Ethanol, 2,2'-oxybis-: Human health tier II assessment

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CAS Number: 111-46-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Diethylene glycol (DEG) 2,2'-Oxydiethanol 2,2'-Oxybisethanol Dihydroxydiethyl ether Diglycol
Structural Formula	
Molecular Formula	C4H10O3
Molecular Weight (g/mol)	106.12
Appearance and Odour (where available)	The chemical is an odourless, colourless, viscous and hygroscopic liquid with a sharply sweetish taste.
SMILES	C(O)COCCO

Import, Manufacture and Use

Australian

The chemical is listed on the 2002 High Volume Industrial Chemicals List (HVICL) with a total reported volume between 1000 and 9999 tonnes. Reported uses include cosmetic ingredients, anti-freezing agents, colouring agents and solvents (NICNAS, 2002).

International

Annual production and/or import volumes of the chemical were reported above 100000 tonnes in the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers.

The following international uses have been identified through the EU REACH dossiers, Galleria Chemica, Substances in preparations in Nordic countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature Cosmetic Ingredients (INCI) database, and US Household Products database.

The chemical has reported cosmetic use including in:

- fragrance ingredients;
- solvents; and
- viscosity decreasing or controlling agents.

The chemical has reported domestic use including in:

- car care products;
- carpet and tile adhesives;
- ink cartridges;
- paints and varnishes; and
- detergents and cleaning/washing agents.

The chemical has reported commercial use including in:

- auto products;
- construction materials;
- cooling agents;
- industrial solvents;
- pigments in paint and printing;
- textile impregnation agents; and
- developers for photographic film.

The chemical has reported site-limited use including in:

- laboratory agents;
- catalysts;
- raw materials for synthesis and intermediate products; and
- plastics production.

Restrictions

Australian

The chemical is listed in the Poisons Standard (SUSMP–Standard for Uniform Scheduling of Medicines and Poisons 2012) in schedules 5 and 6, and Appendix C:

- Schedule 5 'Diethylene glycol (excluding its salts and derivatives) in preparations containing not less than 10 mg/kg of denatonium benzoate as a bittering agent except:

(a) in paints or paint tinters;

(b) in toothpastes or mouthwashes containing more than 0.25 per cent of diethylene glycol; or

(c) in other preparations containing 2.5 per cent or less of diethylene glycol.'

- Schedule 6 'Diethylene glycol (excluding its salts and derivatives) except:

(a) when included in Schedule 5;

(b) in paints or paint tinters;

(c) in toothpastes or mouthwashes containing more than 0.25 per cent of diethylene glycol; or

(d) in other preparations containing 2.5 per cent or less of diethylene glycol.'

- Appendix C 'Diethylene glycol for use in toothpastes or mouthwashes except in preparations containing 0.25 per cent or less of diethylene glycol.'

International

EC Cosmetics Directive Annex II (List of Prohibited Substances):

- DEG is prohibited in cosmetic products.

EC Cosmetics Directive Annex III (List of Restricted Substances):

- DEG (as traces in ingredients) is restricted to 0.1 % maxium in the finished cosmetic products.

Health Canada List of Prohibited and Restricted Cosmetic Ingredients (Hotlist):

- DEG is 'not permitted in oral or leave-on products'.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous with the following risk phrase for human health in HSIS (Safe Work Australia):

Xn; R22 (Harmful if swallowed)

Exposure Standards

Australian

TWA (time weighted average) = 100 mg/m^3 (HSIS, Safe Work Australia).

International

TWA = 101 mg/m^3 [UK] (HSE, 2013).

Health Hazard Information

Toxicokinetics

Diethylene glycol (DEG) is rapidly and almost completely absorbed via the oral route in laboratory animals. Up to 96 % of DEG was absorbed within two hours in rats after single gavage doses of 1120 and 5600 mg/kg bw.

DEG is slowly absorbed via the skin. Dermal bioavailability of DEG was estimated as 9 %. However, since no information is available about how this dermal absorption value was estimated, SCCP (2008) used 100 % dermal absorption in the risk considerations.

No studies on the absorption of DEG after inhalation exposure are available. However, because of its polar and hygroscopic characteristics, DEG in vapour or aerosol form is likely to be absorbed soon after it enters the upper respiratory passages.

