Hexanoic acid, 2-ethyl-: Human health tier II assessment

12 September 2013

CAS Number: 149-57-5

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.

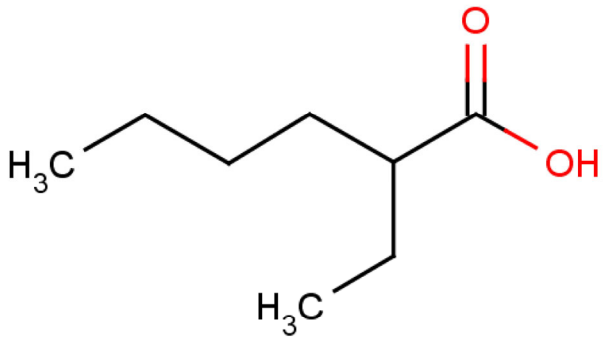
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-Ethylhexanoic acid 2-Ethylhexoic acid 2-Butylbutanoic acid Ethyl hexanoic acid, 2- Octylic acid
Structural Formula	
Molecular Formula	C8H16O2
Molecular Weight (g/mol)	144.2124
Appearance and Odour (where available)	Clear liquid with a mild odour.
SMILES	C(=O)(O)C(CCCC)CC

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, including fuel additives;
- as a solvent; and
- as a viscosity adjuster.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was between 100 and 1000 tonnes.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossier, the Canadian Challenge Substances Screening Assessment report, Galleria Chemica, the Substances and Preparations in the Nordic countries (SPIN) database, the US National Library of Medicine's Household Products Database and via eChemPortal sources including the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

Reported domestic use including:

- as an additive in antifreeze;
- in paints, lacquers and varnishes; and
- as an ingredient in paint driers.

Reported commercial use including:

- as a corrosion inhibitor; and
- in gel thickener and emulsifiers.

Reported site-limited use including:

- as an intermediate in the manufacture of metal 'octoates' (ethylhexoates); and
- as a catalyst promoter in the manufacture of polyester products including low-density polyethylene.

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 II: List of substances which must not form part of the composition of cosmetic products.

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

Existing Work Health and Safety Controls

Hazard Classification

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

Repr. Cat. 3; R63 (Reproductive toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

American Conference of Industrial Hygienists (ACGIH) Threshold Limit Values (TLV):

Time Weighted Average (TWA) = 5 mg/m³

Canada Occupational Exposure Limits:

TWA = 5 mg/m³

Short Term Exposure Limit (STEL) = 10 mg/m³

Ireland Occupational Exposure Limits:

TWA = 4 mg/m³

Health Hazard Information

Toxicokinetics

Toxicokinetic studies in rats showed that the chemical is rapidly absorbed from the gastrointestinal tract, and absorption of up to 5 % of the chemical was observed 96 hours after dermal application (Canada, 2011). The chemical and its metabolites are reported to be rapidly excreted, primarily via urine. In the mouse and rat, distribution of the chemical following absorption was reported to be greatest in the kidneys, liver, and blood. In a study on pregnant mice, the chemical was reported to have crossed the placenta, and was detected in the embryos at levels similar to those in the dams.

The chemical is also a major metabolite of 2-ethylhexanol (CAS No. 104-76-7) (NICNAS) and occurs as a metabolite of a wide range of 2-ethylhexyl or 2-ethylhexanoate compounds.

In a toxicokinetics study in rats (Fischer 344), peak blood levels of the radiolabelled chemical were detected 15–30 minutes following oral administration at doses of 100 or 1000 mg/kg bw (REACH). Approximately 72–75 % of the oral dose was excreted in the urine

within 24 hours. Little radioactivity (<10 %) was excreted after 24 hours. The dose was reported to influence the rate of excretion; within eight hours, 50 % of the radioactivity was excreted after the 100 mg/kg bw dose, while 20 % was excreted after the 1000 mg/kg bw dose. At both doses, 7–12 % was excreted via faeces. Glucuronide conjugates (metabolites) of the chemical and the unmetabolised chemical were detected following urine analysis.

Oxidative and conjugated metabolites of the chemical have also been identified in urine of humans exposed to precursors of the chemical from plasticisers (Canada, 2011).

Acute Toxicity

Oral

The chemical was of low to moderate acute toxicity in animal tests following oral exposure.

