Ethanol, 2-(2-methoxyethoxy)-: Human health tier II assessment

17 May 2013

CAS Number: 111-77-3

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.

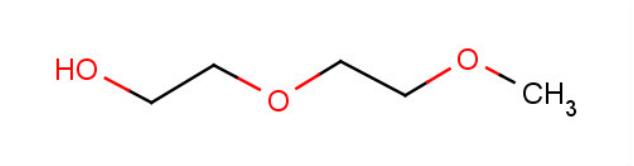
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Diethylene glycol, monomethyl ether Methyl carbitol Methyl diglycol ether 3,6-Dioxa-1-heptanol Methoxydiglycol
Structural Formula	
Molecular Formula	C5H12O3
Molecular Weight (g/mol)	120.147
Appearance and Odour (where available)	Colourless liquid, with a pleasant mild ether like odour and a bitter taste.
SMILES	C(O)COCCOC

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported commercial use including:

- a component of fuel additives

International

The following international uses have been identified via REACH dossiers, EU Risk Assessment Report, Canadian Screening Assessment Report, and OECD SIAR report.

The chemical has reported cosmetic use including as a:

- solvent or viscosity decreasing agent in some hairspray, skin creams and cleansers.

The chemical has reported domestic use including as a:

- component of detergents and cleaning/washing agents; and
- solvent in paints, paint stripper, and aqueous floor polishes. The chemical is reported to be present in a range of these type of products (liquid) up to a concentration of 15 % (Household Products Database, HHPD).

Information from the U.S. Environmental Protection Agency (EPA) 2012 Chemical Data Reporting (CDR) indicates that the chemical may be present in paints and coatings at concentrations > 90 %.

This chemical was reported to have commercial use including:

- an anti-icing agent in jet fuel and a diluent in hydraulic brake fluids;
- in dyes, nitrocellulose, resins and lacquers for setting the twist and conditioning of yarns and cloth;
- various ink and pharmaceutical applications; and
- a component in hydraulic fluids and windshield wiper fluids.

This chemical was reported to have site-limited use including as:

- a coupling agent for preparing miscible organic aqueous systems; and
- an intermediate in metallic solvents and mineral oil mixtures.

The following non-industrial uses have been identified internationally:

- a formulant in pest control products used in various applications; and
- a deactivator and stabiliser for agricultural formulations.

Restrictions

Australian

No known restrictions have been identified.

International

Cosmetics

EU Cosmetic Directive 76/768/EEC Annex II: *List of substances which must not form part of the composition of cosmetic products*.

Health Canada, Consumer Product Safety Bureau, Cosmetics Division, Canada *List of prohibited and restricted cosmetic ingredients* (The Cosmetic Ingredient "Hotlist"), March 2011.

New Zealand Cosmetic Products Group Standard—Schedule 4: *Components cosmetic products must not contain*.

The inclusion on the Health Canada Cosmetic Ingredient 'Hotlist' was an outcome of the 2009 screening assessment for the chemical (Government of Canada, 2009).

Other

European Union (EU), Commission Regulation (EC) No 552/2009 of 22 June 2009 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards Annex XVII. The chemical 'Shall not be placed on the market after 27 June 2010, for supply to the general public, as a constituent of paints, paint strippers, cleaning agents, self-shining emulsions or floor sealants in concentrations equal to or greater than 0.1 % by weight'.

The restriction in Annex XVII was based on the findings of the European risk assessment (EU RAR, 2000) on the chemical (carried out under Regulation (EC) No 1488/44), which concluded there was a need to limit the risks to consumers based on unacceptable estimated margins of exposure.

As an outcome of the 2009 screening assessment for the chemical (Government of Canada, 2009), Health Canada is proposing to introduce a regulatory limit such that the concentration of the chemical in surface coating materials must not exceed 10,000 mg/kg (or 1 % by mass). This measure would place a restriction on the manufacture, import, advertisement and sale of surface coating materials and was considered to adequately protect the health of the unborn foetus.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Repr. Cat. 3; R63

Exposure Standards

Australian

No specific exposure standards are available.

International

The following are identified (Galleria Chemica):

An exposure limit (OEL, TWA, STEL, PEL or STV) of 45–50 mg/m³ (10 ppm) in different countries such as France, Germany, Ireland, Norway, Spain and the United Kingdom.

