Calcium, potassium and magnesium salts of 2-ethylhexanoic acid: Human health tier II assessment

16 June 2020

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Hexanoic acid, 2-ethyl-, calcium salt	136-51-6
Hexanoic acid, 2-ethyl-, potassium salt	3164-85-0
Hexanoic acid, 2-ethyl-, magnesium salt	15602-15-0

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

Grouping Rationale

The chemicals in this group are the calcium salt, the potassium salt and the magnesium salt of 2-ethylhexanoic acid (also referred to as 2-ethylhexanoate salts). These chemicals have been grouped together based on similar toxicology and use.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the majority of the chemicals in this group. However, the calcium salt of 2-ethylhexanoic acid (CAS No 136-51-6) has reported commercial use in printing inks.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Department of Health and Human Services Household Products Database (HPD); and various international assessments (Government of Canada, 2018).

The calcium and potassium salts of 2-ethylhexanoic acid have reported domestic use in one or more of the following:

- paints, lacquers and varnishes;
- fillers, putties and plasters; and

- adhesives and binding agents.

All of the chemicals in this group have reported commercial use, including as:

- lubricant agents or additives; and
- reprographic agents.

The chemicals in this group have reported site-limited use, including as polymerisation catalysts.

Calcium ethylhexanoate is reported to be used in the manufacture of resins used in food-packaging materials (Government of Canada, 2018).

Restrictions

Australian

The chemicals in this group are salts of 2-ethylhexanoic acid; therefore, they are covered by the listing of 2-ethylhexanoic acid in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 6, as 'a Schedule entry includes preparations containing the poison in any concentration and all salts and derivatives of the poison unless it specifically states otherwise' (SUSMP, 2019).

Schedule 6:

'2-ETHYLHEXANOIC ACID and its alkyl esters except in preparations containing 5 per cent or less calculated as 2-ethylhexanoic acid.'

Schedule 6 chemicals are described as 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label'. Schedule 6 chemicals are labelled with 'Poison' (SUSMP, 2019).

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are 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

The chemicals in this group are all soluble salts (REACHa; REACHb; REACHc); under biologically-relevant conditions, each exists as a solution, and is expected to almost completely dissociated into its 2-ethylhexanoate anion and respective calcium, potassium, or magnesium cation (REACH). Each of the cation components has been assessed by NICNAS and determined to be of low concern in regards to human health (NICNASa) and these are not expected to contribute to the toxicity of the chemicals in this group. The common anion component, 2-ethylhexanoic acid (2-EHA; CAS RN 149-57-5), has been assessed by NICNAS (NICNASb), and where relevant, available information for 2-EHA has been included in this report.

Acute Toxicity

Oral

There are no available acute toxicity data on the specific chemicals in this group. However, the chemicals are expected to have low acute toxicity based on studies of each of the relevant dissociation products (i.e. the 2-ethylhexanoate anion and respective cation); the oral median lethal dose (LD50) values are all reported to be >2000 mg/kg bw in rats (REACHa; REACHb; REACHc). Signs of toxicity have not been reported.

Dermal

The chemicals in this group are all expected to have low acute dermal toxicity, with calculated dermal LD50 values reported to be >2000 mg/kg bw, for each, based on study data for the relevant dissociation products (REACHa; REACHb; REACHc). Signs of toxicity have not been reported.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

There is sufficient evidence to warrant hazard classification for potassium 2-ethylhexanoate and magnesium 2-ethylhexanoate as a Category 2 skin irritant, with the hazard statement ‘Causes skin irritation' (H315), in the HCIS (Safe Work Australia).

Based on the available data from animal studies, calcium 2-ethylhexanoate is not considered to be irritating to the skin, while both the magnesium and the potassium 2-ethylhexanoate are potential skin irritants.

In available in vivo skin irritation studies conducted according to the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 404, 500 mg of either calcium 2-ethylhexanoate or potassium 2-ethylhexanoate was applied to the shaved skin of female Himalayan rabbits (3/study) under semi-occlusive conditions, for an exposure period of 4 hours. While no skin reactions were reported over the course of the 72-hour observation period in animals exposed to calcium 2-ethylhexanoate (REACHa), erythema (redness of the skin) was reported in 2/3 animals exposed to potassium 2-ethylhexanoate, which was not fully reversible within the 14-day observation period; mean erythema scores reported for those animals were 3 out of 4, and 2 out of 4, respectively (REACHb).

