1-Hexanol, 2-ethyl-, manufacture of, by product from, distillation residues: Human health tier II assessment

10 March 2017

CAS Number: 68609-68-7

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-ethylhexanol, distillation residuum
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Appearance and Odour (where available)	Clear, light-brown liquid, with a slight odour.

Import, Manufacture and Use

Australian

The substance has Australian industrial site-limited use, including in flotation agents, as reported under previous mandatory and/or voluntary calls for information.

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information, was 100–1000 tonnes per annum (tpa).

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; and the United States (US) Environmental Protection Agency's High Production Volume Information System (USEPA HPVIS).

The substance has reported site-limited use, including:

- in the production of organic solvents;
- in flotation agents; and
- as an intermediate.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The substance is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

This assessment report applies to the substance of the unknown or variable composition, complex reaction products or biological materials type (UVCB substance), '1-hexanol, 2-ethyl-, manufacture of, by-products from, distillation residues', identified by the unique CAS RN 68609-68-7. The substance is stated as being 'the complex combination of products produced

by the distillation of products from a 2-ethyl-1-hexanol manufacturing process. It consists predominantly of organic compounds such as alcohols, aldehydes, esters, carboxylic acids and acetals having carbon numbers predominantly in the range of C4 through C16 and boiling in the range of 150 °C to 308 °C' (ChemIDPlus; REACH).

As it is a UVCB substance, there is expected variability in the composition of its chemical constituents, as such, only limited health hazard information exists for this specific substance, with the majority of available data based on studies using chemical constituents of the substance. The chemicals 2-ethylhexanol (2-EH; CAS RN 104-76-7), 2-ethylhexyl 2-ethylhexanoate (2-EHEH; CAS RN 7425-14-1) and ethylhexanediol (CAS RN 94-96-2), are listed as three of six expected constituents of this substance (REACH). The chemicals 2-EH, 2-EHEH and ethylhexanediol have been assessed by NICNAS (NICNASa; NICNASb; NICNASc), and where relevant, information for these chemicals have been included in this report.

The description of the test substance in a number of studies within the REACH dossier is unclear, with only trade names available in a number of cases. However, the dossier does not indicate that any of the tests (as cited in this report) are on analogue substances. It is unclear if the trade names refer only to the chemical, or to unspecified formulations.

Acute Toxicity

Oral

The substance is considered to have low acute oral toxicity, based on results from animal tests following oral exposure.

In a study in male and female Sprague Dawley (SD) rats, conducted according to the Organisation of Economic Co-operation and Development (OECD) Test Guideline (TG) 401, the median lethal dose (LD50) for a trade name substance was reported to be >5000 mg/kg bw, following administration of the substance as a single oral dose by gavage (REACH). Observed sub-lethal effects included lethargy, raised fur, changes in motor activity and reduced respiratory rate.

In another study in female SD rats, conducted according to OECD TG 423, the LD50 was reported to be >2000 mg/kg bw, following administration of the substance as a single oral dose by gavage (REACH). Observed sub-lethal effects included lethargy and raised fur.

Dermal

No data are available.

Inhalation

The substance is considered to be of low acute toxicity based on results from one animal test following inhalation exposure.

In a study in male and female Wistar rats, conducted according to OECD TG 403, the median lethal concentration (LC50) of a trade name substance was reported to be >5.4 mg/L, following nose only inhalation exposure to the material, as an aerosol, for a four-hour period (REACH). No mortalities were reported. Observed sub-lethal effects included raised fur, reduced activity and secretions from the nose.

Corrosion / Irritation

Skin Irritation

The substance is considered to be a skin irritant based on results from one animal study. Hazard classification is warranted (see **Recommendation** section)

In a skin irritation study in three New Zealand White (NZW) rabbits, conducted according to OECD TG 404, significant skin reactions in 2/3 animals (erythema; mean score of 2) treated with a trade name substance were reported, following dermal application of 0.5 mL of the substance (REACH). Effects in these animals were not fully reversible within the seven-day study observation period. Slight oedema and desquamation (peeling of the skin) were also reported in 2/3 animals, with reactions extending beyond the application site in one animal.

Eye Irritation

The substance is not considered to be a significant eye irritant based on the results from one animal study.