Health Hazard Information

Toxicokinetics

In vivo studies (HSDB, 2013) have shown that the chemical can be absorbed across the skin of rabbits and from the gastrointestinal tract of rats. In vitro studies in humans showed that the chemical (98 % purity) was readily absorbed through the human epidermis at a rate of 0.206 ± 0.156 mg/cm²/hr (EU RAR, 2000).

Acute Toxicity

Oral

The chemical was reported to have low acute toxicity from oral exposure;

(LD50 in rats > 5500 mg/kg bw) (EU RAR, 2000).

Dermal

The chemical was reported to have low acute toxicity from skin exposure;

(LD50 in rabbits > 6540 mg/kg bw) (EU RAR, 2000).

Inhalation

The chemical was reported to have low acute toxicity via inhalation. LC50 (one hour) in rats > 200 mg/L. The chemical produced no mortality in rats exposed to the saturated vapour at 20 °C with eight hours of exposure (EU RAR, 2000).

Corrosion / Irritation

Skin Irritation

The chemical was reported to not cause irritation following occluded dermal application in rabbits (EU RAR, 2000).

Eye Irritation

In an eye irritation study in rabbits, application of the chemical (0.1 ml) resulted in a primary irritation score of 0.53. In a further study conducted in rabbits, slight erythema was observed three hours after application of the chemical. This effect resolved within 24 hours of application (REACH). Effects were not sufficient to warrant a hazard classification (EU RAR, 2000).

Sensitisation

Skin Sensitisation

No evidence of sensitisation was observed in a guinea pig maximisation test with the chemical (EU RAR, 2000).

Observation in humans

The chemical was applied in a patch test on 25 subjects at concentrations of 25 and 20 %; no signs of sensitisation were observed (EU RAR, 2000).

Repeated Dose Toxicity

Oral

There are three separate oral gavage studies on rats with the chemical where the dose period ranged from 11 days to six weeks (EU RAR, 2000; Government of Canada, 2009). The lowest no observed adverse effect level (NOAEL) (in the 6-week study) was 900 mg/kg bw/d, based on effects in the liver, kidneys, heart and testis at the higher doses.

Dermal

In a 90 day study in guinea pigs with occlusive application of the chemical for 5 days/week and 6 hours/day at doses of 40, 200 or 1000 mg/kg bw/day, decreased spleen weight was seen at doses of ≥ 200 mg/kg bw/day (EU RAR, 2000). There were also slight histopathological changes (hepatocellular vacuolar fatty change) in the liver and elevated urinary calcium levels at ≥ 40 mg/kg bw/day, and hence the lowest observed effect level (LOEL) was set at 40 mg/kg bw/d. The histopathological changes in the liver were observed at a higher incidence at the higher doses, although no associated liver effects such as increased liver weight were observed at any dose (EU RAR, 2000; REACH; 2011).

Inhalation

In a 90 day study in rats at the maximum practically obtainable concentration, no adverse effects were observed (EU RAR, 2000; Government of Canada, 2009). The NOAEC is > 1060 mg/m³.

Genotoxicity

Overall the data reveal that the chemical has no mutagenic or genotoxic potential. The chemical was not mutagenic to bacteria and did not cause chromosomal aberrations in mammalian cells, both with and without metabolic activation (EU RAR, 2000).

Carcinogenicity

No data are available for the chemical, although, considering data for similar chemicals (DEGBE (CAS No. 112-34-5) and EGBE (CAS No. 111-76-2)), there is limited evidence of a carcinogenic effect (EU RAR, 2000).

Reproductive and Developmental Toxicity

The chemical is currently classified as hazardous as a Category 3 reproductive toxin with the risk phrase ‘Possible risk of harm to the unborn child’ (T; R63) in HSIS (Safe Work Australia). The available data support this classification.

The chemical did not produce any adverse effects on rats or mice in oral fertility studies at doses up to 4000 mg/kg bw/d in drinking water, or 610 mg/kg bw/d by gavage. However, in an oral gavage repeat dose toxicity study, testicular atrophy and altered sperm production, along with significantly reduced absolute and relative testes weights, were seen at a dose rate of 3600 mg/kg bw/day. Significantly reduced relative testes weights were also observed at 2000 mg/kg bw per day in a 20-day gavage study in rats. The NOAEL was established as 900 mg/kg bw/day (Government of Canada, 2009; EU RAR, 2000).