In an in vitro/ex vivo study conducted according to OECD TG 439 (in vitro skin irritation: reconstructed human epidermis test method), magnesium 2-ethylhexanoate was applied to human-derived epidermal tissue for an exposure period of 60 minutes,

followed by an observation period of 42 hours. A mean tissue viability value of 2.9 % was reported for the chemical in this study, and it was determined to be at least irritating to the skin (REACHc). Interpretation of results obtained from OECD TG 439 studies do not allow for distinction between irritation and corrosion (OECD, 2019); as no reliable skin corrosion study data are available for magnesium 2-ethylhexanoate, it is not possible to rule out the potential for the chemical to cause corrosive effects on the skin.

Eye Irritation

Based on the available data, both the calcium and the potassium 2-ethylhexanoate are considered to be eye irritants; there is sufficient evidence to warrant hazard classification for these two chemicals as Category 1 eye irritants, with the hazard statement ‘Causes serious eye damage' (H318), in the HCIS (Safe Work Australia).. There is insufficient evidence to determine the eye irritancy potential of magnesium 2-ethylhexanoate.

In an in vivo eye irritation study conducted according to OECD TG 405, calcium 2-ethylhexanoate was applied to the conjunctival sac of the right eye of one New Zealand White (NZW) rabbit, with the untreated left eye serving as the control (REACHa). Mean scores for corneal opacity and iris effects observed at 24, 48 and 72 hours after treatment, were 1 out of 4 and 1 out of 2, respectively, with all effects fully reversible within 14 days. Mean conjunctival redness and chemosis scores were 2 out of 3 and 2 out of 4, respectively; these effects were reported to not be fully reversible within the 21-day observation period. Severe to minimal discharge from the eye was reported to be observed from 1 hour after treatment, for up to 7 days, in addition to alopecia (hair loss) around the treated eye, an area of haemorrhage, and formation of a scab inside the lower eyelid, all noted at the 7-day observation. At the 14-day observation, a small area of haemorrhage on the nictitating membrane was noted in the treated eye. Based on these observations, the chemical was considered to be severely irritating to the eyes.

In an in vitro/ex vivo study conducted according to OECD TG 437 (bovine corneal opacity and permeability test method for identifying ocular corrosives and severe irritants; BCOP assay), 0.75 mL of a 20 % (w/v) solution of potassium 2-ethylhexanoate was applied to 3 bovine corneae per experiment (REACHb). Although three consecutive sets of experiments were conducted in this study, a valid conclusion is able to be made from the first experiment alone, for which a mean in vitro irritation score (IVIS) of 55.57 was reported. Although 1 of the 3 corneas gave a discordant prediction (IVIS of 45.16) from the mean value, this discordant result is <10 IVIS units from the cut-off threshold of 55 for classification as causing serious eye damage; this is considered acceptable according to the OECD TG 437 criteria for borderline results (OECD, 2017). No conclusive predictions were able to be made from both the second and third experiments, with mean IVIS values of 35.59 (score range: 1.03–94.75) and 26.36 (score range: 1.79–51.24), respectively.

A BCOP assay using magnesium 2-ethylhexanoate is also available, in which 0.75 mL of a 10 % (w/v) solution of the chemical was applied to 3 bovine corneae (REACHc). Moderate opacity of the tissue was noted in each cornea, with a reported increase of corneal opacity and permeability in all 3 corneas relative to the negative control. However, as a mean IVIS value of 10.05 was reported for the chemical, according to the assay guidelines, no conclusive prediction regarding eye irritancy can be made from this study.

Sensitisation

Skin Sensitisation

While no sensitisation data on these specific chemicals are available, the chemicals in this group are not expected to be skin sensitisers based on studies of each of the relevant dissociation products (i.e. the 2-ethylhexanoate anion and respective cation) (NICNASa; NICNASb; REACHa; REACHb; REACHc).

