Ethanol, 2-phenoxy-: Human health tier II assessment

12 September 2013

CAS Number: 122-99-6

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.

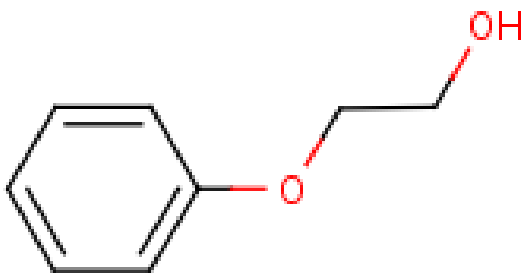
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-Phenoxyethanol Phenoxyethanol Phenylglycol ether Ethylene glycol monophenyl ether 2-hydroxyethyl phenyl ether
Structural Formula	
Molecular Formula	C8H10O2
Molecular Weight (g/mol)	138.16
Appearance and Odour (where available)	Colourless liquid with faint aromatic odour
SMILES	c1(OCCO)ccccc1

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 as a:

- softening agent; and
- solvent.

The following non-industrial uses have been identified in Australia:

- as an approved active constituent, in an agricultural or veterinary chemical product, by the Australian Pesticides and Veterinary Medicines Authority (APVMA).

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal: OECD High Production Volume chemical program—OECD HPV, the US Environmental Protection Agency's Aggregated Computer Toxicology Resource—ACToR, and the US National Library of Medicine's Hazardous Substances Data Bank—HSDB.

The chemical has reported cosmetic use in a range of products as a preservative and fixative for perfumes. It is reported to be present in a range of personal care products up to a concentration of 7 % (Household Products Database, US Department of Health and Human Services).

The chemical has reported domestic use including in:

- cleaning products;
- laundry cleaning products;
- textile colourants for hobby use; and
- children craft products such as acrylic paints and glitter glue.

Consumer products are reported to typically contain 5-15 % of the chemical (Household Products Database, US Department of Health and Human Services; OECD 2004).

The chemical has reported commercial use including in:

- textile processing;
- metal working;
- construction;
- coatings and inks;
- adhesives; and
- lubricants and greases.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- EU Cosmetic Directive 76/768/EEC Annex V—List of preservatives allowed in cosmetic products;
- New Zealand Cosmetic Products Group Standard - Schedule 7: Preservatives cosmetic products may contain with restrictions - Table 1: List of preservatives allowed; and
- ASEAN Cosmetic Directive Annex VI Part 1: List of preservatives allowed for use in cosmetic products.

The chemical is allowed as a preservative in cosmetic products at a maximum concentration, in ready for use preparations, of 1 %.

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):

Xn; R22 (acute toxicity)

Xi; R36 (irritation)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA, STEL, PEL or STV) of 100–230 mg/m³ (20−40 ppm) in different countries such as Germany, Canada (Ontario), Poland and Switzerland.

Health Hazard Information

Toxicokinetics

Rapid absorption of the chemical following oral and dermal administration has been observed in vivo (animal studies) and in vitro (human and rat skin). In the in vitro studies, up to 60 % dermal absorption was observed, although the contribution of the solvent (methanol) to this absorption was not clear (OECD 2004, REACH).

Following absorption, the chemical is widely distributed throughout the body. The majority of the chemical is excreted in the urine. The major metabolite is 2-phenoxyacetic acid. This is consistent with other monosubstituted glycol ethers for which alcohol dehydrogenase isozyme ADH-3 catalyses the conversion of the terminal alcohol to an aldehyde (which is a transient metabolite) and then further rapid conversion of the aldehyde by aldehyde dehydrogenase produces the 2-alkoxy acetic acid.

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). A large amount of acute toxicity data of varying reliability was available. Several studies considered reliable reported median lethal dose (LD50) values in the range of 1300−2000 mg/kg bw, supporting this classification (OECD 2004; REACH). Reported signs of toxicity include lethargy, increasing weakness, changes in motor activity and laboured respiration.

Dermal

The chemical was of low acute toxicity in animal tests following dermal exposure. The median lethal dose (LD50) in rats is greater than 2000 mg/kg bw. Observed sub-lethal effects included haemorrhagic lungs (OECD 2004; REACH).