Due to its high water solubility and low partition coefficient, DEG is rapidly distributed from the blood throughout the aqueous tissues of the body with lower concentrations in adipose tissues in the order: kidneys > brain > spleen > liver > muscle > fat (i.e. the same order as the blood flow) with the volume of distribution determined as 1 L/kg bw, indicating widespread distribution.

In animals, the metabolic pathway for DEG is oxidation via alcohol dehydrogenases and aldehyde dehydrogenases (ADH/ALD). Identified DEG metabolites include CO_2, 2-(hydroxyethoxy)acetic acid (2-HEAA), and oxalic acid. In rats, oxalic acid is not a significant metabolite.

DEG and its metabolites are readily cleared from the blood and excreted in the urine. Depending on the dose administered, approximately 45−70 % of the total oral dose is excreted unchanged in the urine within 48 hours, and 11−37 % as 2-HEAA after oxidative metabolism. The plasma half-life of DEG was found to be dose-dependent and the metabolism and/or elimination (either via urine or exhaled CO_2) may become saturated. An elimination half-life of 3.6 hours was calculated following multiple dosing, which followed a first order kinetic pattern. Excretion in the faeces accounts for minor amounts, between 0.7−2.2 % of the total dose (Health Council of the Netherlands, 2007; NICNAS, 2009; SCCP, 2008).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). While the animal data are not in the range for classification, the available human data support this classification.

The chemical was of low acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) was 15600 mg/kg bw in rats. Acute exposure to DEG at 15600 caused effects in the nervous system, the kidney and, to a lesser extent, the liver. Macroscopic and histopathological effects included hydropic degeneration of the kidney tubules and centrilobular areas of the liver, with oedema and haemorrhages (NICNAS, 2009; SCCP, 2008).

Animals and humans show similar clinical signs of toxicity (See **Observation in humans**).

Dermal

The chemical was of low acute toxicity in animal tests following dermal exposure. The median lethal dose (LD50) was 12500 mg/kg bw in rabbits (NICNAS, 2009).

Inhalation

The chemical was of low acute toxicity in animal tests following inhalation exposure, with no mortalities or toxic effects observed (median lethal concentration—LC50 > 4600 mg/m³/4 hours (aerosol) in rats and LC50 > 130 mg/m³/2 hour in mice) (NICNAS, 2009).

Observation in humans

Accidents in humans following acute DEG exposure have been recorded. A large number of mass poisonings in humans involving substitution of DEG for more expensive, non-toxic, glycols in medicinal preparations have been documented over the past 70 years. Typical features of acute toxicity include neurological impairment, metabolic acidosis and acute renal failure. Early mortality and morbidity are high, with most deaths occuring within the first two weeks following DEG exposure. Humans appear to be 10 times more susceptible to acute oral toxic effects of DEG compared with experimental animals, with median lethal dose of 1490 mg/kg bw in humans compared with > 15000 mg/kg bw in rats (NICNAS, 2009).

Corrosion / Irritation

Skin Irritation

The chemical is reported to slightly irritate skin in human and animal studies. The effects were not sufficient to warrant a hazard classification (NICNAS, 2009; OECD, 2004).

Eye Irritation

The chemical is reported to be a slight eye irritant in animal studies. Effects were not sufficient to warrant a hazard classification (NICNAS, 2009; OECD, 2004).

Sensitisation

Skin Sensitisation

The negative result observed for the chemical in an animal study (guinea pig maximisation test) supports a conclusion that the chemical is not a skin sensitiser (NICNAS, 2009; OECD, 2004; REACH, 2013).

Repeated Dose Toxicity

Oral

Available animal data suggest that repeated oral exposure to the chemical is associated with adverse health effects, mainly in the kidneys (oxalate crystalluria, increased urine volumes, hydropic degeneration and tubular necrosis) and, to a lesser extent, the liver (vacuolar degeneration). The 98-day and 225-day studies in rats established a no observed adverse effect level (NOAEL) of 300 mg/kg bw/d based on renal hydropic degeneration (histopathological findings) at 1600 mg/kg bw/d, and a NOAEL of 100 mg/kg bw/d based on increases in urine volume at 230 mg/kg bw/d.