The median lethal dose (LD50) in rats is >2000 mg/kg bw (REACH). Observed sub-lethal effects included apathy, difficult or laboured breathing, and a high, steppy gait. However, in guinea pigs, reported LD50 values were between 800 and 1600 mg/kg bw (Canada, 2011).

Dermal

The chemical was of low to moderate acute toxicity in animal tests following dermal exposure.

The LD50 value in rats was reported to be >2000 mg/kg bw (REACH), while, in rabbits, an LD50 value of 1260 mg/kg bw was reported (Canada, 2011).

Inhalation

The chemical was of low acute toxicity in animal tests following inhalation exposure.

The median lethal concentration (LC50) values in rats and guinea pigs were reported to be >2356 mg/m³, following exposure to the chemical for six hours (Canada, 2011).

In an acute inhalation study in rats, no mortalities were observed following whole body exposure to the chemical vapours at 0.11 mg/L for eight hours (REACH).

Corrosion / Irritation

Skin Irritation

A skin irritation study in rabbits (OECD TG 404; semi-occlusive patch) reported erythema and eschar formation still visible after the 14-day observation period (REACH). Oedema was visible intermittently throughout the observation period.

There is sufficient evidence to classify the chemical as irritating to the skin.

Eye Irritation

There are reports that the chemical is a severe eye irritant in rabbits (study guideline or methods not specified) based on irreversible effects including clouding of the cornea, severe reddening and oedema formation, iritis, and ocular discharge (Canada, 2011). However, one study in rabbits, following OECD TG 405, reported the chemical as not irritating to eyes, with all effects fully reversible within seven days (REACH).

There is insufficient evidence to classify the chemical as an eye irritant.

Sensitisation

Skin Sensitisation

The chemical was not found to induce dermal sensitisation in guinea pigs in a maximisation study similar or equivalent to OECD TG 406 (REACH).

Repeated Dose Toxicity

Oral

In a 90-day dietary study in rats, a lowest observed adverse effect level (LOAEL) of 917 mg/kg bw/day was reported based on reduced body weight gain in conjunction with reduced feeding (Canada, 2011). A lowest observed effect level (LOEL) of 303 mg/kg bw/day was also reported based on increased relative liver weight and hepatocyte hypertrophy.

In a 90-day dietary study in mice, a LOAEL of 1040 mg/kg bw/day was reported based on reduced body weight (Canada, 2011; REACH). A LOEL of 885 mg/kg bw/day was also reported based on effects including increased relative liver weight, hepatocyte hypertrophy, kidney effects and forestomach lesions.

The available information is not sufficient to draw conclusions on the adversity of effects at the reported LOEL. However, based on the findings in the reproductive and developmental section below, the lack of detailed data here is not critical.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The chemical was reported to be negative in bacterial point mutation tests, positive in several in vitro mammalian cell genotoxicity tests, and negative in one in vivo micronucleus assay in mice.

In vitro

The chemical was reported to not be mutagenic in *Salmonella typhimurium* bacterial strains TA97, TA98, TA100. TA1535, TA1537 and TA1538; and *Escherichia coli* strain WP2uvrA with and without metabolic activation.

However, application of the chemical reportedly induced DNA damage in rat hepatocyte cells with and without metabolic activation, and also increased the frequency of sister chromatid exchanges in Chinese hamster ovary (CHO) cells with and without metabolic activation. In a chromosomal aberration study using CHO cells, the chemical was weakly positive in the presence of metabolic activation, and negative without activation.

In vivo

In the only available in vivo genotoxicity study, the chemical was reported to not induce micronuclei in bone marrow in male and female mice following oral administration of 400, 800 or 1600 mg/kg bw/day, over two doses within 24 hours (REACH). Although the authors stated that the study was conducted according to OECD TG 474, a post-exposure period of zero hours for the micronucleus test was reported, as opposed to the 18–24 hour post-exposure period recommended in the OECD TG 474 document (OECD, 1997).

While there is an indication of genotoxicity based on in vitro mammalian cell studies, there is insufficient consistent evidence across the available studies to classify the chemical for genotoxicity.

Carcinogenicity

While no specific data are available on this chemical, it is a major metabolite of 2-ethylhexanol (CAS No. 104-76-7) which was reported to not be carcinogenic in a two-year study (equivalent or similar to OECD TG 451) in rats (NICNAS).

