1-Hexanol, 2-ethyl-: Human health tier II assessment

12 September 2013

CAS Number: 104-76-7

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.

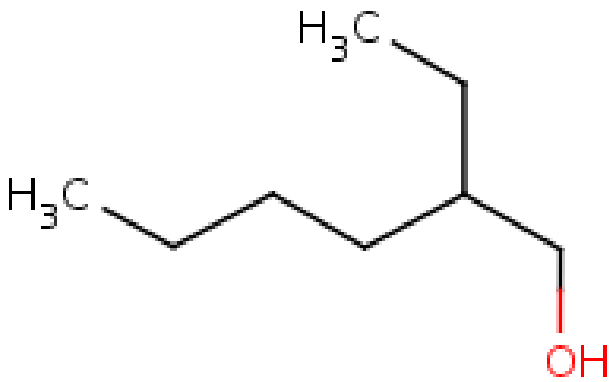
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-Ethyl-1-hexanol 2-Ethylhexyl alcohol 2-Ethylhexanol Ethylhexanol Octyl alcohol
Structural Formula	
Molecular Formula	C8H18O
Molecular Weight (g/mol)	130.229
Appearance and Odour (where available)	Clear, colourless liquid with an odour described as sweet, floral or intense.
SMILES	C(CCCC)(CC)CO

Import, Manufacture and Use

Australian

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

Reported commercial use including:

- in lubricants and additives;
- as a solvent;
- in colouring agents;
- as a softener; and
- as a viscosity adjuster.

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of 1000–9999 tonnes.

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, the substances and preparations in the Nordic countries (SPIN) database, the European Commission Cosmetic Ingredients and Substances (CosIng) database, the US National Library of Medicine's Household Products Database, and from eChemPortal sources including the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Reported cosmetic use as:

- a perfuming ingredient.

Reported domestic use including in:

- cleaning/washing agents; and
- printing inks.

Reported commercial use including:

- in anti-freezing agents;
- in reprographic agents; and
- as a solvent for dyes, resins and oils.

Reported site-limited use including:

- as an intermediate in the synthesis of platicisers, hexyl esters and acrylates.

Restrictions

Australian

While no known restrictions have been identified, the chemical is listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) under 'Octyl alcohols' in Appendix B, as not requiring control by scheduling for any use, due to low toxicity.

International

No known restrictions have been identified. However, the chemical is listed on the Ingredient Disclosure List (regulation (SOR 88-64) under Canada's Hazardous Products Act, 2006) with a disclosure limit of 1 % w/w; if the chemical is found in a controlled product above this concentration cut-off, its identity and concentration must be disclosed on a material safety data sheet (MSDS).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

Austria's Occupational Exposure Limits—Maximum Workplace Concentration (MAK):

Time Weighted Average (TWA) = 270 mg/m³ (50 ppm)

Short Term Exposure Limit (STEL) = 540 mg/m³ (100 ppm)

Switzerland's Occupational Exposure Limits:

TWA = 110 mg/m³ (20 pmm)

STEL = 110 mg/m³ (20 pmm)

Poland's Occupational Exposure Limits:

TWA = 160 mg/m³

STEL = 320 mg/m³

Health Hazard Information

Toxicokinetics

The chemical was reported to be rapidly absorbed, metabolised, and excreted, mainly via urine (80–82 %), within 28 hours following oral administration to rats (REACH). Excretion was also detected via faeces (8–9 %) and respiration (6–7 %). The major metabolite was reported to be 2-ethylhexanoic acid (CAS No. 149-57-5), present in urine, with only 3 % of the chemical in urine excreted unchanged. Both single (9–500 mg/kg bw) and repeated (50 mg/kg bw) dose administration to rats showed similar absorption and excretion profiles, with some evidence of saturation reported at the 500 mg/kg dose level.

Acute Toxicity

Oral

Acute oral studies (rat, mouse, guinea pig, rabbit) reported the chemical to be of low toxicity; median lethal dose (LD50) values were reported to be >3000 mg/kg bw (OECD, 1995).

