosulfate presents the most critical studies pertinent to the risk assessment of sodium thiosulfate 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).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Disodium sulfanidesulfonate

CAS RN: [redacted]

Molecular formula: $Na_2S_2O_3$

Molecular weight: 158.1

Synonyms: Sodium thiosulfate; disodium sulfanidesulfonate; sodium thiosulphate; thiosulfuric acid, disodium salt; disodium sulfurothioate

SMILES: [O-]S(=O)(=S)[O-].[Na+].[Na+]

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Sodium Thiosulfate

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colorless crystalline solid	2	ECHA
Melting point	<500°C (decomposition occurs)	1	ECHA
Density	1.69 g/cm^3 @ 20°C	2	ECHA
Water solubility	764 g/L @ 25°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

Sodium thiosulfate dissociates in aqueous media to sodium (Na^+) and thiosulfate ($S_2O_3^{2-}$) ions. The thiosulfate anion is stable in neutral or alkaline media, but not in acidic media (EPA, 2007). In aqueous media, thiosulfate irreversibly disproportionates to sulfide and sulfate (EPA, 2007).

Biodegradation is not applicable to inorganic compounds. Sodium thiosulfate is not expected to bioaccumulate; it will dissociate to ions that are ubiquitous in the environment. Sodium

thiosulfate is not expected to absorb to soil or sediment because of its dissociation properties and high water solubility.

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The substance is of low acute and chronic toxicity via oral dosing. It is not an irritant nor does it illicit skin sensitization effects. The substance does not exhibit genotoxicity, mutagenicity or reproductive/developmental toxicity .

B. Acute Toxicity

No acute toxicity studies are available for sodium thiosulfate.

The oral LD_{50} of potassium thiosulfate in rats is >2,500 mg/kg (ECHA) [Kl. score = 2]. The oral LD_{50} of calcium thiosulfate in rats is >2,000 mg/kg (ECHA) [Kl. score = 1].

The inhalation 4-hr LC_{50} of potassium thiosulfate in rats is >2,500 mg/kg (ECHA) [Kl. score = 2].

The dermal LD_{50} of potassium thiosulfate in rabbits is >2.6 mg/L aerosol. The mass median aerodynamic diameter was 2.1 μm (ECHA) [Kl. score = 2].

C. Irritation

No reliable skin irritation studies are available for sodium thiosulfate or other thiosulfate salts.

Instillation of 0.1 mL ammonium thiosulfate into the eyes of rabbits was not irritating. The mean of the 24, 48, and 72 hour scores were: 0.00 for corneal opacity; 0.00 for iridial lesions; 0.56 for conjunctival redness; and 0.11 for chemosis (ECHA) [Kl. score = 2].

D. Sensitization

Ammonium thiosulfate was not considered to be a skin sensitizer in a mouse local lymph node assay (ECHA) [Kl. score = 1].

E. Repeated Dose Toxicity

<u>Oral</u>
No studies are available on the thiosulfate salts. Under acidic conditions, thiosulfates will disproportionate in aqueous mediate to form polythionic acids and bisulfite (HSO_3^-) ions plus sulfur dioxide gas (SO_2) (ECHA). A 2-year three-generation rat study on sodium metabisulfite will be used to read-across to sodium thiosulfate because sodium metabisulfite dissociates in water to form sodium (Na^+) ions, disulfite ($S_2O_5^{2-}$) ions, and sulfur dioxide (SO_2). The disulfite ions can form bisulfite (HSO_3^-) and sulfite ions (SO_2^{3-}) in varying proportions dependent on the pH of the solution (OECD, 2001).

Male and female Wistar rats were fed in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulfite for up to two years and over three generations. The diet was enriched with thiamine to prevent thiamine deficiency as a result of the sulfite-induced destruction of this vitamin. During storage up to the time of consumption, the losses of sulfite from the feed containing sodium metabisulfite at levels of 0.125, 0.25, 0.5, 1.0, and 2.0% averaged 22, 14,12, 8, and 4.5%, respectively, while the decrease in thiamine was 2.7, 1.7, 8.3, 14.5, and 15.4%, respectively. The addition of thiamine to the diet prevented thiamine deficiency in rats at all dose levels based on measurements of thiamine levels in the urine and liver. The general condition of the rats was good during the first 72 weeks of the F_0 generation, as well as the other two generations. After 72 weeks, there was a rapid increase in mortality in all groups. Survival in the treated groups was higher than the controls, except for the 2% F_1 males; no deaths occurred in the 2% F_2 females. A marginal reduction in body weight gain was observed in the 2% dose group (both sexes) in the F_1 and F_2 generations. Feed consumption was similar was between treated and control groups. There were no changes in haematology and clinical chemistry parameters and urinalysis that were considered toxicologically significant. The ≥1% dietary groups had occult blood in their feces. Relative kidney weights were increased in the 2% F_2 females, but there were no pathological changes noted in the kidneys from this group. Hyperplastic changes in the fore- and glandular stomachs were noted in the ≥1% groups in all three generations. Some slight alterations were also noted in stomachs of the 0.5% F_2 rats. The NOAEL for systemic toxicity is 1.91% in the diet. This was estimated to be 955 mg/kg-day based on a rat body weight of 400 g and a daily feed intake of 20 g. The histopathologic effects on the stomach and the occult blood in feces are considered to be the result of localised irritation (a site-of-contact effect) from the ingestion of sodium metabisulfite (Til et al., 1972; ECHA). [Kl. score = 2]

Inhalation
No studies are available.

Dermal
No studies are available.

F. Genotoxicity

In Vitro Studies

No studies are available on sodium thiosulfate. The in vitro genotoxicity studies on ammonium thiosulfate are presented below in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Ammonium Thiosulfate

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* and *E. coli* strains)	-	-	1	ECHA
Mammalian cell gene mutation	-	-	1	ECHA

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
(mouse lymphoma L5178Y cells)				
Chromosomal aberration (Chinese hamster ovary cells)	-	-	1	ECHA

*+, positive; -, negative

In Vivo Studies

No studies are available.

G. Carcinogenicity

Oral

No studies are available on the thiosulfate salts. Under acidic conditions, thiosulfates will disproportionate in aqueous mediate to form polythionic acids and bisulfite (HSO_3^-) ions plus sulfur dioxide gas (SO_2) (ECHA). A 2-year three-generation rat study on sodium metabisulfite will be used to read-across to sodium thiosulfate because sodium metabisulfite dissociates in water to form sodium (Na^+) ions, disulfite ($S_2O_5^{2-}$) ions, and sulfur dioxide (SO_2). The disulfite ions can form bisulfite (HSO_3^-) and sulfite ions (SO_2^{3-}) in varying proportions dependent on the pH of the solution (OECD, 2001).

Male and female Wistar rats were fed in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulfite for up to two years and over three generations. There was no increased incidence of tumours in the treated groups compared to the controls (Til et al., 1972). [Kl. score = 2]

Male and female ICR/JCL mice were given in their drinking water 0, 1, or 2% potassium metabisulfite for two years. There was no increased incidence of tumours in the treated groups compared to the controls (Tanaka et al., 1979). [Kl. score = 2]

H. Reproductive Toxicity

No studies are available on the thiosulfate salts. Under acidic conditions, thiosulfates will disproportionate in aqueous mediate to form polythionic acids and bisulfite (HSO_3^-) ions plus sulfur dioxide gas (SO_2) (ECHA). A 2-year three-generation rat study on sodium metabisulfite will be used to read-across to sodium thiosulfate because sodium metabisulfite dissociates in water to form sodium (Na^+) ions, disulfite ($S_2O_5^{2-}$) ions, and sulfur dioxide (SO_2). The disulfite ions can form bisulfite (HSO_3^-) and sulfite ions (SO_2^{3-}) in varying proportions dependent on the pH of the solution (OECD, 2001).

Male and female Wistar rats were fed in their diet 0, 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulfite for up to two years and over three generations. The diet was enriched with thiamine to prevent thiamine deficiency as a result of the sulfite-induced destruction of this vitamin. During storage up to the time of consumption, the losses of sulfite from the feed

containing sodium metabisulfite at levels of 0.125, 0.25, 0.5, 1.0, and 2.0% averaged 22, 14,12, 8, and 4.5%, respectively, while the decrease in thiamine was 2.7, 1.7, 8.3, 14.5, and 15.4%, respectively. The addition of thiamine to the diet prevented thiamine deficiency in rats at all dose levels based on measurements of thiamine levels in the urine and liver. The effects other than reproductive and developmental toxicity are discussed above in the Repeated Dose Toxicity section. There were no treatment-related effects on female fertility, the number of young per litter, or birth weight or mortality of the offspring. The number of F_{2a} pups was significantly reduced in the $\geq$0.5% groups during the first breeding cycle, but there was no dose-response, and the reduction did not occur during the second breeding cycle. Slight growth retardation was observed in the F_1 and F_2 generation rats both before and after weaning. The NOAEL for reproductive toxicity is 1.91% in the diet. This was estimated to be 955 mg/kg-day based on a rat body weight of 400 g and a daily feed intake of 20 g (Til et al., 1972; ECHA). [Kl. score = 2]

Male and female rats were given sodium metabisulfite in their drinking water for up to 2.5 years and three successive generations. The doses were 375 and 750 ppm as sulfur dioxide (SO_2). There was no evidence of systemic toxicity in either dose group. The number of offspring of either the F_1 and F_2 generation and the proportion surviving to the end of lactation were similar between treated and control groups. The NOAEL for reproductive toxicity is 750 ppm (as SO_2) in drinking water. Assuming an average rat body weight of 400 g and a daily water intake of 28 mL, 750 ppm (as SO_2) corresponds to 53 mg/kg-day sodium metabisulfite (Lockett and Natoff, 1960; ECHA). [Kl. score = 2]

I. Developmental Toxicity

Pregnant female Wistar rats were dosed by oral gavage with 0, 4, 19, 86, or 400 mg/kg sodium thiosulfate on GD 6 to 15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 400 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 2].