In an eye irritation study in three NZW rabbits, conducted according to OECD TG 405, 0.1 mL of a trade named substance was instilled into the conjunctival sac of the right eye, with the left eye serving as a control (REACH). Animals then were observed for 72 hours following treatment. Slight iridial inflammation (in 2/3 animals) and slight conjuctival redness and swelling (in 3/3 animals) was observed one hour after application of the substance. However, all effects had completely resolved within 24-48 hours. No other significant eye irritation effects are reported.

Sensitisation

Skin Sensitisation

The substance is not considered to be a skin sensitiser based on the results from one animal study.

In a skin sensitisation test in 10 male Hartley guinea pigs, conducted according to OECD TG 406 (guinea pig maximisation test), induction exposure to the chemical was conducted by intradermal injections (5 % w/w in sesame oil) followed by epidermal application seven days later (100 %). Challenge doses were applied two weeks later, as an epidermal applications of the chemical at 25 % in sesame oil on one flank of each animal, and 12.5 % in sesame oil on the other flank of each animal. Sensitisation reactions were assessed 24 and 48 hours after the challenge applications.

Skin reactions (slight erythema) were observed in 7/10 and 2/10 animals, at 24 and 48 hours after application of the challenge exposure of the substance at the 50 % sites, respectively. No skin reactions were observed at the 12.5 % challenge application sites (REACH).

Repeated Dose Toxicity

Oral

Considering the no observed adverse effect level (NOAEL) available from a 90-day rat study (750 mg/kg bw/day), and based on the treatment-related effects reported in various repeated dose toxicity studies, repeated oral exposure to the substance is not considered to cause serious damage to health.

In a 90-day oral repeat-dose toxicity study in Wistar rats, conducted according to OECD TG 408, the test material (a trade name substance) was administered by oral gavage to 10 animals/sex/dose, at 100, 300 or 750 mg/kg bw/day (REACH). An additional 5 animals/sex were administered 750 mg/kg bw/day for the same 90-day period and allowed to recover after the last treatment dose for a further 28 days (recovery group). Mild clinical signs of toxicity were observed, including prone position, raised fur and excess salivation. Slight, but statistically significant, reduction in body weight gain was reported in males only treated at 750 mg/kg bw/day.

Liver weights were increased in both males and females treated at 750 mg/kg bw/day. However, no difference in liver weights was reported in the recovery group compared to control group animals. Increased relative kidney weight was reported in animals from the 750 mg/kg bw/day group and males only from the 300 mg/kg bw/day group. Increased thyroid/parathyroid weight was also reported in the 300 and 750 mg/kg bw/day group animals.

At histopathological examination, effects in the kidneys (hyaline droplets in the renal cortex) were observed in males only, at all dose levels. However, these were reported to consist of a2µ-globulin. This mode of action is specific to male rats, and not biologically relevant to humans. In the liver, hepatocellular hypertrophy (considered to be associated with observed the increased liver weights) was reported in males and females from the 300 and 750 mg/kg bw/day groups. No liver lesions or other histopathological effects in the liver were reported. While histopathological changes in the thyroid were reported in both treated males and females, no further details on these effect were provided. However, the study authors considered the changes in the thyroid to be secondary in nature, and the effects were considered to have recovered almost completely based results from the histopathological examination of recovery group animals.

An NOAEL of 750 mg/kg bw/day for females is reported based on the considerations that no significant clinical or systemic toxic findings occurred and no histopathological liver lesions were detected. While a NOAEL for males was not established by the authors due to the observed kidney lesions, it is noted that nature of the kidney lesions are likely to be male rat-specific and not relevant to humans. The NOAELs for both males and females in this study are difficult to evaluate due to the limited available details on the reported thyroid effects.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the results of vitro assays, the substance is not considered to be genotoxic. No in vivo studies are available.

In two separate bacterial reverse mutation assays (Ames tests), conducted according to OECD TG 471, a trade name substance did not induce mutations in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 or *Escherichia coli* strain WP2 uvr A at test concentrations of 1–5000 µg/plate, with or without metabolic activation (REACH).

In an in vitro mammalian cell gene mutation test, conducted according to OECD TG 476, the substance did not induce gene mutations at the hprt locus in Chinese hamster ovary (CHO) cells under the following test conditions (REACH):

- at concentrations of 6.25–500 µg/mL with metabolic activation, for an exposure period of five hours;
- at concentrations of 2.5–100 µg/mL without metabolic activations, for an exposure period of five hours; and
- at concentrations of 1.25–100 µg/mL without metabolic activations, for an exposure period of 24 hours.