2-Ethylhexanol 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 is classified as hazardous as a Category 3 reproductive toxin with the risk phrase ‘Possible risk of harm to the unborn child’ (Xn; R63) in HSIS (Safe Work Australia). The available data support this classification. There is also sufficient evidence to classify the chemical as potentially toxic in relation to fertility.

Developmental toxicity

The chemical was reported to cause developmental toxicity in several studies in rats following exposure via the oral route (Canada, 2011; Pennan et al., 1992; REACH). These effects were noted in the absence of signs of maternal toxicity. The lowest developmental toxicity LOAEL was reported to be 100 mg/kg bw/day.

In a developmental toxicity study, pregnant female Wistar rats were administered the chemical on gestation days 6–19 via drinking water at 0, 100, 300 or 600 mg/kg bw/day (Canada, 2011; Pennan et al., 1992; REACH). Skeletal variations in foetuses were observed at the lowest dose. A dose-dependent increase in club foot was observed in foetuses of the treatment group (statistically significant at the highest and intermediate dose); this anomaly was not observed in any foetuses of the control group. A statistical increase in wavy ribs was also observed in the foetuses of all treatment groups compared to controls. A dose-dependent increase in malformation of the legs, reported as 'flabby legs (external, slightly paralysed)' was also observed in foetuses of all treatment groups; this was not observed in any foetuses of the control group.

While a maternal toxicity LOAEL of 600 mg/kg bw/day (highest dose) was reported from this study, based on decreased maternal body weight gain (Canada, 2011; Pennan et al., 1992), a REACH dossier reported maternal toxicity (slightly lower pregnancy rates and reduced body weights) at 300 mg/kg bw/day. A developmental LOAEL of 100 mg/kg bw/day was determined from this study in both reports.

Foetal skeletal variations, malformations, reduced foetal body weights and early foetal deaths have also been reported in several other developmental toxicity studies in rats following oral exposure to the chemical (Canada, 2011; REACH). For each of these studies, developmental effects were observed in the absence of maternal toxicity.

In one study in rabbits, the chemical was administered via oral gavage at 0, 25, 125, or 250 mg/kg bw/day during gestation days 6–18. Treatment-related deaths, one abortion and clinical signs of toxicity were observed in the dams at 125 and 250 mg/kg bw/day. No developmental effects in foetuses were reported. Further study details are not available.

Reproductive toxicity

In a reproductive toxicity study in Wistar rats, the sodium salt of the chemical was administered via drinking water at 100, 300 or 600 mg/kg bw/day (Pennan et al., 1993; REACH). Males were exposed to the chemicals for 10 weeks prior to mating and for three weeks during mating; females were exposed for two weeks prior to mating and throughout the entire gestation and lactation period. Effects on the male reproductive system (reduction in sperm motility) were observed at 100 mg/kg bw/day, and increases in abnormal sperm were

observed at 300 and 600 mg/kg bw/day. Dose-dependent delays in mating at 300 and 600 mg/kg bw/day were also reported, in addition to some animals being reported to be 'totally infertile'.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (reproductive and developmental toxicity). The chemical may also cause skin and eye irritation.

Public Risk Characterisation

The chemical is not reported to be used in cosmetic products in Australia. It is also restricted for use in cosmetic products overseas.

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 are from the US National Library of Medicine's Household Products Database, indicating use in:

- liquid form auto products (antifreeze) at up to 8 %;
- a home maintenance product (paint drier) at up to 5 %; and
- an arts and craft stain product at less than 4 %.

There are no restrictions in Australia on using this chemical in products available to the public. However, an approximate margin of exposure (MOE) was calculated by Canada (2011) based on domestic use of the chemical in similar types of products identified in this report (alkyd paints), using similar levels of bioavailability, and LOAELs. The calculations resulted in the determination that the MOE was acceptable, particularly given the expected episodic exposure of the general population to the chemical from normal use of these products.

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

Products containing the chemical should be labelled in accordance with state and territory legislation.

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]
Irritation / Corrosivity	Irritating to skin (Xi; R38)	Causes skin irritation - Cat. 2 (H315)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)* Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)	Suspected of damaging fertility or the unborn child - Cat. 2 (H361fd)

[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;
- 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 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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