Pregnant female CD-1 mice were dosed by oral gavage with 0, 5.5, 25.5, 118, or 555 mg/kg sodium thiosulfate on GD 6 to 15. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 555 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 2].

Pregnant female Dutch-belted rabbits were dosed by oral gavage with 0, 5.8, 27, 125.4, or 580 mg/kg sodium thiosulfate on GD 6 to 18. There was no maternal or developmental toxicity. The NOAEL for maternal and developmental toxicity is 580 mg/kg-day, the highest dose tested (ECHA) [Kl. score = 2].

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

A. Non-Cancer

Oral

An oral reference dose and drinking water guidance value was not derived for sodium thiosulfate. NICNAS does not consider sodium thiosulfate to pose an unreasonable risk to the health of workers and public health on the basis of the Tier I IMAP assessment.[1]

The Australian drinking water guideline values for sodium and sulfate may apply to sodium thiosulfate.

B. Cancer

Sodium or potassium metasulfite were not carcinogenic to rodents in two-year dietary studies. Thus, a cancer reference value was not derived for sodium thiosulfate.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sodium thiosulfate does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

The substance does not appear to exhibit significant acute aquatic toxicity. No data are available for chronic toxicity studies.

B. Aquatic Toxicity

Acute Studies

No data are available on sodium thiosulfate. Table 3 lists the results of acute aquatic toxicity studies conducted on ammonium thiosulfate.

Table 3: Acute Aquatic Toxicity Studies on Ammonium Thiosulfate

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Lepomis macrochirus	96-hr LC_{50}	510	1	ECHA
Salmo gairdneri	96-hr LC_{50}	770	1	ECHA
Daphnia magna	48-hr EC_{50}	230	1	ECHA

[1] https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/human-health-assessments#cas-A[redacted]

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pseudokirchneriella subcapitata	72-hr EC_{50}	>100	1	ECHA

Chronic Studies
No data are available.

C. Terrestrial Toxicity

No terrestrial toxicity data are available for this substance.

D. Calculation of PNEC

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

PNEC water
Experimental results are available on ammonium thiosulfate for three trophic levels. Acute $E(L)C_{50}$ values are available for fish (510 mg/L), Daphnia (230 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 $E(L)C_{50}$ value of 100 mg/L for algae. The $PNEC_{water}$ for ammonium thiosulfate is 1.0 mg/L. Conversion of this value to sodium thiosulfate using the molecular weights of ammonium thiosulfate (148.21 g/mol) and sodium thiosulfate (258.11 g/mol) results in a $PNEC_{water}$ value for sodium thiosulfate of 1.1 mg/L.

PNEC sediment
No experimental toxicity data on sediment organisms are available. Sodium thiosulfate 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 thiosulfate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{sediment}$. Based on the its properties, no adsorption of sodium thiosulfate 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 thiosulfate is dominated by its water solubility. Sorption of sodium thiosulfate 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 thiosulfate. Thus, the equilibrium partitioning method cannot be used to calculate the $PNEC_{soil}$. Based on the its properties, sodium thiosulfate 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 thiosulfate is an organic salt that dissociates completely to sodium, sulfide, and sulfate ions in aqueous solutions. Biodegradation is not applicable to these inorganic ions; these ionic species 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 thiosulfate or its dissociated ions.

Sodium thiosulfate dissociates to ionic species. The sulfide ion can be oxidized by bacteria to sulfate. The sodium and sulfate ions are essential to all living organisms and their intracellular and extracellular concentrations are actively regulated. Thus, sodium thiosulfate is not expected to bioaccumulate.

There are no chronic toxicity studies on sodium thiosulfate. The acute $EC(L)_{50}$ values are >1 mg/L in fish, invertebrates and algae. Thus, sodium thiosulfate does not meet the screening criteria for toxicity.

The overall conclusion is that sodium thiosulfate is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

No signal word.

C. Pictogram

None

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

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.

Ingestion
Rinse mouth with water and then drink plenty of water. Do not induce vomiting. Never give anything by mouth to an unconscious person. Seek medical attention.

B. Fire Fighting Information

Extinguishing Media
Water spray or fog, carbon dioxide, dry powder.

Specific Exposure Hazards
Burning produces harmful and toxic fumes.

Special Protective Equipment for Firefighters
Wear a self-contained breathing apparatus.

C. Accidental Release Measures

Personal Precautions
No special precautions are necessary. Ensure adequate ventilation.

Environmental Precautions
Do not discharge into drains, sewers, or waterways.

Steps to be Taken if Material is Released or Spilt
For large amounts: dike spillage and pump off the product. For residues: pick up with suitable absorbent material. Dispose of contaminated material as prescribed.

D. Storage And Handling

General Handling
Handle in accordance with good industrial hygiene and safety practice.

Other Handling Precautions
Protect against fire and explosion: prevent electrostatic charge; sources of ignition should be kept well clear, and fire extinguishers should be kept handy.

Storage
Keep container tightly closed and dry. Protect against heat. Store below 25oC.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Occupational exposure standards for the low molecular weight PEGs have not been established.

Engineering Controls

Provide local exhaust ventilation to control vapours and mists.

Personal Protection Equipment
Respiratory Protection: Respiratory protection in case of vapours/aerosol release. Wear a certified organic vapour/particulate respirator.

Hand Protection: Chemical resistant protective gloves.

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

Eye protection: Body protection must be chosen depending on activity and possible exposure.Safety glasses with side-shields.

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.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards
Workplace Australia has not established an occupational exposure standard for sodium thiosulfate.

Engineering Controls
Provide local exhaust ventilation to control vapours and mists.

Personal Protection Equipment
Respiratory Protection: Respiratory protection in case of vapours/aerosol release. Wear a certified organic vapour/particulate respirator.

Hand Protection: Chemical resistant protective gloves.

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

Eye protection: Body protection must be chosen depending on activity and possible exposure.Safety glasses with side-shields.

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

Sodium thiosulfate 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

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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

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SORBITAN MONOOLEATE POLYOXYETHYLENE DERIVATIVE

This dossier on sorbitan monooleate polyoxyethylene derivative presents the most critical studies pertinent to the risk assessment of sorbitan monooleate polyoxyethylene derivative 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) and the European Food and Safety Authority (EFSA, 2015). Where possible, study quality was evaluated using the Klimisch scoring system (Klimisch et al., 1997).

I. SUBSTANCE IDENTIFICATION

Chemical Name (IUPAC): Sorbitan monooleate polyoxyethylene derivative

CAS RN: [redacted]

Molecular formula: Not available (UVCB substances)

Molecular weight: Not available (UVCB substances)

Synonyms: See below.

SMILES: No available (UVCB substances)

The composition of sorbitan monooleate polyoxyethylene derivative (CAS No. [redacted] is unknown. The CAS No. [redacted] is a generically CAS No. that can include at least the following UVCB substance groups (CIR, 2015):

1. An ethoxylated sorbitan ester of oleic acid with an average of 3 moles of ethylene oxide (e.g., PEG-3-sorbitan oleate). PubChem CID: 78382488

2. A mixture of oleate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 5 moles of ethylene oxide (e.g., Polysorbate 81).

3. An ethoxylated sorbitan ester of oleic acid with an average of 6 moles of ethylene oxide (e.g., PEG-6 sorbitan oleate).

4. An ethoxylated sorbitan ester of oleic acid with an average of 20 moles of ethylene oxide (e.g., PEG-20 sorbitan oleate).

5. A mixture of oleate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 20 moles of ethylene oxide (e.g., Polysorbate 80).

This dossier will include information from the following substances: sorbitan monooleate, ethoxylated (1-6.5 moles ethoxylated), Polysorbate 80, and sorbitan monolaurate, ethoxylated (1-6.5 moles ethoxylated) [CAS RN [redacted]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of sorbitan monooleate, ethoxylated (1 – 6.5 Moles Ethoxylated) [CAS No. [redacted]

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Organic Liquid	2	ECHA
Melting Point	-32.7°C @ 101.3 kPa -33.9°C @ 101.3 kPa	2 2	ECHA
Boiling Point	No data	-	ECHA
Density	1030 kg/m^3 @ 25°C	2	ECHA
Vapour Pressure	0 Pa @ 20°C (QSAR)	2	ECHA
Partition Coefficient (log K_{ow})	4.51 to 5.06 (QSAR)**@ 25°C	2	ECHA
Water Solubility	0.035 to 0.1 g/L @ 20°C***	1	ECHA
Flash Point	256°C	4	ECHA
Auto flammability	Not flammable in air	-	ECHA
Viscosity	Not applicable for this non-newtonian fluid	-	ECHA
Henry's Law Constant	Not available	-	ECHA

*Data located in REACH database for dehydrated sorbitol, C18 (unsaturated) fatty acid esters, ethoxylated (EC No. 701-203-3).
**QSAR (KOWWIN v1.68): sorbitan monooleate, ethoxylated 5EO and sorbitan monooleate, ethoxylated 3EO, respectively.
***Sorbitan monooleate, ethoxylated 3EO: ~100 mg/L; sorbitan monooleate, ethoxylated 5EO: ~35 mg/L.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

The substance is likely to biodegrade, has a low potential to bioaccumulate and, based on its non-ionic surfactant properties, will adsorb to soils. The data supporting these conclusions are discussed below.

