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

28 June 2013

CAS Number: 108-01-0

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.

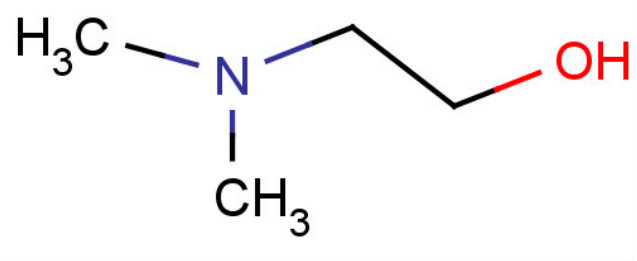
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Aminoethanol, 2-(dimethyl)- Dimethylamino ethanol Dimethylethanolamine N,N-Dimethyl-2-aminoethanol DMAE or Deanol
Structural Formula	
Molecular Formula	C4H11NO
Molecular Weight (g/mol)	89.136
Appearance and Odour (where available)	A colourless to slightly yellow volatile liquid, miscible with water with a amine like odour.
SMILES	C(O)CN(C)C

Import, Manufacture and Use

Australian

The following uses have been reported under previous mandatory and/or voluntary calls for information (NICNAS, 2006):

- used as a component of adhesives and binding agents, and in colouring agents; and
- a component of flotation agents and process regulators.

International

The following international uses have been identified through the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIARs), European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Substances in preparations in nordic countries (SPIN), Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) and the European Commission Cosmetic Ingredients and Substances (CosIng) database.

The chemical has reported cosmetic use:

- as a buffering agent in cosmetic products.

The chemical has reported domestic use including in:

- paints, lacquers and varnishes; and
- cleaning/washing agents.

The chemical has reported commercial use as:

- a dispersant aid and neutralising agent in waterborne paint products; and
- an additive in concrete and cement.

The chemical has reported site-limited use as a:

- catalyst in the production of flexible and rigid polyurethane foams and polyurethane lacquers;
- reactant in the manufacture of ion exchange resins and pharmaceuticals; and
- component of corrosion inhibitor formulations.

Restrictions

Australian

This chemical is listed in the Poisons Standard (SUSMP) under Schedule 4 (prescription only medicine, or prescription animal remedy).

International

EU regulation (EC) No 1223/2009 Annex III: List of substances which cosmetic products must not contain except subjected to the conditions laid down. Conditions—This chemical is restricted under 'trialkylamines, trialkanolamines, and their salts' where the maximum concentration allowed in leave-on products is 2.5 %; The following conditions apply to all products—do not use with nitrosating systems; minimum purity 99 %; maximum secondary amine content 0.5 % (applies to raw materials); maximum nitrosamine content 50 µg/kg; and keep in nitrite-free containers.

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; R20/21/22 (acute toxicity)

C; R34 (corrosive)

Exposure Standards

Australian

The chemical has an exposure standard of 7.4 mg/m³ (2 ppm) time weighted average (TWA) and 22 mg/m³ (6 ppm) short-term exposure limit (STEL).

International

The estimated exposure in the workplace is up to 5 ppm (OECD, 2001).

Health Hazard Information

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). The data available support this classification.

The chemical was administered by gavage to Sprague Dawley rats at doses of 800, 1200 or 2500 mg/kg bw. The animals were observed daily for toxicological effects through to day 14. The test material caused dose-dependent mortalities in the exposed animals. Decreased activity and muscle tone, ptosis (drooping) of the eyelid, abnormal gait, abnormal stance, chromodacryorrhea (tears that have some blood in them), diarrhoea, tremors, prostration and dyspnoea (difficulty breathing) were observed in treated animals. A post mortem of the animals that died during the study revealed fluid-filled and distended stomachs and intestines. No visible lesions were observed in animals examined after death. Based on the results, the LD50 in rats was estimated as 1183 mg/kg bw (1203 mg/kg bw in males and 1220 mg/kg bw in females).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in HSIS (Safe Work Australia). The dermal LD50 of 1220 mg/kg bw in rabbits supports this classification.

Dermal LD50 values of 1220 and 3135 mg/kg bw have been reported in rabbits. Signs of toxicity were not reported (OECD, 2001).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in HSIS (Safe Work Australia). Although the LC50 value available does not support this classification, based on the limited human evidence available (see **Observations in humans**), this classification was not amended.

