Propanoic acid, 2-hydroxy-, ethyl ester: Human health tier II assessment

08 March 2019

CAS Number: 97-64-3

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.

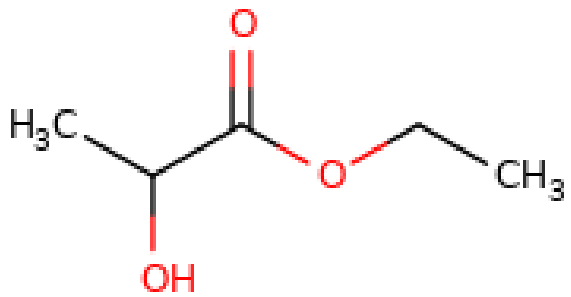
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	ethyl lactate ethyl 2-hydroxypropanoate 2-hydroxypropanoic acid ethyl ester (±)-ethyl lactate lactic acid, ethyl ester
Structural Formula	
Molecular Formula	C5H10O3
Molecular Weight (g/mol)	118.13
Appearance and Odour (where available)	Colourless liquid with a mild, characteristically ester-like odour
SMILES	C(=O)(C(C)O)OCC

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 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 International Fragrance Association (IFRA) transparency list; and the US Department of Health and Human Services's Household Products Database (HPD).

The chemical has reported cosmetic use including:

- as an ingredient in fragrance compounds (at up to 0.8 %; HSDB); and
- as a solvent (at up to 50 % in nail enamels; CIR, 2013).

The chemical has reported domestic use including:

- in adhesives and sealants; and
- in cleaning products and detergents (at up to 0.2 %; HSDB).

The chemical has reported commercial use including:

- as a solvent in cellulose and resins products and paints;
- as an additive in lubricants;
- in industrial cleaners (at up to 40 %; HPD); and
- in reprographic and photographic agents.

The chemical has the following reported non-industrial uses:

- as a food additive;
- as a therapeutic treatment for acne;
- as a solvent for pharmaceutical agents; and
- in pet products.

The chemical also has use as a flavouring component in e-cigarette liquids.

Restrictions

Australian

The chemical is listed in the Poisons Standard — the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in Appendix B — Substances considered not to require control by scheduling, for its low toxicity and for the purpose of any use (SUSMP, 2019).

No other restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Specific target organ toxicity (single exposure) – Category 3; H335 (May cause respiratory irritation)
- Eye damage – Category 1; H318 (Causes serious eye damage)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- 25 mg/m^3 (5 ppm) Time Weighted Average (TWA) in Finland and Sweden, and 49 mg/m^3 (10 ppm) short-term exposure limit (STEL) in Finland and Sweden.
- US Department of Energy (DOE) Temporary Emergency Exposure Limits (TEELs): 5.7 ppm (TEEL-1), 63 ppm (TEEL-2) and 380 ppm (TEEL-3).

Health Hazard Information

The chemical is a monobasic ester formed from lactic acid and ethanol. It is found naturally in a number of food products in small quantities (PubChem). The chemical is a racemic mixture of two enantiomers: (-)-ethyl lactacte (CAS No. 687-47-8) and (+)-ethyl lactate (CAS No. 7699-00-5). When data for the chemical are not available, data on the enantiomer + or - are included in this assessment and are considered applicable to both enantiomers.

Toxicokinetics

The chemical is readily absorbed by the dermal route, as demonstrated in animal studies (NIWL, 1999), and is expected to be readily absorbed by oral and inhalation routes.

The chemical will be rapidly enzymatically hydrolysed in vivo to lactic acid and ethanol as demonstrated for (-)-ethyl-lactate (REACH).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure.

The oral median lethal dose (LD50) of the chemical was in the range of 5000–8200 mg/kg in rats and 2500 mg/kg in white mice (CIR, 2013). Observed sub-lethal effects included piloerection up to 24 hours post-administration in rats (Clary et al., 1998).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure.

The dermal LD50 of the chemical is greater than 5000 mg/kg (CIR, 2013).

Inhalation

The chemical has low acute toxicity based on results from animal tests following inhalation (vapour) exposure. However, studies with higher doses are not available and; therefore, the available data are insufficient to determine appropriate hazard classification.