B. Biodegradation

In an ISO Standard 14593 ready biodegradation test, degradation of Tween 81 (CAS No. [redacted] was 61% after 28 days, indicating ready biodegradability (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 sorbitan monooleate polyoxyethylene derivative. Using KOCWIN v2.00, the estimated K_{oc} values for the main components in sorbitan monooleate, ethoxylated (1-6.5 moles ethoxylated) [CAS No. [redacted] based on the molecular connectivity

index (MCI) ranged from 794 to 1,259 L/kg (ECHA). Based on these estimated K_{oc} values, the substance is likely to adsorb to soil or sediments.

Further, the molecular structure indicates a potential of surface-active properties, which are not considered by the QSAR model calculations. As a result, the adsorption of non-ionic surfactants to soil is generally high (ECHA). Based on these considerations, there is a low potential for mobility.

D. Bioaccumulation

There are no experimental bioaccumulation studies on sorbitan monooleate polyoxyethylene derivative. The bioaccumulation potential was estimated for sorbitan monooleate, ethoxylated (1-6.5 moles ethoxylated) [CAS No. [redacted] using BCFBAF v3.01 (Arnot-Gobas method, including biotransformation). The calculated BCF values were 12.6 to 14.6 L/kg. When biotransformation was excluded, the BCF values were 18.6 to 42.8 L/kg (ECHA). Thus, sorbitan monooleate polyoxyethylene derivative has a low potential for bioaccumulation.

IV. HUMAN HEALTH HAZARD ASSESSMENT

The information in this section is from studies conducted on read-across polysorbates.

Read-across substance Polysorbate 80 is composed of a sorbitan ring with ethylene oxide polymers attached at three different hydroxyl positions. While the number of repeat ethylene oxide subunits varies at each position, their total number equals 20 and is constant for each polysorbate. The major fatty acid side chains of Polysorbate 80 is oleic acid. The commercial polysorbates are complex mixtures, i.e., UVCB (Unknown or Variable Composition, Complex Reaction Products and Biological Materials) substances. The composition data reported in Kerwin et al. (2008) shows that oleic acid ester of Polysorbate 80 is ≥58% of the total number of fatty acid species; the remaining fatty acids are a mixture of both saturated and unsaturated fatty acids. The average molecular weight of Polysorbate 80 is 1,310 g/mol (Kerwin et al., 2008).

A. Summary

The acute toxicity of Polysorbate 80 is low by the oral and dermal routes. It is non-irritating to the skin and eyes, and it is not a dermal sensitizer. Polysorbate 80 is poorly absorbed from the gastrointestinal tract. Dietary studies conducted for up to two years with Polysorbate 80 indicate that it is essentially non-toxic to rats and mice. Polysorbate 20 is not genotoxic. A similar substance to Polysorbate 20 (Polysorbate 80) was not carcinogenic to mice when given in the diet; nor was it carcinogenic to female rats. Male rats showed a marginal increase in the number of benign adrenal medulla pheochromocytomas in the high-dose male rats. Adrenal medulla hyperplasia, a lesion considered to be the precursor to pheochromocytoma, was increased in the low-dose, but not high-dose, male rats. The increased adrenal medulla pheochromocytomas in the Polysorbate 80-treated male rats does not have relevance to humans. This conclusion is based on the lack of genotoxicity of Polysorbate 80, the equivocal finding in the NTP study, and that pheochromocytomas have been associated with poorly metabolized food additives (i.e., polyols such as sorbitol, xylitol, lactitol; lactose) given to animals at high doses and have been regarded as of no significance to humans. Polysorbates have not shown any indication of reproductive or developmental toxicity when tested in rats.

B. Toxicokinetics/Metabolism

Pharmacokinetic and metabolism studies are available for Polysorbate 20 and 80. These polysorbates have similar absorption, distribution, metabolic fate and elimination, which would be expected given that they only differ in their fatty acid side-chain.

Following the oral administration of polysorbates, the ester link of the polysorbate molecule is hydrolysed in the gastrointestinal tract by pancreatic lipase; the fatty acid moiety that is released is absorbed and metabolized by the same pathways that exist for long-chain fatty acids from dietary sources. The remaining polyoxyethylene sorbitan moiety is not well absorbed from the gastrointestinal tract and is excreted in the feces. The polyoxyethylene sorbitan moiety that is absorbed is not metabolized and is excreted in the urine (CIR, 1984).

Polysorbate 20 with [^{14}C]-labelled lauric acid was fed to rats. Twenty-hours later, 80% of the lauric acid was oxidized and expired as CO_2; 12% was in the carcass; 4% was not absorbed from the gastrointestinal tract; 2.5% was excreted in the urine; and 1.2% was in the liver (Nelson et al., 1966).

In a study with the [^{14}C]-label in the polyoxyethylene portion of Polysorbate 20, 82–90% of the radioactivity was excreted in the feces and 8–11% in the urine, but little to no radioactivity was found in the liver, carcass or expired CO_2 (Nelson et al., 1966). When the sorbitol moiety of Polysorbate 80 was labeled, 91% of the radioactivity was recovered in the feces, 2.1% in the urine, 1.6% in the carcass, and none in expired CO_2, liver, kidney, spleen, adrenals, brain, gonads or fat (Treon et al., 1967).

A similar pattern of polysorbate metabolism occurs in humans as in rats following oral administration (Culver et al., 1951). In four subjects fed 4.5 g of unlabelled Polysorbate 80 per day (study duration not stated), 90–97% of the polyoxyethylene fraction was excreted in the feces, and 2.3–3.1% was excreted in the urine. The analytical method measured the oxyethylene value of Polysorbate 80 and could not distinguish between the free polyoxyethylene moiety and the unhydrolyzed parent ester. Since no fatty acids containing the polyoxyethylene moiety were detected in the urine, it was concluded that it was polyoxyethylene sorbitan excreted in the urine.

The Polysorbates are rapidly hydrolysed by blood esterases following intravenous administration. In a study using mice, plasma concentrations of Polysorbate 80 rapidly declined to about 66% of the initial concentration by 15 minutes after post-bolus intravenous injection, with a plasma concentration of <0.05% (van Tellingen et al., 1999). The released fatty acids are metabolized similar to other fatty acids in the blood, and the remaining polyoxyethylene moiety is not metabolized, but is excreted primarily in the urine (Nelson et al., 1966). A small percentage is found in the feces, indicating biliary excretion (Nelson et al., 1966; Treon et al., 1967).

C. Acute Toxicity

The oral LD_{50} values for Polysorbate 20 in rats are >36,700 mg/kg (ECHA) [Kl.score=4]; >33,800 mg/kg (ECHA) [Kl.score=4]; and >30 mL/kg (ECHA) [Kl. score=4]. The oral LD_{50} value for mice is >30 mL/kg (ECHA) [Kl.score=4].

No acute inhalation studies are available for the Polysorbates.

There are no acute dermal toxicity studies on Polysorbate 20. The dermal LD_{50} value in rats for Polysorbate 60 (polyoxyethylene sorbitan monostearate) is >2,000 mg/kg (ECHA) [Kl.score= 4].

D. Irritation

Application of 0.5 mL Polysorbate 20 to the skin of rabbits for 4 hours under semi-occlusive conditions was not irritating (ECHA) [Kl.score=1]. The mean of the 24-, 48- and 72-hour scores were 0.89 for erythema and 0.00 for edema (ECHA) [Kl.score=1].

Instillation of 0.1 mL Polysorbate 20 into the eyes of rabbits was not irritating. The mean of the 24-, 48- and 72-hour scores were: 0.00 for corneal opacity; 0.00 for iridial lesions; and 0.00 for conjunctival redness (ECHA) [Kl.score=2].

E. Sensitisation

Polysorbate 20 was not considered a skin sensitizer when tested in a guinea pig maximization test (ECHA) [Kl.score=1].

F. Repeated Dose Toxicity

The polysorbates have been well-studied in multiple species, including rats, mice, hamsters, monkeys and dogs. A complete review of all the studies can be found in JECFA (1974) and EFSA (2015). Two of the more reliable polysorbate studies were conducted on polyoxyethylene sorbitan monostearate or Polysorbate 60 (CAS No. [redacted]

There does not appear to be any toxicological differences between the polysorbates. No target organs were identified in these studies, and diarrhea is the primary non-neoplastic effect at concentrations of >5% in feed. The diarrhea is related to the composition of the diet. Polysorbates in diets without dietary fiber resulted in exfoliated or damaged brush border membrane of the small intestinal cells, inducing diarrhea and reduced body weight (Kimura et al., 1982).

<u>Oral</u>

Male and female Sprague-Dawley rats were given 0, 1, 2 or 5% Polysorbate 60 in their feed for 13 weeks. Effects were noted only in the 5% dietary group and consisted of diarrhea, increased water consumption, enlarged cecum and slightly decreased hemoglobin. The NOAEL for this study is 2% in the diet, which corresponds to 1,355 and 1,565 mg/kg-day for males and females, respectively (BIBRA, 1981; EFSA, 2015) [Kl.score=2].