An LC50 value of 6.5 mg/L was obtained in an inhalation study in rats. Signs of toxicity included respiratory difficulties, loss of coordination and decreased motor activity (OECD, 2001).

Observation in humans

In humans, no adverse effects were recorded in a case of deliberate ingestion of 2500 mg of the chemical (OECD, 2001).

One case report on the chemical states that a spray painter suffered from respiratory symptoms including wheezing and dyspnoea. However, exposure details were not available for this incident (OECD, 2001).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase 'Causes burns' (C; R34) in HSIS (Safe Work Australia). The data available support this classification.

The chemical is corrosive in animal tests, causing extreme reactions to the skin and eyes. Therefore, it would be expected to cause dermal, eye and respiratory tract irritation in humans (OECD, 2001).

Exposure to the undiluted chemical is likely to cause unpleasant local effects including burns. Several studies have shown the chemical to be an eye irritant (REACH, 2012).

Sensitisation

Skin Sensitisation

The available data suggest that the chemical is a skin sensitiser at concentrations above 10 %. The chemical did not produced skin sensitising effects at 5 % or 6 % concentration. In a mouse local lymph node assay (LLNA) with the chemical, the test/control ratio for lymphocyte proliferation was well above the threshold value of three at 30 % concentration. Therefore, the chemical is classified as a skin sensitiser.

A mouse local lymph node assay (LLNA) conducted in 1989 reported positive results for the chemical at a 30 % concentration, indicating that the chemical has the potential to cause skin sensitisation. The chemical was tested at 0, 3, 10 and 30 % weight/volume. The test/control ratios were 0, 1.93, 2.13 and 14.50 respectively (ratio > 3.0 is considered an indication of a potential sensitiser) (OECD, 2001).

In a study conducted in 1988 (REACH, 2012), guinea pigs were treated epicutaneously with an occlusive (closed) dressing with a 6 % solution of the chemical in water for six hours per exposure. The chemical did not cause contact sensitisation after 10 applications at 6 % over a 3.5 week induction period. In the study, two guinea pigs were tested with 50, 25, 12.5 and 6.25 % each; 6 % was established as the highest non-irritating dose tested.

In another study conducted in 1998 (REACH, 2012), guinea pigs were intradermally challenged with a 5 % solution of the chemical in ethanol or water. This was followed after 14 days by epicutaneous induction with a 5 % solution of the chemical. The substance showed no clear skin responses suggestive of sensitisation. No allergic contact dermatitis was induced at a 5 % concentration. All positive control animals (challenged with 0.1 % of DNBC) showed clear effects.

Based on the positive results of the mouse LLNA (ratio > 3), the chemical is a skin sensitiser above a 10 % concentration, which would warrant a classification for skin sensitisation. However, the chemical is corrosive and the highest non-corrosive

concentration was not defined in the assay as required by OECD TG 429. In addition, the second study reported the highest non-irritating concentration as 6 %, at which it was not a skin sensitiser.

In a review article of recent advances and limitations of the LLNA (Anderson et al., 2011), the level of false positives was reported as one of the limitations. The LLNA may give an unacceptable number of false positives when non-sensitising irritants are tested. However, the stimulation index (SI) values (test/control ratio) obtained for non-sensitising irritants in the LLNA were most often low and close to the threshold level of three. In the LLNA with the chemical, the test/control ratio of lymphocyte proliferation was well above the threshold value (14.5) at a 30 % concentration.

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

Apart from decreased body weight gain and lesions in exposed areas due to the corrosive nature of the chemical, no other adverse systemic effects were reported in the single study available.

Groups of 20 rats/sex were exposed to the chemical vapour at 0, 8, 24 or 76 ppm for six hours/day, five days/week for 13 weeks. Decreased body weight gain and histopathological lesions of the eye, respiratory and olfactory epithelium were observed at 76 ppm. Transient corneal opacity occurred at the end of each of the exposure periods at 24 and 76 ppm. This reversible effect is likely to be due to the corrosive properties of the undiluted substance. The study included histopathological examination of the testes—no adverse effects were reported for this organ. The no observed adverse effect concentration (NOAEC) for systemic effects was 24 ppm, but the NOAEC was 8 ppm for local effects on the eye (OECD, 2001).

Genotoxicity

Based on the data available, the chemical is not considered genotoxic.

Three in vitro assays (bacterial mutagenicity, mammalian gene mutation (HGPRT) and sister chromatid exchange) gave negative results for genotoxicity (OECD, 2001).