Inhalation

The chemical was of low acute toxicity in animal tests following inhalation exposure with no mortalities or clinical signs of toxicity observed with the median lethal concentration (LC50) > 1000 ppm) (OECD 2004; REACH).

Corrosion / Irritation

Skin Irritation

The chemical is reported to slightly irritate skin in animal studies, particularly following repeated exposure. The effects were not sufficient to warrant a hazard classification (OECD 2004; REACH).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data support this classification.

In an eye irritation study in rabbits, the chemical was found to be irritating with well defined conjunctival redness and slight corneal opacity observed at 24, 48 and 72 hours (REACH). The majority of effects were reversible within the 15 day observation period.

Observation in humans

The chemical is reported to be non irritating to human skin up to concentrations of 10 % in several patch tests studies (OECD, 2004). Mild reactions were observed in five out of 12 people following application of the undiluted chemical to skin (REACH).

Sensitisation

Skin Sensitisation

The negative results seen for the chemical from several skin sensitisation guinea pig studies support a conclusion that the chemical is not a skin sensitiser (REACH).

Observation in humans

There is limited evidence of skin reactions consistent with allergic sensitisation in several patch test studies that have been conducted in humans (OECD, 2004, REACH). Weak sensitisation responses have been observed in some patients with contact dermatitis (REACH). This includes:

- one out of 3726 patients, suspected of having reacted to cosmetics, experienced an allergic reaction patch tested with 2-phenoxyethanol (0.4 % in petrolatum);
- a positive patch test for one patient out of 11 patients with dermatitis (5.0 % phenoxyethanol in petrolatum); and
- a positive patch test for one patient out of 501 patients with dermatitis (5.0 % phenoxyethanol in petrolatum).

Several negative patch test studies for the chemical tested up to 10 % have also been reported (maximum number of patients was 2736) (OECD 2004; REACH).

Repeated Dose Toxicity

Oral

Considering the no-observed-adverse-effect level (NOAEL) values and treatment-related effects reported in various repeat dose toxicity studies, the chemical is not considered to cause serious damage to health from repeated oral exposure.

In a 90-day oral gavage study in rats conducted according to OECD Test Guideline (TG) 408, a no-observed-adverse-effect level (NOAEL) of 700 mg/kg bw/day (nominal top dose tested in males) was reported. No significant toxicological effects were observed. Functional observation battery, motor activity data and the reflex testing did not provide indications of treatment related neurotoxic effects (REACH).

In an older, non guideline, 13-week gavage study, a NOAEL of 80 mg/kg bw/day was reported based on inflammation of the kidney observed at 400 mg/kg bw/day. Effects consistent with haemolysis were only observed at high doses (2000 mg/kg bw/day). Equivocal findings of tubular atrophy in the testes were also observed at this high dose (OECD 2004, REACH).

Haemolysis was observed at all doses (≥ 100 mg/kg bw/day) in a 10 day study in rabbits. Increased erythrocyte fragility was found in collected blood (REACH).

Dermal

Considering the no-observed-adverse-effect level (NOAEL) values and treatment-related effects reported in various repeat dose toxicity studies, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a 13 week dermal study in rabbits no significant toxicological effects including haemolytic changes were observed. The NOAEL was reported to be 500 mg/kg bw/day (top dose tested). Similar observations were reported in other rabbit studies (OECD 2004, REACH).

Inhalation

In a 14-day repeat dose inhalation toxicity study (OECD TG 412) in male and female Sprague Dawley rats, the no observed adverse effect concentration (NOAEC) for the chemical was reported to be 48.2 mg/m³ based on histopathological findings in the respiratory tract. Morphological changes indicating irritation potential of the test compound were found in nasal cavity, larynx and lung of animals treated with mid (246 mg/m³) and high (1000 mg/m³) doses.

Observation in humans

Three women who were occupationally exposed dermally and also possibly by inhalation to the chemical experienced headaches and symptoms of intoxication, as well as diminished sensation and strength in their hands and fingers. Although a persistent neuropathy was not observed, after 1–2 years of exposure, the women showed a gradual onset of symptoms of cognitive impairment and an inability to work. There are a number of limitations to these reports which makes it difficult to directly link the symptoms with exposure to the chemical (OECD, 2004; REACH).