Male and female Osborne-Mendel rats were given 0, 2, 5, 10 or 25% Polysorbate 60 in their feed for 24 months. There was no treatment-related mortality or in feed consumption. In the 25% dietary group, there was severe diarrhea and reduced body weight gain the males. Liver weights were increased with no corresponding histopathologic changes. The cecum was also enlarged, but the histopathologic examination showed no treatment-related changes. The only changes seen in the 10% and 5% dietary groups were moderate and slight diarrhea, respectively. The NOAEL for this study is 2% in the diet, which corresponds to 1,000 mg/kg-day (Fitzburgh et al., 1959; EFSA, 2015) [Kl.score=2].

Male and female F344/N rats were given 0, 3,100, 6,200, 12,500, 25,000 or 50,000 ppm Polysorbate 80 in their feed for 13 weeks. There were no treatment-related effects. The NOAEL for this study is 50,000 ppm in the diet, which corresponds to 4,500 mg/kg-day (NTP, 1992a) [Kl.score=2].

Male and female B6C3F$_1$ mice were given 0, 3,100, 6,200, 12,500, 25,000 or 50,000 ppm Polysorbate 80 in their feed for 13 weeks. There were no treatment-related effects. The NOAEL for this study is 50,000 ppm in the diet, which corresponds to 10,000 mg/kg-day (NTP, 1992a) [Kl.score=2].

Male and female F344/N rats were given in their feed 0, 25,000 or 50,000 ppm Polysorbate 80 in their feed for two years. There was reduced survival in the male, but not female, rats; there were no other non-neoplastic treatment-related effects. The NOAEL for this study is 50,000 ppm in the diet, which corresponds to 2,500 mg/kg-day (NTP, 1992a) [Kl.score=2].

Male and female B6C3F$_1$ mice were given 0, 25,000 or 50,000 ppm Polysorbate 80 in their feed for two years. The 50,000 ppm animals had forestomach squamous hyperplasia, and the 50,000 ppm females had forestomach ulcers. These effects were the localized effects of the test material and not due to systemic toxicity. The NOAEL for systemic toxicity in this study is 50,000 ppm in the diet, which corresponds to 3,700 mg/kg-day (NTP, 1992a) [Kl.score=2].

Inhalation

No data are available.

Dermal

No data are available.

G. Genotoxicity

In Vitro Studies

The *in vitro* genotoxicity studies on Polysorbate 80 are presented in Table 2.

Table 2: *In vitro* genotoxicity studies on Polysorbate 80

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium*)	-	-	2	EFSA, 2015
Chromosomal aberration (Chinese hamster fibroblasts)	-	-	2	EFSA, 2015

*+, positive; -, negative

In Vivo Studies

Male CBA mice were given a single oral gavage dose of 0 or 75 mg/kg Polysorbate 80. There was no significant increase in micronuclei in the bone marrow cells of the treated mice compared with controls (Jenssen & Ramel, 1980) [Kl.score=2].

H. Carcinogenicity

Oral

The NTP conducted two-year dietary carcinogenicity studies on Polysorbate 80 in F344/N rats and B6C3F$_1$ mice. The dietary levels were 0, 25,000 or 50,000 ppm Polysorbate 80. The average daily

intakes in rats were 0, 1,174 and 2,415 mg/kg-day for males and 0, 1,344, and 2,745 mg/kg-day for females. There was no evidence of carcinogenic activity for Polysorbate 80 in female rats or in male and female mice at any dose level. In male rats, the incidence of benign or malignant adrenal medulla pheochromocytomas (combined) was significantly increased in the high-dose males (21/50, 19/50, and 29/50 for the 0, 25,000 and 50,000 ppm groups, respectively). The incidence of the high-dose group (58%) exceeded the upper historical control range of 48% for males from the current NTP 2-year dietary studies. But when NTP evaluated the historical control incidence in male F344/N rats based on a broader range of NTP studies than those included in the recent historical control data, the incidence of pheochromocytomas in untreated male rats was as high as 65% (Haseman et al., 1990). The increased incidence of pheochromocytomas in the high-dose males was due to an increase in the number of benign pheochromocytomas occurring in a single gland. The incidence of hyperplasia of the adrenal medulla was increased in the low-dose male rats, but not in the high-dose male rats (11/50, 22/50, 12/50, respectively). The NTP concluded that the marginal increased incidence of pheochromocytomas in combination with the increased incidence of hyperplasia were considered to be an equivocal finding (NTP, 1992a) [Kl.score=2].

A review of the NTP (1992a) data by the EU Scientific Committee on Foods (SCF, 1995) and a subsequent review by the European Food Safety Authority (EFSA, 2015) concluded that the increased adrenal medulla pheochromocytomas in the Polysorbate 80-treated male rats did not have relevance to humans. This conclusion was based on the lack of genotoxicity of Polysorbate 80, the equivocal finding in the NTP study, and that pheochromocytomas have been associated with poorly metabolized food additives (i.e., polyols such as sorbitol, xylitol, lactitol; lactose) given to animals at high doses and have been regarded as of no significance to humans. In the long-term (mainly 2-year) studies on polyols and lactose, adrenal medullary hyperplasia and pheochromocytomas occurred at dietary concentrations of ≥5% and usually at 10–20%, with no proliferative lesions and tumours seen at lower concentrations (reviewed in Lynch et al., 1996). The pheochromocytomas in these studies were seen in rats, but not in mice and dogs, with male rats having a higher incidence than female rats. In their evaluation of the human significance of these tumours from polyols and lactose, Lynch et al. (1996) discuss the significant morphological, functional and etiological differences between rats and humans with regards to the nature of proliferative lesions that occur in the adrenal medulla. They conclude that the rat is much more susceptible to induction of proliferative lesions of the adrenal medulla compared with humans. There are also mechanistic data on polyols and lactose that support a high-dose rat-specific mode-of-action for these adrenal medulla pheochromocytomas. Although there are no mechanistic studies on Polysorbate 80, the similarity in the toxicity profile of Polysorbate 80 with these poorly metabolized carbohydrates would suggest that the pheochromocytomas seen in the male rats in the NTP two-year carcinogenicity study also occurs by a high-dose rat-specific mode-of-action.

Inhalation

There are no studies available.

Dermal

There are no studies available.

I. Reproductive Toxicity

In a three-generation reproductive toxicity study, male and female rats were given in their feed 0, 5, 10 or 20% (0, 2,500, 5,000 or 20,000 mg/kg-day) Polysorbate 80. Diarrhea was seen in the >10% parental animals. There was reduced postnatal survival in the pups in the 20% dietary group as well as reduced lactation and breeding efficiency. There were no other effects that were indicative of

reproductive or developmental toxicity. The NOAEL for reproductive and developmental toxicity is 10% in the diet, which corresponds to 5,000 mg/kg-day (Oser and Oser, 1956a,b; Oser and Oser, 1957a,b) [Kl.score=2].

J. Developmental Toxicity

Oral

Pregnant female SD rats were dosed by oral gavage with 0, 500 or 5,000 mg/kg Polysorbate 80 on GD 6–15. At 500 and 5,000 mg/kg, liver weights were slightly increased in the maternal dams, but the change was not enough to be considered adverse. There was no indication of developmental toxicity. The NOAEL for maternal toxicity is 5,000 mg/kg-day. The NOAEL for developmental toxicity is 5,000 mg/kg-day, the highest dose tested (NTP, 1992b; Price et al., 1994) [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 Polysorbate 80 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

A two-year carcinogenicity study was conducted in rats given 0, 25,000 or 50,000 ppm Polysorbate 80 in feed (NTP, 1992a). For non-cancer effects, there were no adverse findings at any dose level. In female rats, there were no carcinogenic effects; but in the male rats, there was a marginal increase in the number of benign adrenal medulla pheochromocytomas in the high-dose male rats. Adrenal medulla hyperplasia, a lesion considered to be the precursor to pheochromocytoma, was increased in the low-dose, but not high-dose, male rats. The NOAEL for this study is 25,000 ppm for male rats, which corresponds to average daily intake of 1,174 mg/kg-day. The NOAEL of 1,174 mg/kg-day will be used to derive an oral reference dose 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) = 1
UF_D (database uncertainty) = 1
Oral RfD = 1,174/(10 × 10 × 1 × 1 × 1) = 1,174/100 = 12 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 = (11.7 × 70 × 0.1)/2 = 41 mg/L

B. Cancer

A two-year dietary carcinogenicity study on Polysorbate 80 showed a marginal increase in the number of benign adrenal medulla pheochromocytomas in the high-dose male rats. Adrenal medulla hyperplasia, a lesion considered to be the precursor to pheochromocytoma, was increased in the low-dose, but not high-dose, male rats. he increased adrenal medulla pheochromocytomas in the Polysorbate 80-treated male rats did not have relevance to humans. This conclusion was based on the lack of genotoxicity of Polysorbate 80, the equivocal finding in the NTP study, and that pheochromocytomas have been associated with poorly metabolized food additives (i.e., polyols such as sorbitol, xylitol, lactitol; lactose) given to animals at high doses and have been regarded as of no significance to humans. A cancer reference value for Polysorbate 80 was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Sorbitan monooleate polyoxyethylene derivative does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Based on read across from a similar substance, acute and chronic toxicities are relatively low. Data to support this conclusion are discussed below.

B. Aquatic Toxicity

Acute Studies

There are no adequate aquatic toxicity studies on sorbitan monooleate polyoxyethylene derivative. Aquatic toxicity data have been read-across from sorbitan monolaurate, ethoxylated (1-6.5 moles ethoxylated) [CAS No. [redacted] Table 3 lists the results of acute aquatic toxicity studies conducted on Sorbitan Monolaurate, Ethoxylated (1-6.5 Moles Ethoxylated).