In an in vitro mammalian chromosome aberration test, conducted according to OECD TG 473, a trade name substance did not induce chromosomal aberrations in Chinese hamster lung fibroblasts under the following test conditions (REACH):

- at concentrations of 0.76–61.73 µg/mL, with or without metabolic activation;
- at concentrations of 2.29–185.18 µg/mL, with metabolic activation, with a three-hour treatment period and harvest at 20 or 28 hours; and
- at concentrations of 0.25–20.58 µg/mL, without metabolic activation, with a 20-hour treatment period and harvest at 28 hours.

Two expected chemical constituents of the substance, 2-ethylhexanoic acid (2-EHA; CAS RN 149-57-5) and ethylhexanediol (CAS RN 94-96-2), have also been assessed by NICNAS and are not considered to be genotoxic based on both in vitro and in vivo studies (NICNASa; NICNASc).

Carcinogenicity

While no data are available for this specific substance, one of its expected chemical constituents, 2-ethylhexanol (CAS No. 104-76-7), was reported to not be carcinogenic in a two-year study (equivalent or similar to OECD TG 451) in rats (NICNASa). Based on the limited data available, the substance is not expected to be carcinogenic.

A constituent of the substance, 2-ethylhexanol was administered via oral gavage to male and female Fischer 344 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 benign and malignant tumours was lower in the high dose group than in either of the control groups.

Another of the expected chemical constituents, ethylhexanediol (CAS RN 94-96-2), was not considered to be carcinogenic based on limited available data from two animal studies (NICNASc).

Reproductive and Developmental Toxicity

Based on the available data, the substance is not considered to have reproductive toxicity. However, the substance has the potential to cause developmental toxicity, as three of the chemical constituents of the substance, 2-EH, 2-EHEH and ethylhexanediol, are considered to be developmental toxins (NICNASa; NICNASb; NICNASc). Therefore, the substance warrants hazard classification (see **Recommendation** section).

In a reproductive and developmental toxicity study in Wistar rats, conducted according to OECD TG 422, the test substance was administered by oral gavage to 12 animals/sex/dose at 75, 300 or 1000 mg/kg bw/day. Males were dosed for a total of 28 days (14 days pre-mating and 14 days during the mating period), while females were dosed for 14 days pre-mating, up to 14 days during mating, throughout the gestation period and for at least 4 days after delivering pups.

No mortalities or clinical signs of toxicity were reported in parental animals. No significant differences in body weight, food consumption, haematology, clinical chemistry, urinalysis, neurobehaviour, gross pathology or histopathology in parental animals were reported. No changes in reproductive or developmental measures were reported. No gross abnormalities were observed in offspring of treatment group animals. However, similarly to effects observed in the 90-day repeated dose toxicity study (see Repeat dose toxicity - Oral section), increased absolute and relative liver weights were reported in male and female animals from the 300 and 1000 mg/kg bw/day groups. Increased absolute kidney weights were reported in both males and females at 1000 mg/kg bw/day, although increased relative kidney weights were only reported in males. The no observed effect level (NOEL) for both reproductive and developmental toxicity was reported to be 1000 mg/kg bw/day from this study (REACH).

In a developmental toxicity study, conducted according to OECD TG 414, the substance was administered by oral gavage to 24 pregnant female Wistar rats per group, at 100, 300 or 1000 mg/kg bw/day, daily from gestational day (GD) five through to GD 19. Mild signs of clinical toxicity including raised fur and excess salivation were observed in treated animals. Statistically significantly reduced maternal body weights were reported in animals at 1000 mg/kg bw/day. However, no significant effect on gravid uterus weight, number of corpora lutea, live foetuses, resorption, offspring sex ratio, percent preimplantation loss or post implantation loss were reported for the treatment group animals when compared with controls. Examination of foetuses revealed skeletal effects including reduced ossification and craniofacial abnormalities (no further details available); however, the incidences of these effects were reported as not being significantly different between treatment and control groups. The NOAELs of 300 mg/kg bw/day for maternal toxicity and 1000 mg/kg bw/day for teratogenicity were reported for this study (REACH).