In a range of developmental studies, the chemical was administered by oral gavage, subcutaneously or by dermal application on rats, mice and rabbits (EU RAR, 2000). Effects observed in the oral studies in the absence of maternal toxicity include a reduction in the number of viable offspring, delayed ossification and visceral malformations especially of the cardiovascular system and thymus. Effects observed in the dermal study in the absence of maternal toxicity included significantly delayed

ossification in the foetal skull and cervical vertebrae. The maternal NOAEL in the developmental studies was 600 mg/kg bw/day (oral) and 250 mg/kg bw/day (dermal), with the NOAEL for foetotoxicity being 200 mg/kg bw/day (oral) and 50 mg/kg bw/day (dermal).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are systemic and long term, particularly developmental toxicity. The lowest NOAEL from animal studies for developmental effects was 50 mg/kg bw/day. In addition, slight histopathological changes in the liver and elevated urinary calcium levels were observed in guinea pigs, following repeated dermal exposure to the chemical with a LOEL of 40 mg/kg bw/day. In both repeat-dose and developmental studies, effects were seen at lower doses following dermal administration, than for oral administration.

Public Risk Characterisation

The predominant use of the chemical is expected to be in jet fuel. It is unlikely that the public will be exposed to this chemical from this use and, as such, the public risk from this chemical in jet fuel is not considered to be unreasonable.

However, although use in cosmetic/domestic products in Australia is not known, the chemical is reported to have potential use in cosmetic/domestic products overseas at concentrations typically up to 15 % and possibly as high as 90 %.

Canada, New Zealand and the European Union have restricted the use of this chemical in cosmetics. Europe has also restricted the use of the chemical in paints, paint strippers, cleaning agents, self-shining emulsions or floor sealants for supply to the general public. In Canada, a restriction of the chemical in surface coating materials is proposed. Currently, there are no restrictions on the use of this chemical in Australia.

The restrictions in Canada and Europe were based on risk assessments conducted internationally (EU RAR, 2000; Government of Canada, 2009). The margins of exposure estimated in these risk assessments (< 100 for some products) indicate that the chemical may pose an unreasonable risk to the public when present in paint, paint strippers, other surface coatings and floor cleaners at concentrations between

5–10 %. The estimated margins of exposure are considered applicable in the Australian context, therefore the use of the chemical in paint, paint strippers, other surface coatings and floor cleaners has the potential to pose an unreasonable risk in the absence of any regulatory controls. The risks could be mitigated by implementing concentration limits.

Given the potential for developmental effects, the use of the chemical in cosmetics has the potential to pose an unreasonable risk in the absence of any regulatory controls. The risks could be mitigated by implementing concentration limits. The margin of exposure based on the chemical's use in body creams, face cream, facial cleanser and hair spray at a weight fraction of 0.1 % in all these products was calculated to be greater than 100 in the screening assessment conducted by Environment and Health Canada, indicating an adequate margin of safety (Government of Canada, 2009).

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations may also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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), e.g. employer, at a

workplace, has adequate information to determine appropriate controls. Based on the available data the hazard classification in HSIS is considered appropriate.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products be managed through changes to poisons scheduling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Given the risk characterisation, it is recommended that the concentration of the chemical in cosmetics/personal care products and domestic products be restricted. The scheduling of the chemical to prohibit its sale, supply and use in cosmetic products at higher concentrations should also be considered.

Matters to be taken into considerations include:

- Restrictions have been placed on the chemical overseas in domestic and cosmetic products based on inadequate margins of exposure. There are no restrictions on the public availability of the chemical in Australia.
- While there is no information to confirm that the chemical is currently used in cosmetic and domestic products in Australia, these are known uses of the chemical.
- The critical health effect to consider for the chemical is developmental toxicity which appears to meet the factors for Schedule 6 for domestic products, but Schedule 7 for cosmetic products, as the risk cannot be mitigated by warnings or packaging, given that the potential use involves direct dermal application.

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)*	Suspected of damaging fertility or the unborn child - Cat. 2 (H361)

[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 dermal and inhalation 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;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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.

References

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