An in vivo mouse micronucleus study with intraperitoneal administration of the chemical up to 860 mg/kg bw gave negative results for peripheral blood erythrocytes. The highest dose used was considered adequate considering the oral LD50 data (OECD, 2001).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Based on the limited data available, the chemical is not considered to have reproductive or developmental toxicity.

No reproductive studies are available. In a 90-day inhalation study with the chemical, no histopathological changes in the gonads were observed in rats up to 76 ppm (OECD, 2001).

In a developmental toxicity study (according to GLP), pregnant rats were exposed to the chemical (10, 30 or 100 ppm) by inhalation of vapour on gestational days six through to 15. There were no maternal mortalities. Maternal toxicity was observed: reduced body weight (at 100 ppm during and after exposures); reduced weight gain (during exposure, but not after the exposure); and ocular changes (more profound at 30 and 100 ppm, minimal and transient at 10 ppm). At sacrifice, maternal body weight was reduced at 100 ppm, but there were no treatment related changes in gravid uterine weight, body weight corrected for gravid uterine weight, or absolute or relative liver weight. There were no effects due to treatment in any reproductive parameters, including pre-and postimplantation loss and sex ratio. Foetal body weights per litter (for males and females but not for the total) were increased at 100 ppm relative to the controls. There were no dose-related increases in malformations (external visceral or skeletal). The incidence of foetal variations was insufficient to indicate a consistent pattern indicative of foetal toxicity. One foetal variation (split (bipartite) cervical centrum), was elevated at 100 ppm relative to the controls, but other indications of delayed ossification or of reduced foetal body weights were absent. There was no evidence of embryonic or foetal toxicity (including teratogenicity) at any dose level, including those which produced maternal toxicity. The study reported NOAECs of 10 ppm and 100 ppm for maternal and foetal toxicity, respectively (OECD, 2001), indicating that the chemical has no developmental toxicity.

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is the corrosive nature of the chemical. Skin irritation is possible above 6 % concentration. Skin sensitisation was only seen in animal studies at severely irritating concentrations. The chemical may also produce harmful effects by ingestion, skin contact and inhalation. Repeated exposure to vapours may cause transient eye effects.

Public Risk Characterisation

Considering that the chemical is used in cosmetics and domestic products, the main public exposure is expected to be through the dermal route. Inhalation and accidental ingestion may also be possible. However, as the chemical is expected to be used only as a buffering agent in cosmetics, high concentrations of the chemical as the free amine are not expected to be present in cosmetic formulations or products.

Duration of exposure to the chemical will depend on the type of product (i.e. a rinse-off or a leave-on cosmetic product). No data on the Australian use pattern are available for cosmetic use and there are no restrictions for using this chemical in Australia. The EU has restrictions on the use of this chemical in cosmetics (2.5 % maximum in leave-on products).

The irritant and corrosive properties of the chemical can be attributed to its strong alkaline nature. When used as a buffering agent in cosmetic products, extremes of pH are not expected and no irritation risk is likely.

The chemical is used as a dispersant aid and a neutralising agent in waterborne paint products (OECD, 2001). Although up to 5 % concentration is used in industrial products, only a fraction of a percent is used in consumer products (OECD, 2001). Therefore, the chemical at very low concentrations (< 1 %) in consumer products is not expected to cause unreasonable risk to the public.

Occupational Risk Characterisation

Occupational exposure to the chemical may occur through dermal and inhalation routes during manufacture and use (e.g. end product formulation).

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation section**). Given the critical health effects, the risk to workers from this chemical is considered high unless adequate control measures to minimise

occupational exposure to the chemical are implemented.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend the chemical to be risk managed for public safety from the potential use in cosmetics and/or domestic products through scheduling, and occupational health and safety through classification and labelling.

Regulatory Control

Public Health

The chemical (Deanol) is listed in Schedule 4 of the Poisons Standard (SUSMP) for therapeutic use. As a corollary to this scheduling, it is proposed that a separate entry in the Poisons Standard should be created. This should take into account the corrosive/irritant properties of the chemical/mixtures, and may include an exemption at low concentrations.

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 in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1 (H314)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[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 the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular 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 storage, handling and use of a hazardous chemical are dependent 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 isolation of operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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 selection of personal protective equipment can be obtained from Australia, 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 hazardous chemical are prepared; and
- managing risks arising from storage, 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 physical hazards of the chemical has not been undertaken as part of this assessment.

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