Table 3: Acute aquatic toxicity studies on sorbitan monolaurate, ethoxylated (1-6.5 Moles Ethoxylated) [CAS No. [redacted]

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Brachydanio rerio	96-hr LL50	>100 [WAF]	2	ECHA
Pseudokirchneriella subcapitata	72-hr EL50	58.84 [WAF]	2	ECHA

Chronic Studies

The 21-day NOELR (No-Observed-Effect-Loading-Rate) for sorbitan monolaurate, ethoxylated (1-6.5 moles ethoxylated) [CAS No. [redacted] in a Daphnia reproduction test was 10 mg/L WAF (ECHA) [Kl.score=2].

The 72-hr EL_{10} for sorbitan monolaurate, ethoxylated (1-6.5 moles ethoxylated) [CAS No. [redacted] to Pseudokirchneriella subcapitata is 19.05 mg/L WAF (ECHA) [Kl. score = 2].

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for sorbitan monooleate polyoxyethylene derivative follow the methodology discussed in DEWHA (2009).

PNEC Water

Experimental results are available for two trophic levels. Acute $E(L)L_{50}$ values are available for fish (>100 mg/L WAF) and algae (58.84 mg/L WAF). The EL_{10} or NOELR values from chronic studies are available for invertebrates (10 mg/L WAF) and algae (58.8 mg/L WAF). On the basis that the data consist of short-term and long-term studies from two trophic levels, an assessment factor of 50 has been applied to the lowest reported EL_{10} value of 10 mg/L for *Daphnia*. The $PNEC_{water}$ is 0.2 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 3.90mg/kg sediment wet weight.

The calculations are as follows:

$$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$$
$$= (25/1280) \times 1000 \times 0.2$$
$$= 3.90 \text{ mg/kg}$$

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 × 50.36/1000 × 2400]
= 25.0 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]
$Kp_{sed} = K_{oc} \times f_{oc}$
= 1259 × 0.04
= 50.36 L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for for sorbitan monooleate, ethoxylated (1-6.5 moles ethoxylated) [CAS No. [redacted] calculated from EPISUITE™ using the MCI ranged from 794 to 1,259 L/kg. A value of 1,259 L/kg was used for the calculation.

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 3.4 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
= (25.18/1500) × 1000 × 0.2
= 3.4

Where:

Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]
$Kp_{soil} = K_{oc} \times f_{oc}$
= 1,259 × 0.02
= 25.18 m^3/m^3

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for sorbitan monooleate, ethoxylated (1-6.5 moles ethoxylated) [CAS No. [redacted] calculated from EPISUITE™ using the MCI ranged from 794 to 1,259 L/kg. A value of 1,259 L/kg was used for the calculation.
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 monooleate polyoxyethylene derivative is readily biodegradable and thus does not meet the screening criteria for persistence.

The measured BCF in fish ranges from 12.6 to 14.6 L/kg. Thus, sorbitan monooleate polyoxyethylene derivative does not meet the criteria for bioaccumulation.

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

The overall conclusion is that sorbitan monooleate polyoxyethylene derivative is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not 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

Rinse immediately with plenty of running water. If easy to do, remove contact lenses. Get medical attention if symptoms persist.

Skin Contact

Wash with soap and water. Get medical attention if symptoms occur.

Inhalation

Treat symptomatically. Move to fresh air. Get medical attention if symptoms persist.

Ingestion

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

B. Firefighting Information

Extinguishing Media

Water spray, dry chemical, foam, carbon dioxide.

Specific Exposure Hazards

None known.

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.

Environmental Precautions

Not regarded as dangerous to the environment.

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

No special precautions are necessary beyond normal good hygiene practices.

Other Handling Precautions

Wash hands thoroughly after handling.

Storage

Keep container closed.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

Workplace Australia has not established an occupational exposure standard for Polysorbate 80.

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. Eyewash fountains and safety showers must be easily accessible.

F. Transport Information

Polysorbate 80 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

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TRIETHANOLAMINE

This dossier on triethanolamine presents the most critical studies pertinent to the risk assessment of triethanolamine 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-[bis(2-hydroxyethyl)amino]ethan-1-ol

CAS RN: [redacted]

Molecular formula: $C_6H_{15}NO_3$ or $(CH_2OHCH_2)_3N$

Molecular weight: 149.19

Synonyms: Triethanolamine; 2,2',2"-nitrilotriethanol; 2,2',2"-nitrilotris[ethanol]; ethanol, 2,2',2"-nitrilotri- (8Cl); ethanol, 2,2',2"-nitrilotris- (9Cl); nitrilotriethanol; TEA; tris(beta-hydroxyethyl)amine; tris(2-hydroxyethyl)amine

SMILES: C(CO)N(CCO)CCO

II. PHYSICAL AND CHEMICAL PROPERTIES

Table 1: Overview of the Physico-chemical Properties of Triethanolamine

Property	Value	Klimisch score	Reference
Physical state at 20°C and 101.3 kPa	Colorless to pale-yellow liquid with an amine-like odor.	2	ECHA
Melting Point	20.5°C	2	ECHA
Boiling Point	336.1°C	2	ECHA
Density	1.12 g/cm^3 @ 20°C	2	ECHA
Vapor Pressure	Negligible	2	ECHA

Property	Value	Klimisch score	Reference
Partition Coefficient (log K_{ow})	-1.9 @ 25°C [Experimental]	2	ECHA
Water Solubility	>1,000 g/L @ 20°C	2	ECHA
Flash Point	179°C	2	ECHA
Auto flammability	324°C	2	ECHA
Viscosity	830.2 mm^2/s @ 20°C 181.5 mm^2/s @ 40°C	2	ECHA

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

Triethanolamine is readily biodegradable, and it has a low potential to bioaccumulate. Triethanolamine will not adsorb significantly to suspended solids and sediments in water and would be highly mobile in soil.

B. Biodegradation

Triethanolamine is readily biodegradable. In an OECD 301E test, there was 96% degradation after 19 days (ECHA). [Kl. score = 2]

Triethanolamine was completely degraded after incubation in municipal activated sludge for 1 or 5 days (West and Gonsior, 1996). The rate constants in all test batches for degradation and mineralization were reported to be >0.359. Thus, triethanolamine can be considered to be readily biodegradable. [Kl. score = 2]

C. Environmental Distribution

<u>Adsorption/desorption</u>
No experimental data are available for triethanolamine. Using KOCWIN in EPISUITE™ (EPA, 2017), the estimated K_{oc} value from log K_{ow} of -2.48 is 0.3046 L/kg. The estimated K_{oc} value from the molecular connectivity index (MCI) is 10 L/kg.

D. Bioaccumulation

Triethanolamine has been tested in a bioconcentration flow-through fish (OECD 305) test using *Cyprinus carpio*. The BCF was determined to be <0.4 and <3.9 at

triethanolamine concentrations of 2.5 and 0.25 mg/L, respectively (ECHA). [Kl. score = 2]

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

The acute toxicity of triethanolamine by the oral, dermal, and inhalation routes is very low. Triethanolamine is not a skin or eye irritant; it is not a skin sensitizer to guinea pigs, but it may cause an allergic skin reaction in a small proportion of individuals. Repeated exposure by the oral route in rats showed no adverse effects. Repeated exposure by the inhalation caused effects to the respiratory tract and skin, respectively, in rats as a result of chronic irritation; but no target organs were identified from systemic exposure. Triethanolamine is not genotoxic, and lifetime oral and dermal studies in rats showed no clear carcinogenic effects. Developmental toxicity was seen in rats at oral doses that caused maternal toxicity.

B. Acute Toxicity

The oral LD_{50} in rats is 6,400 mg/kg (ECHA) [Kl. score = 2], and the dermal LD_{50} in rabbits is >2,000 mg/kg (ECHA) [Kl. score = 2]. No deaths seen in rats following an 8-hour exposure to a saturated vapor atmosphere [approximately 1.8 mg/m^3] (ECHA) [Kl. score = 2].

C. Irritation

Application of 0.5 mL to the skin of rabbits for 4 hours under occlusive conditions was not irritating. The mean of the 24, 48, and 72 hours erythema and edema scores were zero (ECHA). [Kl. score = 1]

Instillation of 0.1 mL into the eyes of rabbits were minimally irritating (Griffith *et al.*, 1980). [Kl. score = 2]

D. Sensitization

Triethanolamine was not considered a skin sensitizer when tested in a guinea pig maximization test (ECHA). [Kl. score = 1]

Patch test results with triethanolamine on patients from 1992 to 2007 were collected and evaluated. There were 85,098 patients that were tested with triethanolamine; of these, 323 (0.35%) patients tested positively to triethanolamine. The positive reactions that were interpreted as allergic seem to be caused by exposure to triethanolamine in cosmetics and/or topical therapeutic preparations possibly on damaged skin (Lessmann *et al.*, 2009).

