# 1,3-Hexanediol, 2-ethyl-: Human health tier II assessment

**01 July 2016**

## CAS Number: 94-96-2



## 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.

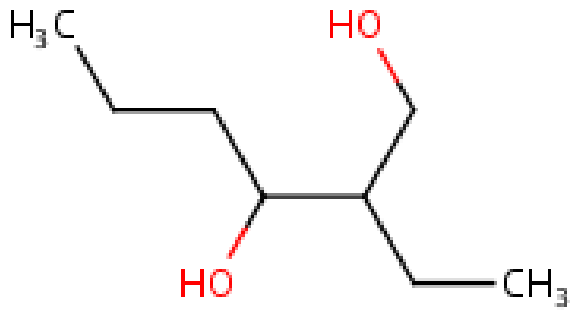
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | hexanediol<br>octylene glycol<br>ethohexadiol<br>ethylhexanediol |
| Structural Formula |  |
| Molecular Formula | C8H18O2 |
| Molecular Weight (g/mol) | 146.22 |
| Appearance and Odour (where available) | colorless, odourless, slightly oily liquid. |
| SMILES | C(C(O)CCC)(CC)CO |

# Import, Manufacture and Use

## Australian

No specific Australian use, import, or manufacturing information has been identified.

## International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS) (Bailey, 2011); and various international assessments (Andersen, 1994; Ballantyne, 2005; MAK, 2012).

The chemical has reported cosmetic uses as:

- a solvent and an emollient in cosmetic and personal care products (up to 5 % concentration); and
- as a fragrance ingredient.

Some of the reported domestic uses for the chemical were identified in the SPIN database. However, it should be noted that SPIN does not distinguish between direct use of the chemical, or use of the materials that are produced from chemical reactions involving the chemical. The reported domestic uses for the chemical include:

- in washing and cleaning products;
- as a solvent in metal-working fluids;
- as a blending agent in printing inks, latex paints and resins; and
- as an ingredient in adhesives and sealing agents.

The chemical has reported commercial uses, including:

- as a reactive component in urethane coatings;
- as a chelating agent for boric acid;
- as a viscosity reducer;
- in the manufacture of two-package urethanes;
- as a conditioning agent for cork products; and
- as a film-coalescing aid for latexes.

The chemical has reported site-limited uses as an intermediate for producing antioxidants and corrosion inhibitors.

The chemical has non-industrial uses, including in:

- pharmaceuticals;
- insect attractants, repellents and chemosterilants; and
- food products.

# Restrictions

## Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedules 4 and 10 (SUSMP, 2016).

Schedule 4 chemicals are described as 'Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.' Schedule 4 chemicals are labelled with 'Prescription Only Medicine', or 'Prescription Animal Remedy' (SUSMP, 2016).

Schedule 10 chemicals are described as 'Substances which are prohibited for the purpose or purposes listed for each poison.' The entry prohibits use of the chemical for any uses other than those allowed under schedule 4 (SUSMP, 2016).

## International

No international restrictions have been identified.

# 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):

- Xi; R41 (Risk of serious damage to eyes).

## Exposure Standards

### Australian

No specific exposure standards are available.

### International

No specific exposure standards are available.

# Health Hazard Information

## Toxicokinetics

The chemical is rapidly absorbed following oral exposure, but slowly absorbed through the skin. It is eliminated via the urine (as two major water soluble metabolites) and in the faeces.

In an in vivo toxicokinetics study conducted similarly to the Organisation of Economic Co-operation and Development (OECD) Test Guideline (TG) 417, male Fischer 344 (F344) rats (n = 6/dose) were intravenously injected with the radiolabelled chemical