It is noted that SCCP (2008) identified a 225-day NOAEL of 50 mg/kg bw/d based on the formation of oxalate crystals in the kidneys at 100 mg/kg bw/d. However, for the crystalluria, there were inconsistent findings between male and female rats and

questionable dose-response relationships. For example, the number of male rats with urinary oxalate crystals was not increased at the highest dose tested in the 225-day study. In addition, the observed increase in urinary volumes was possibly caused by the osmotic diuretic effect of DEG. The oxalate crystalluria could not be explained in view of oxalic acid being a minor metabolite of DEG in rats. Therefore, the significance of elevated oxalate formation was regarded as unclear and was considered a biomarker, not an indication of toxicity (Health Council of the Netherlands, 2007; NICNAS, 2009; OECD, 2004).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Severe adverse health effects including deaths have been documented in humans from inadvertent ingestion of DEG used as a glycerine substitute, or as a contaminant in medicinal preparations.

Early mortality and morbidity are high in cases of human DEG toxicity, with most deaths occurring within the first two weeks post exposure. A small number of cases of neurologic impairment (encephalopathy, demyelinating neuropathy, optic neuritis, unilateral facial paralysis, cerebral oedema and haemorrhages) have been reported.

Neurological effects were also noted during severe intoxications after uptake of DEG in patients with burns. The patients developed acute anuric renal failure with metabolic acidosis and concomitant severe neurological abnormalities progressing to coma and finally death. These incidents were attributed to the substitution of DEG for more expensive, non-toxic glycols in medicinal preparations. Typically, paracetamol elixirs have been involved, explaining the preponderance of paediatric deaths. Large overlaps in ranges of lethal and non-lethal doses have been noted for adults and children. After large-scale intoxication of Haitian children with a paracetamol syrup contaminated with DEG, it was estimated that a median lethal dose for DEG is 1490 mg/kg bw based on acute renal failure (O’Brien et al., 1998).

It is not clear from the reports whether the episodes of human ingestion of DEG were single or repeated occurrences.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

DEG was shown to be negative in the majority of gene mutation and chromosome aberration studies in vitro. Some indications of chromosomal damage were seen in vivo only at high doses (NICNAS, 2009).

Carcinogenicity

The available data do not support the carcinogenic potential of the chemical.

Urinary bladder calculus and tumour responses were recorded in some long-term oral studies in the rat. Bladder tumours were found associated with the formation of oxalate-containing bladder stones in a 2-year feeding study. However, DEG did not induce bladder tumours in rats unless a foreign body or lesion was present, such as an oxalate-containing bladder stone or a surgery-induced bladder lesion. These studies concluded that the observed bladder tumours were due to mechanical irritation by oxalate-containing bladder stones, rather than a carcinogenic response to DEG. In more recent studies, DEG did not demonstrate any evidence of carcinogenic effects after oral administration. Several studies in mice also showed that DEG is not carcinogenic after dermal application.

No information was found in the literature concerning the occurrence of bladder stones in humans after ingesting DEG. Overall, although some human carcinogenicity information is available, the data are insufficient (e.g. lack of a quantitative estimate of DEG exposure and sound methodology) to evaluate the carcinogenic potential of DEG. The International Agency for Research on Cancer (IARC) has not evaluated DEG as a carcinogen.

Reproductive and Developmental Toxicity

Available animal studies indicate that DEG induces adverse effects on fertility and development, but only at doses higher than those associated with repeated dose effects and in the presence of maternal toxicity.

Observed effects include reduced litter numbers, litter sizes and live pup weights in mice, and foetal abnormalities in rats and mice such as reduced foetal body weights, skeletal variations and/or malformations, and related mortality at high, maternally toxic doses.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral exposure).

Public Risk Characterisation

The chemical is currently listed on schedules 5 and 6 of the SUSMP, which require a number of warning statements, first aid instructions and safety directions. Appendix C of SUSMP also restricts the use of DEG, except for concentrations of 0.25 % or less in toothpastes or mouthwashes.

Schedule 5 (Caution) includes substances with low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

Schedule 6 (Poison) includes substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.

Appendix C includes substances, other than those included in Schedule 9, of such danger to health as to warrant prohibition of sale, supply and use.

The current controls are considered adequate to minimise the risk to public health posed by domestic and cosmetic products containing the chemical. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

Given the critical systemic acute health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls. Based on the available data, the hazard classification in HSIS is considered appropriate.

NICNAS Recommendation

The current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP).

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to label instructions.

Advice for industry

Control measures to minimise the risk from oral exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure; that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian,

Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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