E. Repeated Dose Toxicity

Oral

Male and female Cox CD rats were fed diets containing 0, 250, 500 or 1,000 mg/kg triethanolamine for 91 days. There were no effects that were considered treatment-related. The NOAEL for this study is 1,000 mg/kg-day (ECHA). [Kl. score = 2]

Inhalation

Male and female Wistar rats were exposed (nose-only) by inhalation to 0, 0.02, 0.1, or 0.5 mg/L triethanolamine aerosol 6 hours/day, 5 days/week for 28 days. There was no mortality; the only clinical signs were reddish crusts on the nasal edges in the 0.5 mg/L animals during the second half of the exposure period. Body weights and body weight gain were similar across all groups. There was no treatment-related changes in the hematology parameters, clinical chemistry, and neurobehavioral endpoints. Local inflammatory changes were observed in the submucosa of the larynx region. In both sexes, there was a tendency for a concentration-dependent increase in incidence and severity of the inflammatory lesions, with the effects greater in males than females. The NOAEC for systemic effects is 0.5 mg/L; the NOAEC for localized effects is 0.02 mg/L (ECHA) [Kl. score = 1].

Dermal

Male and female F344 rats were given dermal applications of 0, 125, 250, 500, 1,000, and 2,000 mg/kg triethanolamine 5 days/week for 90 days. There was deaths during the study. Body weight gain was significantly reduced (-33%) in the 2,000 mg/kg males compared to controls. Body weight gain was also significantly reduced (-13% to 36%) for the ≥125 mg/kg females. The mean final body weights of the 2,000 mg/kg males and females were significantly reduced. The only treatment-related clinical signs occurred at the site of dermal application. Brain weights relative to body weights were significantly elevated in the 2,000 mg/kg animals; because absolute brain weights were unaffected, the changes in brain weights is likely due to reduced body weights in these animals. Absolute kidney weights were increased in the ≥1,000 mg/kg animals; relative kidney weights were elevated in the ≥250 mg/kg males and ≥1,000 mg/kg females. Absolute and relative spleen weights were lower in the 2,000 mg/kg females; relative spleen weights were elevated in the ≥1,000 mg/kg males. Absolute and relative thymus weights were increased in the 2,000 mg/kg males. Relative liver weights were increased in the 500 and 1,000 mg/kg males. Absolute and relative lung weights were lower in the 2,000 mg/kg males. Relative testes weights were increased in the 2,000 mg/kg males. Hematological changes were seen in the 2,000 mg/kg animals and were considered to be due to an inflammatory response from dermal irritation at the application site. Elevated SGOT levels were noted in the 250 and 2,000 mg/kg males; and mean SGPT levels were significantly increased in the 2,000 mg/kg males. Elevated serum urea nitrogen, albumin, SGOT, and SGPR levels were noted in the 2,000 mg/kg females. At

study termination, the specific gravity of urine was elevated in the 2,000 mg/kg males; urine protein levels for the ≥500 mg/kg males were significantly lower. The specific gravity of urine was elevated in the ≥1,000 mg/kg females; urine glucose concentrations were also increased in these two dose groups. Apart for skin lesions at the site of application, there were no treatment-related histopathologic changes. The NOAEL for localized effects is 125 mg/kg-day based on chronic-active inflammation and acanthosis at the site of application in males. The NOAEL for systemic toxicity is 125 mg/kg-day based on increased relative kidney weights in males (ECHA) [Kl. score = 2].

F. Genotoxicity

In Vitro Studies

The findings from the *in vitro* genotoxicity studies on triethanolamine are presented below in Table 2.

Table 2: *In vitro* Genotoxicity Studies on Triethanolamine

Test System	Results*		Klimisch Score	Reference
	-S9	+S9		
Bacterial reverse mutation (*S. typhimurium* strains)	-	-	2	Mortelsman *et al.* (1986); ECHA
Mammalian cell gene mutation (mouse lymphoma L5178Y cells)	-	-	1	ECHA
Chromosomal aberration (CHO cells)	-	-	2	Galloway *et al.* (1987); ECHA
Sister chromatid exchange (CHO cells)	-	-	2	Galloway *et al.* (1987); ECHA

*+, positive; -, negative

In Vivo Studies

Male and female B6C3F$_1$ mice were given dermal applications of triethanolamine, 5 days/week for 13 weeks. There were no increase in the frequency of micronucleated erythrocytes in the peripheral blood (NTP, 2004).

Triethanolamine did not induce sex-linked recessive lethal mutations in germ cells of adult male *Drosophila melanogaster* exposed by feeding or injection (Yoon *et al.*, 1985).

G. Carcinogenicity

Oral

Male and female F344 were given triethanolamine in their drinking water for two years. The doses were 0, 1, and 2%; but starting on week 69, the doses for females were 0.5 and 1%. The estimated daily intakes for 1 and 2% dose groups were approximately 667 and 1,333 mg/kg-day; and the estimated daily intakes for the 0.5% and 1% in females were approximately 333 and 667 mg/kg-day. There were no statistically significant increases in the incidence of tumors between treated and control groups when analyzed by Chi-square test. However, there was an increase in nephrotoxicity which appeared to have an adverse effect on the life expectancy of the treated animals, especially the females. So, an age-adjusted statistical analysis was conducted. There was a positive trend ($p<0.05$) in the occurrence of liver tumors in males and of uterine endometrial sarcomas and renal-cell adenomas in females. These tumors have been observed spontaneously in this strain of rats, and their incidences in the controls were lower than historical controls for other laboratories. The results may indicate that a positive trend in the occurrence of these tumors is not attributable to triethanolamine exposure. Increased incidence of kidney tumors in the high-dose females may have been connected with kidney damage. Histopathologic examination of the kidney effects observed in the treated groups, especially the high-dose females, showed acceleration of chronic nephropathy. Also, mineralization of the renal papilla, nodular hyperplasia of the pelvic mucosa, and pyelonephritis with or without papillary necrosis were also observed (Maekawa *et al.*, 1986; ECHA) [Kl. score = 2]

Male and female $B6C3F_1$ mice were given in their drinking water 0, 1 or 2% triethanolamine (0 and approximately 1,600 and 3,200 mg/kg-day) for 82 weeks. Mortality, organ weights and tumor incidences were similar between treated and control animals (Konishi *et al.*, 1992; ECHA). [Kl. score = 2]

Inhalation

No studies are available.

Dermal

Male and female F344 rats were given dermal applications of triethanolamine, 5 days/week for two years. The doses were: 0, 32, 63 or 125 mg/kg-day for males, and 0, 63, 125 or 250 mg/kg-day for females. There were no treatment-related carcinogenic effects in either sexes (NTP, 1999). [Kl. score = 1]

Male and female $B6C3F_1$ mice were given dermal applications of triethanolamine, 5 days/week for two years. The doses were: 0, 200, 630 and 2,000 mg/kg-day for males, and 0, 100, 300 and 1,000 mg/kg-day for females. In females, there was some evidence of carcinogenicity activity based on increased incidences of hepatocellular adenomas. In males, there was equivocal evidence of carcinogenicity activity based on the incidence of liver hemangiosarcomas (NTP, 2004). [Kl. score = 1]

H. Reproductive/Developmental Toxicity

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-day triethanolamine. Most of the 1,000 mg/kg-day animals and one 100 mg/kg-day animals showed transient salivation for a few minutes immediately after each treatment. This effect was considered to be induced by the unpalatability of the test substance or from local irritation of the upper digestive tract. Body weight gain was slightly lower in the 1,000 mg/kg-day females during gestation and was considered to be caused by the increased postimplantation loss rather than by a systemic effect of the test substance. In the 1,000 mg/kg-day group, there were lower mean number of implantation sites, increased postimplantation loss, and lower average litter size. There were no treatment-related effects in the F_1 pups. The NOAEL for systemic toxicity is 1,000 mg/kg-day. The NOAEL for reproductive toxicity is 1,000 mg/kg-day. The NOAEL for developmental toxicity is 300 mg/kg-day (ECHA). [Kl. score = 1]

V. DERIVATION OF TOXICOLOGICAL REFERENCE AND DRINKING WATER GUIDANCE VALUES

The toxicological reference values developed for triethanolamine 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 were no effects seen in a 91-day dietary study in rats, with a NOAEL of 1,000 mg/kg-day (ECHA). 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 = 1,000/(10 x 10 x 1 x 10 x 1) = 1,000/1,000 = <u>1.0 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 = (1.0 x 70 x 0.1)/2 = 3.5 mg/L

B. Cancer

There were no carcinogenic effects in male and female mice given triethanolamine in their drinking water for 82 weeks (Konishi et al., 1992). In a two-year drinking water study, age-adjust tumor incidence showed increased liver tumors in males, and uterine endometrial sarcomas and renal tubule adenomas in females. These tumors were not attributed to triethanolamine exposure because, in comparison with historical control incidences, the tumors reflected low incidences in the control groups rather than increased incidences in the exposed groups.

In dermal carcinogenicity studies, there was no evidence of carcinogenicity in male and female rats (NTP, 1999). In female mice, there was some evidence of carcinogenicity activity based on increased incidences of hepatocellular adenomas. In male mice, there was equivocal evidence of carcinogenicity activity based on the incidence of liver hemangiosarcomas (NTP, 2004).

A cancer reference value for triethanolamine was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Triethanolamine does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidizing potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

Triethanolamine has low acute toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

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

Table 3: Acute Aquatic Toxicity Studies on Triethanolamine

Test Species	Endpoint	Results (mg/L)	Klimisch score	Reference
Pimephales promelas	96-h LC_{50}	11,800	2	ECHA
Ceriodaphnia dubia	48-h EC_{50}	610	2	Warne and Schifko, 1999
Desmodesmus subspicatus	72-h EC_{50} EC_{10}	512 (neutralized) 216 (un-neutralized) 26 (neutralized)	2	ECHA

Chronic Studies

In a 21-day *Daphnia* reproduction test, the NOEC for mortality is 16 mg/L, the NOEC for reproduction rate was 125 mg/L, and the NOEC for reproduction on the appearance of first offspring was 250 mg/L (Kuehn *et al.*, 1989). [Kl. score = 2]

C. Terrestrial Toxicity

No studies are available.