at doses of 1.5 or 150 mg/kg bw. Temporary narcosis was observed at 150 mg/kg bw, which diminished after 5 minutes—this dose was selected as the maximum tolerated dose (MTD). Blood samples were collected via a jugular cannula at 2.5, 5, 10, 20 and 40 minutes and 1, 2, 4, 6, 12, 18, 24 and 48 hours (h) after dosing and urine was collected 6, 12, 24, 36 and 48 h after dosing. Samples were analysed for radioactivity. The maximum plasma concentrations of the chemical were 2.55 and 262.1 µg/g, for the 1.5 and 150 mg/kg bw doses, respectively. The distribution half-life was 11.0 and 25.7 min, and the elimination half-life was 8.67 and 8.20 h, for the 1.5 and 150 mg/kg bw doses, respectively. The majority of the radiolabelled chemical was rapidly excreted in the urine (72.4 and 64.3 % in the low and high doses, respectively); approximately 5 and 10 % was excreted in the faeces in the low and high doses, respectively; and less than 1 % was excreted in expired air (as $CO_2$) (Ballantyne, 2005; REACH).

In an in vivo toxicokinetics study (similar to OECD TG 417) conducted in male F344 rats (n = 4/dose), radiolabelled chemical was administered at 1.5 or 150 mg/kg bw once via oral gavage, or by dermal application (occlusive) to a clipped area of the back at 150 mg/kg bw for 48 h. There was 95.4 and 100 % absorption after the low and high oral doses, respectively; and 21 % of the chemical was bioavailable in plasma after first pass hepatic metabolism. Most of the chemical following dermal application resided in the occlusion materials and rinses, with recovery at 106.97 ± 6.93 % and 94.58 ± 21.09 % in males and females, respectively. The half-life for oral absorption was 0.14 h and 0.54 h for the low and high doses, respectively; the half-life for elimination was 12.9 h at both doses. The half-life for dermal absorption was 16.48 h, and the half-life for dermal elimination was 6.81 h. When administered by gavage, the chemical was transformed to two unidentified metabolites and excreted primarily in the urine (70–73 %); less was excreted in the faeces (7 %) and expired $CO_2$ (1.2 %). When administered dermally, most of the chemical was recovered from the patch, and elimination was mainly via the urine (Ballantyne, 2005; REACH).

In an ex vivo study conducted on the excised skin of humans (n = 3 females/dose), F344 rats (n = 3/sex/dose) and New Zealand White (NZW) rabbits (n = 3/sex/dose), the radiolabelled chemical was administered neat (under occluded conditions) or at 3 % aqueous solution (under occluded and open conditions). The dose absorbed following exposure to the neat chemical was 0.9 % through human skin; 2.1–3.6 % through rat skin; and 3.7–5.7 % through rabbit skin. Absorption of the diluted chemical (3 % v/v dose) was higher than absorption of the neat chemical: 5.1 % through human skin; and 6.5–9.3 % through rat skin. Approximately 25 % of the neat chemical administered evaporated from the skin. There was no skin metabolism of the chemical, evidenced by recovery of >99 % of the parent molecule in measurements of the receptor fluid (Ballantyne, 2005; REACH).

In a study conducted in dogs (n = 3/dose), the radiolabelled chemical (0.32 mg/$cm^2$) dissolved in 40 mg/mL ethanol was epicutaneously applied (occlusively) to a 5 $cm^2$ area of the dorsal skin for 48 h. Approximately 53 % of the applied dose was recovered from the patch and skin, and 10.3 % was excreted in the urine within four days (MAK, 2012).

In another study in dogs (n = 3, strain not specified), the radiolabelled chemical (79.5 µg) was intravenously injected into the left foreleg. Approximately 50–70 % of the administered dose was detected in the blood after 8 h, and 70–85 % of the administered dose was excreted in the urine within 12 h. Minor amounts of the chemical were excreted in faeces (Ballantyne, 2005; MAK, 2012).

## Acute Toxicity

### Oral

Based on the available data, the chemical has low acute oral toxicity.

The median lethal oral dose (LD50) in rats was reported to be in the range of 2710–9210 mg/kg bw/day. Observed sub-lethal effects included sluggishness, unsteady gait, poor bodily coordination, prostration (weakness/exhaustion) and congestion of the lungs and abdominal viscera (CIR, 1994; Ballantyne, 2005; REACH).

### Dermal

Based on the available data, the chemical has low acute dermal toxicity.