The rat oral LD50 of the chemical was reported to be 3290 mg/kg bw in a study following a protocol similar to OECD Test Guideline (TG) 401(REACH). Deaths occurred within two days, and the animals died in narcosis (a state of unconciousness) without any other signs of toxicity. The dose levels administered and the number of animals per dose level were not reported.

Dermal

The chemical was reported to have low dermal toxicity in rats and rabbits. LD50 values were reported to be >2000 mg/kg bw (OECD, 1995)

The dermal rat LD50 was reported to be >3000 mg/kg bw (REACH) in an OECD guideline (TG 402) study. Five animals of either sex were exposed to 3000 mg/kg bw for 24 hours under a semi-occlusive dressing. No mortalities were observed within the 14-day observation period. Animals were reported to be excited for one hour following administration of the chemical. Observations reported during necropsy were red-coloured urine noted in one animal, and hyperaemic mucosa of the small intestine in two animals. No other observations were reported.

Inhalation

The chemical is considered to have moderate toxicity via inhalation. The rat median lethal concentration (LC50) was reported to be <5 mg/L (REACH).

Male and female Sprague Dawley (SD) rats were exposed to the chemical at 0.89 mg/L (vapour) or 5 mg/L (80 % aerosol, 20 % vapour mix) via inhalation for four hours (equivalent or similar to OECD TG 403). No mortalities or clinical signs of toxicity were noted in the 0.89 mg/L group within the seven-day observation period. However, all animals in the 5 mg/L group died, four of them during the exposure or shortly thereafter.

There is sufficient evidence to classify the chemical as an acute inhalation hazard.

Corrosion / Irritation

Skin Irritation

A skin irritation study in rabbits (OECD TG 404; semi-occlusive patch) reported severe erythema and oedema in all treated animals at 24 hours after treatment, persisting until 72 hours (REACH). Severe irreversible skin reactions, scab formation, desquamation and formation of new skin in all animals were reported during days six through 14 after patch removal. Scars and peeling scabs were observed within two weeks in all animals, indicative of full thickness destruction of skin tissue, and consistent with the criteria for classification of corrosive chemicals.

There is sufficient evidence to classify the chemical as corrosive (R34; causes burns).

Eye Irritation

In an eye irritation study in rabbits (OECD TG 405), severe iritis and moderate corneal opacity were seen in all animals at 24 and 48 hours after treatment (REACH). Slight chemosis (swelling and/or oedema of the conjunctiva) was reported in two animals and moderate reddening of the conjunctivae was seen in all animals at 24 and 48 hours after treatment. The effects were reported to be fully reversible within 21 days.

Observation in humans

In a study in 15 healthy males, sensory irritation symptoms (for eyes, nose and odour annoyance) were assessed and measured following four hours of inhalation exposure to the chemical vapour. The potential for sensory irritation at concentrations ≥10 ppm was supported (REACH).

Sensitisation

Skin Sensitisation

The chemical is not expected to be a skin sensitiser based on the limited data available (REACH).

In a dermal sensitisation study, the chemical was tested on 29 male human volunteers. For induction, 1.0 mL of the test substance was applied for 48 hours under occlusive conditions in five alternating repetitions. After a rest period of 10–14 days, a challenge exposure, consisting of a single occlusive application of 0.4 mL of the chemical was applied for 48 hours. Immediately after removal of the patch and after 48 hours, skin reactions were recorded. No allergic reactions were observed in any of the test subjects.

Repeated Dose Toxicity

Oral

OECD (1995) reported the no observed adverse effect level (NOAEL) in a repeat dose 90-day toxicity study in rats to be 125 mg/kg bw/day based on reported effects on the liver and stomach at the lowest observed adverse effect level (LOAEL) of 250 mg/kg bw/day.

A REACH dossier reported 'the NOEL (no observable effect level) was 125 mg/kg bw/day. A NOAEL (no observable adverse effect level) was not derived, but may be estimated to be 250 mg/kg bw/day'. An increase in relative liver, forestomach, and kidneys weights ($p<0.01$) was reported in male and female groups at 250 and 500 mg/kg bw/day. An increase in relative testis weights and a decrease in relative ovary weights were also noted at both doses. However, histopathology was reported to reveal changes only in the high dose (500 mg/kg bw/day) animals.