The chemical 2-EH (CAS RN 104-76-7), a component of the UVCB, is classified as a reproductive toxin – category 2, with the hazard statement 'Suspected of damaging the unborn child' (H361d) in the HCIS (Safe Work Australia). It was reported to cause developmental toxicity in rats following oral administration (NICNAS a). Effects were noted in the absence of signs of marked maternal toxicity, and included reduced mean foetal body weights and a higher number of foetuses with skeletal malformations, variations and retardations. The NOAEL for developmental toxicity was reported to be 130 mg/kg bw/day.

The chemical component 2-EHEH (CAS RN 7425-14-1) is classified as a reproductive toxin – category 2, with the hazard statement 'Suspected of damaging the unborn child' (H361d) in the HCIS (Safe Work Australia). While there are no specific data available for 2-EHEH, it readily hydrolyses to form 2-EH and 2-ethylhexanoic acid (2-EHA; CAS RN 149-57-5) (NICNASb), and 2-EHA is classified as hazardous, as a Category 2 reproductive toxin, with the hazard statement 'Suspected of damaging the unborn child' (H361d) in the HCIS (Safe Work Australia). Developmentally toxic effects were reported in several studies in rats

following treatment with 2-EHA via the oral route. These effects were noted in the absence of signs of maternal toxicity. The lowest observed adverse effect level (LOAEL) for developmental toxicity was reported to be 100 mg/kg bw/day. Effects on fertility were also reported, with evidence being sufficient to warrant classification as potentially toxic to fertility.

While ethylhexanediol (CAS RN 94-96-2) is not classified as hazardous to reproduction or development in the HCIS, it has been demonstrated to show specific developmental toxicity, but only at high doses (NICNASc).

The substance is a UVCB, and there is expected variability in the composition of its chemical constituents. However, based on the developmentally toxic properties of its expected chemical constituents, specifically 2-EH and 2-EHEH, the substance should also be considered as toxic to development and classified as hazardous.

Risk Characterisation

Critical Health Effects

The substance is considered to be a potential developmental toxin. It is also irritating to the skin.

Public Risk Characterisation

Currently, there are no restrictions in Australia on using this substance in cosmetics or domestic products. However, given the uses identified for the substance, it is unlikely that the public will be exposed. Hence, the public risk from this substance is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, 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 substance at lower concentrations could also occur while using formulated products containing the substance. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the substance could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The substance 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.

NICNAS Recommendation

Assessment of the substance 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 substance should be labelled in accordance with state and territory legislation (SUSMP, 2016).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. The classification for reproductive toxicty should apply if the UVCB substance contains concentrations of ≥0.1 % of 2-EH or 2-EHEH. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Not Applicable	Causes skin irritation - Cat. 2 (H315)
Reproductive and Developmental Toxicity	Not Applicable	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 substance should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral and dermal exposure to the substance 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 substance is used. Examples of control measures that could 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 substance, 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 substance.

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 substance 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 substance has not been undertaken as part of this assessment.

References

ChemIDPlus Advanced. Accessed October 2016 at http://chem.sis.nlm.nih.gov/chemidplus/

Galleria Chemica. Accessed October 2016 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for 1-Hexanol, 2-ethyl- (CAS No. 104-76-7). Available at http://www.nicnas.gov.au

National Industrial Chemicals Notification and Assessment Scheme (NICNASb). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II assessment for hexanoic acid, 2-ethyl, 2-ethylhexyl ester (CAS No. 7425-14-1). Available: http://www.nicnas.gov.au

National Industrial Chemicals Notification and Assessment Scheme (NICNASc). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II assessment for 1,3-Hexanediol, 2-ethyl- (CAS No. 94-96-2). Available at http://www.nicnas.gov.au

Registration, Evaluation and Authorisation of Chemicals (REACH) Dossier. 1-Hexanol, 2-ethyl-, manuf. of, by-products from, distn. residues (CAS RN 68609-68-7). Accessed November 2016 at https://echa.europa.eu/information-on-chemicals/registered-substances

Safe Work Australia. Hazardous Chemicals Information System (HCIS). Accessed February 2017 at http://hcis.safeworkaustralia.gov.au/HazardousChemical

Substances in Preparations in Nordic Countries (SPIN). Accessed October 2016 at http://spin2000.net/

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2016. Available at https://www.tga.gov.au/publication/poisons-standard-susmp

US EPA High Production Volume Information System (HPVIS). Accessed October 2016 at http://www.epa.gov/hpvis/index.html

Last update 10 March 2017

Share this page