The dermal LD50 was reported as 8960–18700 mg/kg bw in rabbits, with sub-lethal effects including sluggishness, unsteady gait and prostration (CIR, 1994; Ballantyne, 2005; REACH).

### Inhalation

Based on the available data, the chemical has low acute inhalation toxicity.

No mortalities were reported in acute inhalation toxicity studies in rats at up to 3.8 mg/L after 4 h. A no observed adverse effect concentration (NOAEC) of 3.8 mg/L was reported (CIR, 1994; Ballantyne 2005; REACH).

## Corrosion / Irritation

### Skin Irritation

The chemical is reported to slightly irritate skin in animals and humans (see **Observation in humans** below). The effects are not sufficient to warrant hazard classification.

In an acute dermal irritation/corrosion study conducted according to OECD TG 404 in NZW rabbits (n = 3/sex), 0.5 mL of the undiluted chemical was applied occlusively to clipped dorsal trunk skin for a duration of 4 h and animals were observed for 14 days. Five animals were reported to show slight local erythema (redness) and one showed well-defined local oedema (swelling). All the effects were fully reversed within 24–48 h. The study was concluded that the chemical was slightly irritating to skin (CIR, 1994; Ballantyne, 2005; REACH).

In another study, 0.5 mL of undiluted chemical was applied occlusively to the shaved dorsal skin of guinea pigs (n = 5), nine times over 11 days. Slight erythema (in 2/5 animals) was observed after three applications and slight to moderate erythema (in 3/5 animals) was observed by the end of the study (CIR, 1994; MAK, 2012).

In an acute toxicity study conducted on NZW rabbits (n = 5/sex/group), the undiluted chemical was applied once under occlusive patches to the clipped skin of the trunks for 24 h at a dose of 8, 11.3 or 16 mL/kg bw in males and 4, 8 or 16 mL/kg bw in females. The rabbits were observed for 14 days. There were signs of inflammation, redness and swelling at the dosing site. Redness and swelling reversed by day seven, but desquamation (skin peeling) was still evident at the end of the study (CIR, 1994).

In a lifetime study in female Swiss mice (n = 50/dose), 0.2 mL of the chemical at concentrations of 10, 50 or 100 % in acetone was applied to shaved dorsal skin, twice weekly. Minimal local inflammatory changes including moderate dermatitis were observed (REACH).

### Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Risk of serious damage to eyes' (Xi; R41) HSIS (Safe Work Australia). The persistence of iris irritation for longer than 21 days in one study supports the existing classification.

In an ocular irritation study conducted in female rabbits (n = 3), 0.1 mL of the undiluted chemical was applied into the conjunctival sac of one eye. Clouding of the cornea, irritation of the iris and reddening and swelling of the conjunctivae were observed within one hour of chemical administration. Effects on the cornea were reversed within one week, effects on the conjunctivae reversed after 10 days, while the iris irritation remained after 21 days. The chemical was reported to be moderately irritating, with a Draize score of 35/110. Similar effects were reported in another two studies (MAK, 2012). No further details are available.

In an acute eye irritation study (similar to OECD TG 405) conducted in NZW rabbits (n = 6/treatment), the chemical was instilled into the conjunctival sac (0.1 mL) in one group and onto the cornea of the eye (0.01 or 0.005 mL) in two other groups. Animals were examined after 1 h, 24 h and 2, 3 and 7–14 days. The animals treated with 0.1 mL developed mild to severe conjunctivitis, mild to severe chemosis and mild to marked discharge. Moderate iris inflammation and moderate corneal injury were observed. Animals that were administered 0.01 or 0.005 mL had moderate to severe conjunctivitis at the first 24 h. An overall irritation

score of 80/110 was reported for the 1 h observation time point, with all effects being fully reversed within seven days (CIR, 1994; Ballantyne, 2005; REACH).