In a 21-day oral subchronic study in rats, the LOAEL was reported to be 100 mg/kg bw/day based on effects on the liver, kidneys and blood chemistry of both males and females (ESIS, 2000).

In a two-year study, the chemical was administered via oral gavage to male and female Fischer F344 rats at 0 (water), 0 (vehicle), 50, 150 or 500 mg/kg bw/day, five days per week, for two years. A dose-related increase in mortality was observed in female rats, with 52 % mortality reported at the highest dose. Significant increases in stomach, kidney and brain relative weights were also noted in male and female rats at 150 mg/kg bw/day, in addition to an increase in relative testis weight in male rats at 500 mg/kg bw/day. A NOAEL from this study is considerd to be 50 mg/kg bw/day.

Dermal

The chemical is reported to have a dermal subacute NOAEL of <1660 mg/kg bw/day (OECD, 1995).

In nine-day dermal repeated dose study, male and female rats (10 animals/sex/dose) were exposed to the chemical at either 417 or 834 mg/kg bw/day (REACH). Lymphopaenia (decreased blood levels of lymphocytes) and decreased spleen weight of high dose females, and increased triglycerides for females at both dose levels, compared with controls, were noted. Histopathological lesions were reported only at the site where the chemical was applied, and were associated with the irritancy of the chemical. No other treatment-related effects on clinical pathology measurements or organ weights were reported for males or females at either dose level. The LOAEL for systemic toxicity from this study is considered to be 417 mg/kg bw/day.

In another report, 10 male rats were exposed to the chemical for five days per week for 14 days at 2 mL/kg bw/day (1660 mg/kg bw/day) (REACH). On histological examination, effects were seen in the liver, lungs, kidney, heart, testes, thymus and adrenals. These included reduced thymus weight and decreased spermiogenesis.

Inhalation

In a repeated dose 90-day inhalation toxicity study in rats (OECD TG 413), the no observed adverse effect concentration (NOAEC) was reported to be 120 ppm; equivalent to 638.4 mg/m³ air (REACH).

No treatment-related effects were noted in male and female Wistar rats (10 rats/sex/dose) following exposure to either 15, 40, or 120 ppm (120 ppm was reported to be equivalent to saturation at 20 °C) compared with control groups.

Genotoxicity

The chemical was reported to be negative in bacterial point mutation tests and negative in both in vitro and in vivo chromosomal aberration tests (OECD, 1995).

In vitro

The chemical was reported to not be mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without metabolic activation, at concentrations between 3.3 and 330 µg/plate (REACH). Cytotoxicity, but not genotoxicity, was reported at the highest concentration.

In a gene mutation study similar to OECD TG 476 using mouse lymphoma cells (L5178Y), the chemical did not increase mutation frequency with or without metabolic activation at doses between 0.018 and 0.24 µL/ mL (REACH).

In vivo

In a cytogenetic assay using male rats (Fischer 344), the chemical did not induce detectable chromosome aberrations following oral administration at 0.02, 0.07 or 0.21 mL/kg bw/day for five days (ESIS, 2000). No significant increase in chromatid and chromosome breaks, or structural rearrangements, were noted.

Carcinogenicity

The chemical was reported to not be carcinogenic in a two-year study (equivalent or similar to OECD TG 451) in rats.

The chemical was administered via oral gavage to male and female Fischer F344 rats at 0 (water), 0 (vehicle), 50, 150 or 500 mg/kg bw/day, for two years, five days per week. It was reported that the number of primary, benign and malignant tumours was lower in the top dose group than in either of the control groups.

Reproductive and Developmental Toxicity

The chemical was reported to cause developmental toxicity, but not teratogenicity, in rats following exposure via the oral route (REACH). These effects were noted in the absence of signs of marked maternal toxicity. The OECD (1995) has reported the developmental toxicity NOAEL to be 130 mg/kg bw/day.

In a developmental toxicity study (OECD TG 414; deviation of 10 animals rather than 20 animals/group), female Wistar rats were administered the chemical on gestation days 6–15 via oral gavage at 0 (water), 0 (vehicle), 130, 650 or 1300 mg/kg bw/day (REACH).