The median lethal concentration (LC50) (4 h) of the chemical is greater than 5.4 mg/L (REACH).

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the hazard category 'Specific target organ toxicity (single exposure) – Category 3' and hazard statement 'May cause respiratory irritation (H335)' in the HCIS (Safe Work Australia). The limited data available support this classification.

In a 28-day repeated dose inhalation study (OECD TG 412), Wistar rats (n = 5/sex/dose) were exposed to the chemical (whole body exposure) at concentrations of 0, 150, 600 or 2500 mg/m^3 for six hours/day, five days/week. In the 600 and 2500 mg/m^3 dose groups degenerative changes of the nasal olfactory epithelium were seen, and in addition hyperplasia of the goblet cells. In several animals exposed to 2500 mg/m^3 locally there was hardly any epithelium recognisable.

Skin Irritation

Based on the available data, the chemical is not a skin irritant.

In a skin irritation study following OECD TG 404, three New Zealand White (NZW) male rabbits were exposed to undiluted (-)-ethyl-lactate under semi-occlusive patch for four hours. No oedema or erythema were observed in any of the treated animals (REACH).

Eye Irritation

The chemical is classified as hazardous with the hazard category 'Eye damage – Category 1' and hazard statement 'Causes serious eye damage (H318)' in the HCIS (Safe Work Australia). The available data support this classification.

In an ex vivo chicken enucleated eye test (CEET), the chemical was tested for corneal swelling, corneal opacity and fluorescein retention when applied to enucleated chicken eyes (n = 3) for 10 seconds. The chemical caused moderate to severe corneal opacity, and severe fluorescein retention via damaged epithelial cells. In addition, the three test eyes showed wrinkling of the corneal epithelium (REACH).

In another eye irritation study (guideline not identified), a 50 % solution of chemical applied to the eyes of three albino rabbits caused moderate eye irritation (CIR, 2013).

Observation in humans

Ethyl lactate (8 % in petroleum) produced no skin irritation after a 48-hr closed-patch test in human subjects (CIR, 2013).

Sensitisation

Skin Sensitisation

The chemical is not expected to be a skin sensitiser based on a negative result in a local lymph node assay (LLNA) for (-)-ethyl-lactate (REACH).

In a LLNA study following OECD TG 429, (-)-ethyl-lactate was applied to female CBA/J mice at concentrations of 0, 25, 50 and 100 % (5 females/dose). No irritation of the ears was observed in any of the animals and all lymph nodes of the animals of the experimental and control groups were considered normal in size. The SI values calculated for the substance concentrations 25, 50 and 100 % were 0.9, 1 and 0.8 respectively. An EC3 value could not be calculated.

Observation in humans

There is no evidence of the chemical producing sensitisation in humans.

A maximisation test on 25 volunteers (8 % chemical in petroleum) did not result in sensitisation reactions (CIR, 2013).

Repeated Dose Toxicity

Oral

Based on the limited available data, the chemical is not expected to cause systemic toxicity following repeated oral exposure. The main metabolites, ethanol and lactic acid, occur naturally in the body and are not systemically toxic.

In a 12-day feeding study, the chemical was administered to a group of 8 male weanling rats at 5000 mg/kg bw/day. One of 8 animals died during the course of the experiment. There was no indication of the cause of death. No adverse effects were observed in the surviving animals (NIWL, 1999).

The chemical is reported to be a central nervous system depressant and lethal to animals at high concentrations (levels and route of administration not stated), causing respiratory paralysis (HSDB).

Dermal

No data are available on the chemical (see **Reproductive & Developmental Toxicity** section).

Inhalation

Based on the available data, the chemical is not considered to cause systemic toxicity following repeated inhalation exposure. However, the chemical is classified as hazardous based on respiratory irritation effects.