In another study conducted using NZW rabbits (n = 6), 0.1 mL of the neat chemical was instilled into the conjunctival sac of one eye; the eyes of three rabbits were washed immediately after chemical instillation, whilst the eyes of the other three rabbits remained unwashed. Both groups were observed immediately and after 1, 24, 48 and 72 h and 7 and 14 days after instillation. Fluorescein staining of the eyes was undertaken 24 h after dosing. Moderate to severe erythema and oedema of the conjunctivae and nictitating membranes (inner eyelids); slight erythema and oedema of the eyelids; slight corneal opacity; and discharge were observed in the unwashed eyes at 24 h. Irritation was less severe in the rinsed eyes, with slight to moderate erythema observed in the conjunctivae and nictitating membranes of the eyes at 1 h. Signs of irritation were reduced by seven days, and fully reversed by 14 days (CIR, 1994).

### Observation in humans

In a 21 day cumulative skin irritation study (equivalent or similar to the Draize method), human volunteers (n = 27, two males and 25 females) were administered two separate applications of the chemical (0.2 mL) under semi-occlusive and occlusive conditions for 24 h. This was repeated 15 times over 21 consecutive days. Slight skin irritation was observed for both exposure conditions. After 12 exposures, 70.3 % of the semi-occlusive sites showed barely perceptable erythema; and after 14 applications, 1/27 showed definite erythema. After 10 applications under occlusive conditions, 93 % of subjects had barely perceptable erythema; and after 12 applications, 4/27 showed definite erythema. It was concluded that repeated exposure produced minor primary skin irritation (CIR, 1994; Ballantyne, 2005; REACH).

In a primary irritation study (equivalent or similar to the Draize method), the chemical was applied to human volunteers undiluted (n = 30, 3 males and 27 females) or at 5 % in an aqueous solution (n = 106, 15 males and 91 females). The chemical was applied to two sites on the infraclavicular (below the clavicle) region of the skin; one occlusive and one semi-occlusive patch for 48 h. Observations were made immediately and 24, 48 and 72 h after removal of the patches. The chemical at 5 % produced barely perceptable erythema in 1/106 subjects in the occlusive (immediately after) and semi-occlusive application (immediately and 24 h after). Undiluted chemical produced barely perceptable erythema in 2/30 under semi-occlusive and 4/30 under occlusive applications at all time periods; and one subject had definite erythema after 72 h (CIR, 1994; Ballantyne, 2005; REACH).

## Sensitisation

### Skin Sensitisation

Based on the available data in animals and humans (see **Observation in humans** below), the chemical is not expected to be a skin sensitiser.

In a Magnusson and Kligman maximisation test, female guinea pigs (n = 20) were intracutaneously induced using the chemical at 1 %  in corn oil. Undiluted chemical was used for topical induction and challenge. No positive reactions were observed on challenge after 24–48 h (MAK, 2012).

A sensitisation test (according to the Kodak footpad method) was conducted using female Hartley guinea pigs (n = 10). Animals were exposed to the chemical at an induction dose of 0.05 mL of 1 % v/v in Freund's complete adjuvant (FCA), followed by a challenge dose of 1 mL of 10% v/v in a mixture of acetone/dioxane/guinea pig fat. No skin reactions were reported (CIR, 1994; MAK, 2012). No further details are available.

### Observation in humans

In a repeated insult patch test conducted in human volunteers (n = 203, 31 males and 172 females), 0.2 mL of the undiluted chemical was applied occlusively for 24 h, three times per week for three weeks. Following a two week rest period, a challenge patch was applied for 24 h on an untreated area of skin and observations made 24–48 h post-treatment. There were two incidences of definite erythema 48 h after the challenge patch was removed. With further testing, one of these subjects showed

a definite sensitisation response. Overall, it was concluded that the chemical is a weak skin sensitiser (CIR, 1994; Ballantyne, 2005; REACH).

## Repeated Dose Toxicity

### Oral

Based on the available data from experimental studies in animals, the chemical is not considered to cause serious health effects from repeated oral exposure.