In the 650 mg/kg bw/day dose group, foetotoxic effects included reduced mean foetal body weights (p = 0.01) and increased frequency of foetuses with skeletal variations and retardations. Piloerection observed in two dams was the only maternal toxic effect reported in the study at this dose.

In the highest dose group, maternal toxic effects reported included reduced body weights, severe clinical symptoms including lying in the lateral position, unsteady gait and apathy, in addition to discolouration of the liver and distinctly reduced mean uterus weights. Embryotoxic and foetotoxic effects reported at this dose included increased number of resorptions and postimplantation loss in dams, markedly reduced mean foetal body weights and a higher number of foetuses with skeletal malformations, variations and retardations.

No adverse substance related effects were reported in dams or foetuses at 130 mg/kg bw/day.

Although the study concluded that the maternal toxicity NOAEL was 130 mg/kg bw/day based on piloerection observed in two dams in the 650 mg/kg bw/day group, the developmental effects reported at this dose, in the presence of minimal maternal toxicity, provide sufficient evidence to classify this chemical as potentially toxic to development.

In other oral developmental toxicity studies, no maternal or developmental toxic effects were observed in mice at doses up to 191 mg/kg bw/day (US NTP, 1991), while in another study both maternal toxicity and foetoxicity were reported in rats at 1525 mg/kg bw/day (the only dose tested) (USEPA, 2006).

In a dermal study in rats, the chemical was administered by occluded dermal applications for six hours per day on gestation days 6–15 at doses of 0, 252, 840, and 2520 mg/kg bw/day. A NOAEL for maternal toxicity of 252 mg/kg bw/day was reported based on skin irritation; the developmental NOAEL was >2520 mg/kg bw/day, with no teratogenicity or treatment-related developmental effects reported (REACH).

The chemical's major metabolite, 2-ethylhexanoic acid (CAS No. 149-57-5), has also been assessed (NICNAS), and is classified as a Category 3 hazardous substance toxic to reproduction, with the risk phrase ‘Possible risk of harm to the unborn child’ (Xn; R63) in HSIS (Safe Work Australia).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (potential developmental toxicity), systemic acute effects (acute toxicity by the inhalation route of exposure), and local effects (corrosivity).

Public Risk Characterisation

Although the chemical is listed on CosIng, indicating potential use in cosmetic products, it is not listed in the US Personal Care Products Council's International cosmetic ingredient dictionary and handbook, or the *Compilation of ingredients used in cosmetics in the United States* (CIUCUS, 2011), nor are any cosmetic products containing the chemical listed on the US National Library of Medicine's Household Products Database. As the chemical is reported to have potential perfumery use, it is expected that any exposure due to this use would be at low concentrations, which would result in minimal risk. Considering this in addition to no reported cosmetic use of the chemical in Australia, the likelihood of public exposure to cosmetic products containing the chemical is low.

While use of the chemical in domestic products in Australia is not known, it is reported to be used in domestic products overseas. The only available information in regard to concentration in domestic products is from the US National Library of Medicine's Household Products Database, indicating historical use in liquid form auto products at up to 5 % (reported as discontinued products).

Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products. However, given the available overseas information on the use of the chemical in cosmetic and/or domestic products, it is unlikely that the public will be exposed to the chemical at appreciable concentrations. Therefore, the risk to the public is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical health effects, the chemical may pose an unreasonable risk to workers, unless adequate control measures to minimise 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.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation section**).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Although there is no recommendation for public health risk management based on the known spectrum of use of the chemical, its inclusion in Appendix B of the SUSMP is considered innapropriate, as the chemical cannot be considered to be of low toxicity based on the results of this assessment.

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 by inhalation (Xn; R20)	Harmful if inhaled - Cat. 4 (H332)
Irritation / Corrosivity	Causes burns (C; R34)	Causes severe skin burns and eye damage - Cat. 1 (H314)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)	Suspected of damaging the unborn child - Cat. 2 (H361d)

[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 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;
- 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;
- 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 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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