D. Calculation of PNEC

The PNEC calculations for triethanolamine 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 (11,800 mg/L), invertebrates (610 mg/L), and plants (512 mg/L). Results from chronic studies are available for invertebrates (NOEC = 16 mg/L) and algae (EC_{10} = 26 mg/L). On the basis that the data consists of chronic studies for two trophic levels,

an assessment factor of 50 has been applied to the lowest reported EC_{10} of 16 mg/L for *Daphnia*. The $PNEC_{aquatic}$ is 0.32 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 0.25 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (0.99/1280) \times 1000 \times 0.32$
$= 0.25$

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]

$K_{sed\text{-}water} = 0.8 + [0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [0.2 \times 0.4/1000 \times 2400]$
$= 0.99$

Where:
Kp_{sed} = solid-water partition coefficient (L/kg).
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]

$Kp_{sed} = K_{oc} \times f_{oc}$
$= 10 \times 0.04$
$= 0.4$

Where:
K_{oc} = organic carbon normalized distribution coefficient (L/kg). The K_{oc} for triethanolamine calculated from EPISUITE™ using MCI is 10 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 0.04 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (0.2/1500) \times 1000 \times 0.32$
$= 0.04$

Where:
Kp_{soil} = soil-water partition coefficient (m^3/m^3)
BD_{soil} = bulk density of soil (kg/m^3) = 1,500 [default]

$Kp_{soil} = K_{oc} \times f_{oc}$
$= 10 \times 0.02$
$= 0.2$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for triethanolamine calculated from EPISUITE™ using the MCI is 10 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).

Triethanolamine is readily biodegradable; thus it does not meet the screening criteria for persistence.

The BCF values for triethanolamine in fish was <3.9; thus it does not meet the criteria for bioaccumulation.

The NOEC or EC_{10} values from chronic aquatic toxicity studies on triethanolamine is >0.1 mg/L. Thus triethanolamine does not meet the criteria for toxicity.

The overall conclusion is that triethanolamine is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

Not classified.

B. Labelling

Danger
According to the classification provided by companies to ECHA in REACH registrations this substance causes serious eye damage and is suspected of damaging fertility or the unborn child.

Additionally, the classification provided by companies to ECHA in CLP notifications identifies that this substance causes serious eye 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. If effects occur, get medical attention immediately, preferably a physician for an ophthalmologic examination.

Skin Contact
Remove contaminated clothing. Wash thoroughly with soap and water. Seek medical attention if irritation persists.

Inhalation
If inhaled, remove from area to fresh air. Give artificial respiration if victim is not breathing. Get medical attention.

Ingestion
Rinse mouth with water and then drink plenty 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

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: nitrogen oxides, carbon monoxide, carbon dioxide.

Special Protective Equipment for Firefighters
Wear self-contained breathing apparatus and chemical-protective clothing.

C. Accidental Release Measures

Personal Precautions
Use appropriate protective equipment. Handle in accordance with good industrial hygiene and safety practice. 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
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
The workplace exposure standard for triethanolamine in Australia is 5 mg/m^3 as an 8-hour TWA, with a sensitization notation.

Engineering Controls
Good general ventilation should be used. Use local exhaust ventilation, or other engineering controls to maintain airborne levels below exposure limit guidelines.

Personal Protection Equipment
Respiratory Protection:
Use respiratory protection in case of vapor or aerosol release.

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

Triethanolamine 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

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TRIBUTYL TETRADECYL PHOSPHONIUM CHLORIDE

This dossier on tributyl tetradecyl phosphonium chloride (TTPC) presents the most critical studies pertinent to the risk assessment of TTPC 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): Tributyl(tetradecyl)phosphonium;chloride

CAS RN: [redacted]

Molecular formula: $C_{26}H_{56}PCl$

Molecular weight: 435.15 g/mol

Synonyms: Tributyl tetradecyl phosphonium chloride; TTPC; tri-n-butyltetradecylphosphonium chloride; Bellacide 350; Bellacide 355

SMILES: CCCCCCCCCCCCCC[P+](CCCC)(CCCC)CCCC.[Cl-]

II. PHYSICO-CHEMICAL PROPERTIES

Table 1: Overview of the physico-chemical properties of TTPC

Property	Value	Klimisch Score	Reference
Physical state at 20°C and 101.3 kPa	Clear, colourless liquid	4	BWA Additives (2016)
Melting Point	Not available	-	-
Boiling Point	100°C* @ 101.3 kPa	4	BWA Additives (2016)
Specific Gravity	0.98–1.00 @ 20°C	4	BWA Additives (2016)
Density	Not available	-	-
Vapour Pressure	Not available	-	-
Partition Coefficient (log K_{ow})	2.45 @ X°C	4	BuruEnergy
Water Solubility	Not available	-	-
Flash Point	Not available	-	-
Auto flammability	Not available	-	-
Viscosity	55-65 mm^2/s @ 25°C	4	BWA Additives (2016)
Henry's Law Constant	Not available	-	-

*5% aqueous solution of TTPC

TTPC is a non-oxidizing biocide. Information on TTPC in this dossier has been obtained from BWA™ Water Additives, a producer of TTPC. BWA™ Water Additives produces a 5% or 50% aqueous

solution of TTPC, which is sold under the product names Bellacide® 355 and Bellacide® 350, respectively.

III. ENVIRONMENTAL FATE PROPERTIES

A. Summary

TTPC is stable over a wide pH range and is not susceptible to photodegradation. TTPC is biodegradable, but not readily biodegradable. It will strongly adsorb to soil and sediment. TTPC is not expected to bioaccumulate.

B. Abiotic Degradation

TTPC is considered stable to hydrolysis at environmentally relevant pH values, and therefore, hydrolysis is not expected to be a significant route of transformation in waterbodies. In addition, TTPC is not expected to undergo photolysis. Based on its negligible vapour pressure, volatilization of TTPC from moist soil or water surfaces is not expected (Health Canada, 2018).

C. Biodegradation

OECD Ready Biodegradability studies conducted by the United States Environmental Protection Agency (USEPA) for re-registration of TTPC as a biocide determined that TTPC degraded with a first-order half-life of 6.6 hours (USEPA, 2018).

TTPC was identified as readily biodegradable and not persistent in a qualitative (screening) environmental risk assessment (ERA) conducted by the Australian Department of the Environment and Energy, Bureau of Meteorology, CSIRO and Geoscience Australia, Australia.[1]

However, abiotic biodegradation experiments for TTPC produced mixed results. In the subsurface, TTPC showed little to no degradation at temperatures below 105°C. However, when shale was present, increasing temperature increased rates of degradation and the presence of other hydraulic fracturing chemicals also enhanced degradation. In addition, the loss of TTPC is influenced by the adsorption of TTPC to the surface of the shale organic matter. TTPC was observed to be highly immobile in the subsurface as it significantly adsorbed to the rocks in the formation. In flowback water, TTPC exhibited partial degradation (Lupton et al., 2024).

Overall, TTPC is expected to ultimately biodegrade in the environment. If a chemical is found to be inherently or readily biodegradable, it is categorised as Not Persistent since its half-life is substantially less than 60 days (DoEE, 2017).

D. Environmental Distribution

Using KOCWIN in EPISuite™ (USEPA, 2019), the estimated K_{oc} value for TTPC using the MCI method is 4.555×10^7 L/kg.

In research conducted to demonstrate the environmental fate of hydraulic fracturing chemicals, TTPC was “shown to be generally highly adsorbing and likely to be hardly mobile in the subsurface.”

[1] Kirby, J.K., Golding, L., Williams, M., Apte, S., Mallants, D., & Kookana, R. (2020) Qualitative (screening) environmental risk assessment of drilling and hydraulic fracturing chemicals for the Cooper GBA region. Technical appendix for the Geological and Bioregional Assessment: Stage 2. Department of the Environment and Energy, Bureau of Meteorology, CSIRO and Geoscience Australia, Australia.

Soil adsorption coefficient (K_{oc}) values measured from batch experiments were 920 L/kg and 25,629 L/kg (Lupton et al., 2024). Health Canada (2018) reported K_{oc} values of 61,443 L/kg – 607,518 L/kg in six soil types with the highest values reported in loamy sand.

E. Bioaccumulation

No bioaccumulation studies are available on TTPC. TTPC is not expected to bioaccumulate based on the experimental log K_{ow} of 2.45 (BuruEnergy) [Kl.score=4].

IV. HUMAN HEALTH HAZARD ASSESSMENT

A. Summary

TTPC exhibits moderate acute toxicity by the oral route but is highly toxic by the inhalation route. It is corrosive to the skin and eyes, but it is not a skin sensitizer. No target organ effects were noted in a 90-day rat drinking water study. TTPC was not mutagenic in a bacterial reverse mutation (Ames) test. There are no carcinogenicity studies on TTPC. In rats, developmental toxicity was shown to occur at oral dose levels that were not maternally toxic; whereas, in rabbits, developmental toxicity occurred only at maternally toxic doses.

B. Acute Toxicity

An oral LD_{50} in rats for Bellacide 350 (50% aq. solution of TTPC) was reported to be >1,002 mg/kg (BWA Additives, 2011) [Kl.score=4]. An oral LD_{50} in rats for Bellacide 355 (5% aqueous solution of TTPC) was reported to be >4,000 mg/kg (BWA Additives, 2009) [Kl.score=4].