In a repeated dose oral toxicity study (conducted similarly to OECD TG 407) in CD(SD)BR rats (n = 5/sex/dose), the chemical (in corn oil) was administered by gavage at doses of 0, 100, 300 or 1000 mg/kg bw/d, five days per week for 29 days. A no observed adverse effect level (NOAEL) of 100 mg/kg bw/d was reported, based on a dose-dependent increase in the mean leukocyte count in treated female groups, which was statistically significant at 300 and 1000 mg/kg bw/d. Treated males also had increased leukocyte counts, although this was not significant compared with controls. Females in the 1000 mg/kg bw/d also showed significantly lower platelet count, and increased relative and absolute liver weights. Significant increases in relative liver and spleen weights were observed in males at 1000 mg/kg bw/d. There were non-significant weight reductions in males at 300 and 1000 mg/kg bw/d on days 21 and 28. No mortalities or other signs of toxicity were reported (CIR, 1994; Ballantyne, 2005; REACH).

In a 90-day repeated dose oral toxicity study (conducted similarly to OECD TG 409) in Springer Spaniel dogs (n = 2–3/dose; 1 male, remaining females), the chemical was orally administered in diet at concentrations of 0, 0.1 or 0.5 mL/kg bw/d (equivalent to approximately 0, 93 and 466 mg/kg bw/d). Analysis was undertaken on blood samples collected after 0, 30, 60 and 87 doses. The NOAEL was determined to be >466 mg/kg bw/d, as no significant health effects were reported. There were no signs of abnormalities in the livers or kidneys (REACH).

In another 90-day study, the chemical was administered in diet to rats (strain not specified; n = 10) at doses of 200, 480 or 700 mg/kg bw/d. An NOAEL of 480 mg/kg bw/d was reported, based on reduced growth at the highest dose. No other treatment-related effects were seen (CIR, 1994; Ballantyne, 2005; REACH).

In a 2-year feeding study, rats were administered the chemical at 2, 4 or 8 % (equivalent to 1000, 2000 or 4000 mg/kg bw/d) in the diet. Reduction in growth rates were observed in all treatment groups. All animals in the 8 % dose group died within 18 weeks of the study due to anorexia. No other treatment-related effects were reported (MAK, 2012).

### Dermal

Based on the available data, repeated dermal exposure to the chemical is not considered to cause serious damage to health.

In a study conducted in F344 rats (n = 20/sex/dose; an extra 5 rats/sex were used in the high dose group and control), the chemical in water was administered via occlusive patch, at 0, 0.5, 2.0 or 4.0 mL/kg bw/d (equivalent to 471, 1884 and 3768 mg/kg bw/d) for 6 h/d, 5 days/week for 13 weeks. A subset of rats from the vehicle control and high dose group had a further six-week recovery period, where treatment was discontinued. An NOAEL of 1884 mg/kg bw/d was reported, based on significant decreases in body weight gain in females, and increases in relative liver weights in males, at the highest dose. These effects were reversed during the recovery period (Ballantyne, 2005; REACH).

In a study conducted in male albino rabbits (n = 8), the chemical at a dose of 0.9 mL/kg bw/d was rubbed into the clipped skin of the abdomen until absorbed, five times per week for 18 weeks. No evidence of toxicity was reported (CIR, 1994; Ballantyne, 2005).

### Inhalation

No data are available.

## 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.

The chemical gave mostly negative results in the following in vitro tests (CIR, 1994; Ballantyne, 2005; MAK, 2012; REACH):

- negative in an Ames test (similar to OECD TG 471) in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 exposed to the chemical at 0.3–28 mg/plate, with and without metabolic activation;
- positive with and without metabolic activation in a mammalian chromosome aberration test (similar to OECD TG 473) in Chinese hamster ovary (CHO) cells incubated with the chemical at 1–4.5 mg/mL, but the effects were not dose-dependent and/or occurred at doses where there was concurrent cytotoxicity;
- positive with metabolic activation in a mammalian chromosome aberration test (similar to OECD TG 473) using CHO cells exposed to the chemical at 1–4.5 mg/mL, but negative without metabolic activation using CHO cells exposed to the chemical at 1.3–2 mg/mL; and
- negative in a sister chromatid exchange (SCE) assay in CHO cells treated with the chemical at 1–3 mg/mL, with and without metabolic activation.