In a 28-day repeated dose inhalation study (OECD TG 412), Wistar rats (n = 5/sex/dose) were exposed to the chemical (whole body exposure) at concentrations of 0, 150, 600 or 2500 mg/m^3 for six hours/day, five days/week. In the 600 and 2500 mg/m^3 groups degenerative changes of the nasal olfactory epithelium were seen, and in addition hyperplasia of the goblet cells. In several animals exposed to 2500 mg/m^3, there was hardly any epithelium recognisable. Growth retardation and reduced food intake was observed in the high dose group, which the study authors attribute to the impaired ability of the animals to smell and taste as a result of severe damage to the olfactory epithelium. A no observed adverse effect concentration (NOAEC) of 150 mg/m^3 was determined in this study (REACH).

In another 28-day repeated dose inhalation study (OECD TG 412), Wistar rats (n = 5/sex/dose) were exposed to the chemical (whole body exposure) at concentrations of 0, 25, 75 or 200 mg/m^3 for six hours/day, five days/week. No treatment related effects in mortality; clinical signs; body weight or gross and histological pathology were observed; the NOAEL was 200 mg/m^3. However, local effects were noted in all groups; the respiratory epithelium of the nasal cavity showed changes (REACH).

Genotoxicity

Based on the available in vitro data, the chemical is not expected to be genotoxic. The main metabolites ethanol and lactic acid are not mutagenic.

The chemical gave negative results in a bacterial reverse mutation assays (Ames test, OECD TG 471) with *Salmonella typhimurium* (TA 98, 100, 1535 and 1537), with or without metabolic activation (REACH) – concentrations of 667, 1000, 3333, 6667 and 10 000 µg/plate.

(-)-Ethyl-lactate gave negative results in several in vitro assays for genotoxicity (REACH):

- mammalian chromosome aberration test (OCED TG 473) in Chinese hamster ovary (CHO) cells, with or without metabolic activation – concentrations of 100, 333 and 1180 µg/mL;
- mammalian cell gene mutation assays (OECD TG 476) in mouse lymphoma cells (L5178), with or without metabolic activation – concentrations of 0.3, 1, 3, 10, 33, 100, 333 and 1080 µg/mL.

Carcinogenicity

No data are available on the chemical. The metabolites ethanol and lactic acid are not considered carcinogenic apart from effects from consumption of alcoholic beverages.

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical does not show specific reproductive or developmental toxicity. The main metabolites, ethanol and lactic acid, are not considered mutagenic apart from effects from consumption of alcoholic beverages.

In a developmental toxicity study the chemical was applied dermally to the backs of Crl:CD(SD)BR pregnant rats (n = 10/sex/dose) at doses of 0, 517, 1551 or 3619 mg/kg bw/day for days 6 through 15 of gestation. The maternal lowest observed adverse effect level (LOAEL) was 3619 mg/kg bw/day, based on slight erythema and/or desquamation. The maternal no

observed adverse effect level (NOAEL) was 1551 mg/kg/ bw/day. No adverse effects on embryo-foetal viability, body weight or morphology were observed. The developmental NOAEL was 3619 mg/kg bw/day (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (eye and respiratory system).

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used overseas in cosmetics. The general public may be exposed to the chemical through eye, dermal and/or inhalation routes.

- Use concentrations in fragrances are expected to be low (<0.8 %; HSDB), and thus eye and respiratory irritations are not expected from exposure to these cosmetic products.
- Nail products (e.g. nail enamels) may contain the chemical at up to 50 % (CIR, 2013) and for these products short-term exposure to skin in the immediate vicinity of the fingernail is likely. However, the volumes will be low. Limited inhalation and eye contact are expected.

Although use in domestic products in Australia is not known, the chemical is reported to be used overseas in domestic cleaning products, where the general public may be exposed to the chemical through dermal and/or inhalation routes. Specifically the US Department of Health and Human Services's HPD reports use in aerosol domestic cleaning products, but concentrations are expected to be low (<0.2 %; HSDB) and thus eye and respiratory irritations are not expected from exposure to these products.

Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, ocular and inhalation exposure might 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 chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise ocular and inhalation exposure to the chemicals are implemented. The chemicals 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.

Based on the available data, the hazard classification in the HCIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Considering the available information to indicate low public risk from this chemical, no regulatory controls are recommended.

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. 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 serious eye damage - Cat. 1 (H318)* May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)*

[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 chemicals should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from 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 local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in 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 safety data sheets (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 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.

References

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