Genotoxicity

The negative results for the chemical from several in vitro and in vivo genotoxicity studies supports a conclusion that the chemical is not genotoxic (OECD 2004; REACH).

Carcinogenicity

No carcinogenicity data are available.

Two carcinogenicity studies in rats and mice (2-year, via inhalation) are available for 2-butoxyethanol (CAS No. 111-76-2). A significant increase in the incidence of liver haemangiosarcomas was seen in male mice and forestomach tumours were observed in female mice. However, several international reviews of this data (OECD, United States and the European Union) have concluded that the results of these studies are not relevant to humans and that 2-butoxyethanol is not considered a human carcinogen (OECD, 2006; SCHER, 2008).

As the chemical is less potent, compared with 2-butoxyethanol, in causing haematotoxicity (which is the proposed mode of actions for the observed tumours (OECD, 2006; SCHER, 2008)), the chemical is not considered a human carcinogen.

Reproductive and Developmental Toxicity

There is no evidence of reproductive toxicity and developmental effects were only observed secondary to maternal toxicity, so the chemical does not show specific developmental toxicity.

In a two generation continuous breeding study in CD-1 mice, the NOAEL for both parental and foetal effects was reported to be 400 mg/kg bw/dose. Parental effects observed at higher doses (≥ 2000 mg/kg bw/day) included decreased body weight and liver weight. Foetal effects included reduced pup weight and higher lethality. Reduced body weight gain (in parents and pups) was also observed in Wistar rats following subcutaneous exposure to 444 mg/kg bw/day of the chemical. The NOAEL was established as 111 mg/kg bw/day. No developmental effects were observed following exposure from gestation days 6 to 18 in either rabbits exposed dermally (NOAEL 600 mg/kg bw/day) or rats exposed orally (NOAEL 1000 mg/kg bw) (OECD 2004; REACH).

Although certain short chain monoethylene glycol ethers such as 2-methoxyethanol (CAS No. 109-86-4) are known to cause reproductive toxicity, the ability of the glycol ethers to cause testicular toxicity decreases with increasing chain length. No effects were observed in % motile sperm, sperm concentration, or % abnormal sperm in cauda epididymidis in the two generation continuous breeding described above. In addition, no microscopic changes of the testes, seminal vesicles and coagulating gland were observed in a six week study in mice to investigate the testicular toxicity of the chemical (OECD 2004; REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity by the oral route of exposure) and local effects (eye irritation). Sensitisation may occur in susceptible individuals.

Although the chemical is also reported to cause haemolysis and associated organ toxicity, the severity of effects differs markedly between species, with humans appearing to be the least sensitive. Modelled data demonstrate that even at saturated concentrations of 2-butoxyethanol (a more potent haemolytic agent than 2-phenoxyethanol) it is not possible to reach haemolytic blood concentrations of the relevant metabolite in humans by the inhalation route of exposure (NICNAS, 1996; OECD, 2006).

Public Risk Characterisation

Although specific use in cosmetic/domestic products in Australia is not known, the chemical is reported to be used in cosmetic/domestic products overseas at concentrations up to 15 %.

Provided that normal precautions are taken to avoid prolonged eye contact, the public health risk posed by domestic and cosmetic products containing the chemical is expected to be minimal at concentrations reported internationally (up to 15 %).

Sensitisation may occur in susceptible individuals. Internationally, the chemical is allowed as a preservative in cosmetic products at a maximum concentration, in ready for use preparations, of 1 %. Currently, there are no restrictions on using this chemical in Australia.

Occupational Risk Characterisation

During product formulation, dermal and ocular 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 maintenance of 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 acute and local health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise 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

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.

Consideration should be given to the following:

- the toxicity profile at concentrations reported to be in use are reasonably consistent with the Scheduling Policy Framework guidelines for listing in Schedule 5;
- internationally, the chemical is allowed as a preservative in cosmetic products at a maximum concentration, in ready for use preparations, of 1 %; and
- generally the chemical was found to be well tolerated in patch testing in humans at up to 10 %.

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)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)

[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

Control measures to minimise the risk from oral and ocular exposure to the chemicals 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:

- 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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Last update 12 September 2013

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