The chemical gave negative results in the following in vivo tests (CIR, 1994; Ballantyne, 2005; MAK, 2012; REACH):

- negative in a mammalian erythrocyte micronucleus test (similar to OECD TG 474) in peripheral blood cells from Swiss Webster mice (n = 5–10/sex/dose) intraperitoneally injected with the chemical once at 18.75–120 mg/kg bw;
- negative in a mammalian erythrocyte micronucleus test (similar to OECD TG 474) in bone marrow from SD rats (n = 5/sex/dose) intraperitoneally dosed with the chemical once at 60, 200 or 600 mg/kg bw; and
- negative in a mammalian erythrocyte micronucleus test (similar to OECD TG 474) in bone marrow from SD rats injected intraperitoneally with 500 mg/kg bw of the chemical in corn oil, once daily for five days.

## Carcinogenicity

The limited available data do not indicate that the chemical is a carcinogen.

In a study conducted in female Swiss mice (n = 50/dose), 0.2 mL of the chemical at 10, 50 or 100 % in acetone was dermally applied to shaved dorsal skin (area = 2.5 $cm^2$), twice weekly for 110 weeks. Survival was similar among the groups. The sites of chemical application showed skin lesions, inflammation and ulceration but few skin tumours (2–4 %). Tumour incidences (combined lymphomas, haemangiosarcomas or liver and lung adenomas) were recorded at 46 %, 56 % and 64 %, in the 10, 50 and 100 % groups, respectively, compared with 42 % in the control group (CIR, 1994; Ballantyne, 2005; MAK, 2012; REACH). The US Environmental Protection Agency (EPA) conducted statistical analyses on the raw data, which indicated oncogenic activity, but concluded the data were insufficient for an assessment (CIR, 1994; Ballantyne, 2005).

In a study, NZW rabbits (n = 5 /dose) were administered 0.02 mL of the chemical at 0, 10, 50 or 100 %, dermally to the left ear, twice a week for the lifetime of the animal. Survival was similar between control and treated groups, and no increases in tumours were reported in the treated groups (CIR, 1994; Ballantyne, 2005).

## Reproductive and Developmental Toxicity

The chemical shows specific developmental toxicity, but only at high doses.

In a developmental toxicity study (similar to OECD TG 414) in pregnant SD rats (n = 8/dose), the chemical (in corn oil) was administered by gavage at 500, 1000, 2000 or 4000 mg/kg bw/d on GD 6-15. The NOAEL for maternal and developmental toxicity was reported to be 1000 mg/kg bw/d. Mortalities were reported in the dams at 2000 mg/kg bw/d (1/8) and 4000 mg/kg bw/d (7/8). At doses ≥2000 mg/kg bw/d, signs of weakness, respiratory difficulty, dehydration, sialorrhoea (excess salivation), gait disturbances, nasal discharge, porphyrin tears, diarrhoea, decreased volume of faeces and unkempt coats were observed

in the dams. Hypothermia, partially closed eyes and excessive tearing were observed in the high dose group only. Lesions at necropsy showed that the chemical had the greatest effect in the stomach and duodenum; there was excess mucous in the caecum and atrophy of the thymus and adipose tissue. In foetuses from the 2000 mg/kg bw/d group, the incidences of malformations significantly increased (rudimentary or filamentous tails, malformation of rear limbs and joints, shortened trunk and umbilical hernia); and there were also increases in the incidence of haematoma (nine foetuses out of four litters). Two foetuses from different litters exposed to the chemical at 1000 mg/kg bw/d and one in the 500 mg/kg bw/d group had rudimentary tails (CIR, 1994; Ballantyne, 2005; MAK, 2012; REACH).