The 4-hour inhalation LC_{50} in male and female rats for a 50% aq. solution of TTPC was <0.05 mg/L (aerosol). The mass median aerodynamic diameter for the aerosol was 1.93 µm (Cytec, 2012) [Kl.score=1]. The 1-hour inhalation LC_{50} in male and female rats for a 50% aq. solution of TTPC is 0.227 mg/L (aerosol). The mass median aerodynamic diameter for the aerosol was 1.92 µm (Cytec, 2013) [Kl.score=1].

C. Irritation

Both Bellacide 350 (50% aq. solution TTPC) and Bellacide 355 (5% aq. solution TTPC) are considered to be corrosive to the skin and eyes (BWA Additives, 2011; 2015) [Kl.score=4].

D. Sensitisation

TTPC is not considered to be a skin sensitizer (BWA Additives, 2011, 2015) [Kl.score=4].

E. Repeated Dose Toxicity

<u>Oral</u>

A 90-day rat drinking water study has been conducted on a product containing TTPC. The LOAEL for the active ingredient (TTPC) is 27.2 and 32.3 mg/kg-day in males and females, respectively, based on various clinical signs and significantly reduced body weights, feed and water consumption. The NOAEL for this study is 8.66 mg/kg-day (EPA, 2006) [Kl.score=2].

Inhalation

No data are available.

Dermal

No data are available.

F. Genotoxicity

In Vitro Studies

TTPC was not mutagenic in a reverse mutation bacterial (Ames) test (BWA Additives, 2015) [Kl.score=4].

In Vivo Studies

No studies are available.

G. Carcinogenicity

No studies are available.

H. Reproductive Toxicity

There are no studies available.

I. Developmental Toxicity

Oral

Female Tif:RAIf(SPF) rats were dosed by oral gavage with 0, 20, 60 or 120 mg/kg Belclene® [50% active ingredient: TTPC] during gestational days (GD) 6 through 15. In the high-dose group, there were two possible treatment-related spontaneous deaths (GD 9 and 14) and another death on GD 15 due to an intubation error. Clinical signs included dyspnea in one mid-dose and four high-dose animals, and vaginal bleeding in one mid-dose female on GD 15. In the high-dose group, maternal body weight gain was significantly lower during the treatment period (GD 6–15) and throughout the gestational period (GD 0–20). Mean food consumption was significantly reduced during GD 6–11 for both the mid- and high-dose animals. The number of females with implantations and the number of implantations/females were similar across all groups. Embryonic and fetal deaths were similar between treated and control groups. There were no soft tissue changes. There was an increased incidence of incomplete ossification of the 5^{th} sternebra in the mid- and high-dose groups. The NOAELs for maternal and developmental toxicity for the active ingredient TTPC in this study is 30 and 10 mg/kg-day, respectively (EPA, 2006) [Kl.score=2].

Female chinchilla rabbits were dosed by oral gavage with 0, 7.5, 22.5 or 45 mg/kg Belclene® [50% active ingredient: TTPC] during gestational days (GD) 6 through 18. In the mid- and high-dose groups, body weight gain was significantly reduced during GD 6–18, and feed consumption was reduced during GD 6–11. Fetal body weights were significantly reduced in the mid-(males only) and high-dose dose groups. There was also an increased incidence of delayed ossification of the hindlimb phalangeal nuclei in the mid- and high-dose groups. The NOAEL for maternal and developmental toxicity for the active ingredient TTPC in this study is 3.75 mg/kg-day (EPA, 2006) [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 TTPC 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 90-day drinking water study based on various clinical signs and significantly reduced body weight and reduced feed and water consumption is 8.66 mg a.i./kg-day (EPA, 2006). This NOAEL will be used to derive the oral Reference Dose.

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 = 8.66/(10 × 10 × 1 × 10 × 1) = 8.66/1000 = 0.009 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 = (0.009 × 70 × 0.1)/2 = 0.03 mg/L

B. Cancer

No carcinogenicity studies are available on TTPC. Thus, a cancer reference dose was not derived.

VI. HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

TTPC does not exhibit the following physico-chemical properties:

- Explosivity
- Flammability
- Oxidising potential

VII. ENVIRONMENTAL HAZARD ASSESSMENT

A. Summary

TTPC has a very high acute toxicity concern to aquatic organisms.

B. Aquatic Toxicity

Acute Studies

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

Table 2: Acute aquatic toxicity studies on TTPC

Test Species	Endpoint	Results (mg/L)	Klimisch Score	Reference
Bluegill sunfish	96-h LC50	58.6	2	ECOTOX
Common Carp	96-h LC50	87	2	ECOTOX
Rainbow trout	96-h LC50	490	2	ECOTOX
Rainbow trout	96-h LC50	200	2	ECOTOX
Daphnia magna	48-h EC50	25.2	2	ECOTOX
Selenastrum capricornutum	72-h EC50	19	4	BuruEnergy

Chronic Studies

No studies are available.

C. Terrestrial Toxicity

Table 3 lists the avian toxicity studies conducted on TTPC.

Table 3: Avian toxicity studies on TTPC

Test Species	Endpoint	Results	Kl. score	Reference
Bobwhite Quail	8-d dietary	LC_{50}: 4,215 ppm NOEL: 1,980 ppm	2	ECOTOX
Mallard Duck	8-d dietary	LC_{50}: 3,663 ppm NOEL: 1,780 ppm	2	ECOTOX

Test Species	Endpoint	Results	Kl. score	Reference
Mallard Duck	14-d oral gavage	LD_{50}: 232 mg/kg NOEL: <178 mg/kg	2	ECOTOX

D. Calculation of PNEC

The PNEC calculations for TTPC 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 (58.6 µg/L), *Daphnia* (25 µg/L) and algae (19 µg/L). No chronic toxicity studies are available on TTPC. 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 effect concentration of 19 µg/L for algae. The $PNEC_{aquatic}$ is calculated to be 0.019 µg/L (1.9×10^{-5} 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 7.316 mg/kg sediment wet weight.

The calculations are as follows:

$PNEC_{sed} = (K_{sed\text{-}water}/BD_{sed}) \times 1000 \times PNEC_{water}$
$= (493/1280) \times 1000 \times 0.019$
$= 7.316$ 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]

$K_{sed\text{-}water} = 0.8 + [(0.2 \times Kp_{sed})/1000 \times BD_{solid}]$
$= 0.8 + [(0.2 \times 1{,}025/1000 \times 2400]$
$= 493\ m^3/m^3$

Where:

Kp_{sed} = solid-water partition coefficient (L/kg)
BD_{solid} = bulk density of the solid phase (kg/m^3) = 2,400 [default]
$Kp_{sed} = K_{oc} \times f_{oc}$
$= 25{,}629 \times 0.04$
$= 1{,}025$ L/kg

Where:

K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for TTPC (25,629 L/kg) calculated from experimental values presented (Lupton et al., 2024 and Health Canada, 2018).
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 6.49 mg/kg soil dry weight.

The calculations are as follows:

$PNEC_{soil} = (Kp_{soil}/BD_{soil}) \times 1000 \times PNEC_{water}$
$= (513/1500) \times 1000 \times 0.019$
$= 6.49$ 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]
$Kp_{soil} = K_{oc} \times f_{oc}$
$= 25,629 \times 0.02$
$= 513\ m^3/m^3$

Where:
K_{oc} = organic carbon normalised distribution coefficient (L/kg). The K_{oc} for TTPC (25,629 L/kg) calculated from experimental values presented (Lupton et al., 2024 and Health Canada, 2018).
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).

TTPC is inherently or readily biodegradable; thus, it does not meet the screening criteria for persistence.

The log K_{ow} for TTPC is 2.45. Thus, TTPC does not meet the screening criteria for bioaccumulation.

There are no chronic aquatic toxicity studies available on TTPC. The lowest acute E(L)C50 value for TTPC is <1 mg/L in algae. Thus, TTPC does meet the criteria for toxicity.

The overall conclusion is that TTPC is not a PBT substance.

IX. CLASSIFICATION AND LABELLING

A. Classification

)
H302 Acute Toxicity Category 4 [Oral]
H330 Acute Toxicity Category 1 [Inhalation]
H314 Skin Corrosion Category 1
H318 Eye Damage Category 1
H400 Aquatic Acute Category 1
H410 Aquatic Chronic Category1

B. Labelling

Danger

C. Pictogram

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.

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

Flush with plenty of fresh water for 15 minutes holding eyelids open, lifting eyelids occasionally to ensure complete removal of the product. DO NOT allow rubbing of eyes or keeping eyes closed. Remove contact lenses. Seek medical advice.

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). Do NOT induce vomiting. Seek medical advice immediately.

B. Firefighting Information

Extinguishing Media

Suitable 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: carbon monoxide, carbon dioxide, phosphorus oxides, chlorine.

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 spilled 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 Spilled

Use an absorbent material to recover as much product as possible, and 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

Keep container closed when not in use. Store in a cool well-ventilated area.

E. Exposure Controls / Personal Protection

Occupational Exposure Standards

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

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: 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

UN2922 CORROSIVE LIQUID, TOXIC N.O.S. (contains tributyltetradecyl phosphonium chloride)
Class 8 and 6.1
Packing Group: II

Environmentally Hazardous Substance.

XI. DISPOSAL MANAGMENT

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

XII. REGULATORY STATUS

Australian AICS Inventory: Listed.

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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

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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

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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

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