In a developmental toxicity study (similar to OECD TG 414) in pregnant SD rats (n = 25 mated females/dose), the chemical was dermally applied (occlusively) at 0, 1, 2 or 4 mL/kg bw/day (equivalent to 0, 935, 1870 and 3740 mg/kg bw/d) for 6 h per day on gestation days (GD) 6–15. Animals were euthanised on GD 21. The NOAEL for maternal reproductive toxicity was reported to be >3768 mg/kg bw/d based on no reported variations in the number of pregnancies, foetal body weights or reproductive factors. At the highest dose, terminal maternal body weights were decreased, and absolute liver weights were significantly increased. Mild skin irritation with exfoliation and crusting were observed in a few females at the mid and high doses. The NOAEL for developmental toxicity was reported to be 942 mg/kg bw/d based on a statistically significant but non-dose-dependent increase in the incidences of skeletal malformation (related to reduced ossification) in the foetuses from the mid and high dose groups, as well as visceral malformation (e.g. unilateral hydroureter) in the foetuses from the high dose groups. It was concluded that the chemical is a weak developmental toxicant (CIR, 1994; Ballantyne, 2005; REACH).

# Risk Characterisation

## Critical Health Effects

The critical health effect for risk characterisation is eye irritation. While there may be specific developmental effects, these are only likely at very high exposures.

## Public Risk Characterisation

Although use in cosmetic/domestic products in Australia is not known, the chemical is reported to be used in cosmetic/domestic products overseas. However, cosmetic use is reported to be limited (Andersen, 2011; Bailey, 2011) and actual domestic use is prohibited in Australia (see **Restrictions - Australian**).

Even exposed to the chemical through cosmetic use, given the low hazard of the chemical, the chemical would not pose an unreasonable risk to public health at concentrations up to 5 %. Existing controls are such that the chemical cannot be used in cosmetics or domestic products in Australia and therefore there is no likely risk.

The chemical is currently listed on Schedules 4 and 10 of the SUSMP. Based on the National Drugs and Poisons Scheduling Committee (NDPSC) record of reasons from the 26th meeting held in February 2000, it can be inferred that concerns about developmental toxicity are the reason for the Schedule 10 entry—'The Committee did not support exemption of ethylhexanediol from Appendix C [Schedule 10] because of the unacceptable risk of teratogenicity associated with the use of the substance' (NDPSC, 2000).

Based on the NDPSC record of reasons from the 49th meeting held in February 2007, it is noted that '… the Schedule 4 entry was only intended to capture animal therapeutic use, and that it remained appropriate for human therapeutic use to be captured by Appendix C [Schedule 10]' (NDPSC, 2007).

## Occupational Risk Characterisation

During product formulation, ocular exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could 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 local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise ocular exposure 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 the appropriate controls.

Based on the available data, the hazard classification in HSIS is considered appropriate.

# NICNAS Recommendation

Current risk management through the Poisons Standard is considered disproportionate for the risks identified. It is recommended that the Chemicals Scheduling Delegate re-evaluate the inclusion of the chemical in Schedules 4 and 10.

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

It is recommended that an amendment to the current listing of the chemical in the SUSMP be considered. Given the risk characterisation, it is recommended that the chemical entry in Schedules 4 and 10 be re-evaluated.

Consideration should be given to the following:

- the only critical health effect identified was eye irritation;
- publicly available data on reproductive toxicity indicated effects at high doses only and/or concurrent with maternal toxicity;
- there are no international restrictions;
- the most recent report on the chemical from the CIR (2011) concluded 'that ethyl hexanediol is safe as a cosmetic ingredient';
- cosmetic and/or domestic use is considered to be limited; and
- the chemicals 2-ethylhexanoic acid (and its alkyl esters) and 2-ethylhexanol (and its derivatives)—which are structurally similar, have similar uses but higher potency for critical health effects—are in Schedule 6 with a 5 % exemption cut-off or currently being considered by NICNAS as to whether Schedule 6 with appropriate low-level cut-offs are required, respectively.

### 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 and environmental hazards.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Irritation / Corrosivity | Risk of serious eye damage (Xi; R41)* | Causes serious eye damage - Cat. 1 (H318) |

[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 instructions on the label.

## Advice for industry

***Control measures***

Control measures to minimise the risk from occular 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 that could 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 help meet 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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