Repeated Dose Toxicity

Oral

No specific data are available for the chemicals in this group.

While experimental data are available for the common hydrolysis product of these chemicals, 2-EHA (NICNASb), the data are limited and insufficient to draw a conclusion for this group of chemicals.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

While no specific data are available on the chemicals in this group, the common hydrolysis products of each of the chemicals, 2-EHA, has been assessed by NICNAS and is not considered to be genotoxic based on both in vitro and in vivo studies (NICNASb).

Carcinogenicity

No carcinogenicity data are available on the specific chemicals in this group, or the common hydrolysis product across the chemicals in this group, 2-EHA. However, 2-EHA is a major metabolite of 2-ethylhexanol (CAS RN 104-76-7) which was reported to not be carcinogenic in a two-year study (equivalent or similar to OECD TG 451) in rats (NICNASb).

The chemical, 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, five days per week, over the 2-year study period. 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

No data are available for the specific chemicals in this group. However, the chemicals almost completely dissociate under biologically-relevant conditions to produce 2-EHA and their respective cation; 2-EHA is classified as hazardous substance toxic to reproduction (Category 2), with the risk phrase ‘Suspected of damaging fertility or the unborn child’ (H361) in the HCIS (Safe Work Australia).

As detailed in the Tier II assessment for 2-EHA, developmental toxic effects were reported in several studies in rats following treatment with 2-EHA via the oral route (NICNASb). These effects, including foetal skeletal variations, malformations, reduced foetal body weights and early foetal deaths, 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 the male reproductive system (reduction in sperm motility) and fertility were also observed at 100 mg/kg bw/day.

The hazard classification for 2-EHA is also considered appropriate for the chemicals in this group (the calcium, potassium and magnesium salts of 2-EHA).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects of reproductive and developmental toxicity. Some of the chemicals in this group can also cause skin and eye irritation.

Public Risk Characterisation

Metal salts of 2-EHA, which include this group of chemicals, are reported to be mostly used as a paint drier, and are used in products available to consumers, including paints and coatings (Government of Canada, 2018). In Australia, calcium 2-ethylhexanoate is reported to be used in commercial printing inks.

While use of these chemical in domestic products (in paints and coatings) in Australia is not known, it is reported to be used in these types of domestic products overseas. In Canada, calcium 2-ethylhexanoate is reported in paint products at use concentrations of <0.5 % (Government of Canada, 2018). The chemicals in this group are not reported to be used in cosmetic products in Australia or overseas.

The chemicals in this group are all salts of 2-EHA; therefore, they are currently covered by the listing of 2-EHA on Schedule 6 of the Poisons Standard (SUSMP) for preparations containing >5 % calculated as 2-EHA. Additionally, a number of warning statements, first aid instructions and safety directions relating to use of the chemical at any concentration, apply. The current controls are considered adequate to minimise the risk to public health posed by domestic products containing the chemicals, therefore, the chemicals are not considered to pose an unreasonable risk to public health.

Calcium 2-ethylhexanoate has been reported to be used in production of food contact materials; however, any residual traces are not likely to pose a risk for reproductive toxicity (Canada, 2018).

Occupational Risk Characterisation

During product formulation, dermal and ocular exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, these chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and ocular exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

The assessment of the chemicals in this group 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 these chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2019).

Work Health and Safety

The chemicals in this group are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below.

Note that the eye irritation classification is only recommended for:

- calcium 2-ethylhexanoate (CAS RN 136-51-6); and
- potassium 2-ethylhexanoate (CAS RN 3164-85-0).

The skin irritation classification is only recommended for:

- potassium 2-ethylhexanoate (CAS RN 3164-85-0); and
- magnesium 2-ethylhexanoate (CAS RN 15602-15-0).

This assessment does not consider classification of physical 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) Causes skin irritation - Cat. 2 (H315)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility or the unborn child - Cat. 2 (H361)

[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 instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal and ocular exposure to the chemicals 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 chemicals are 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 chemicals, 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

References

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Registration, Evaluation, Authorisation and Restriction of Chemicals (REACHb) Dossier for Potassium 2-ethylhexanoate (CAS RN 3164-85-0). Accessed July 2019 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

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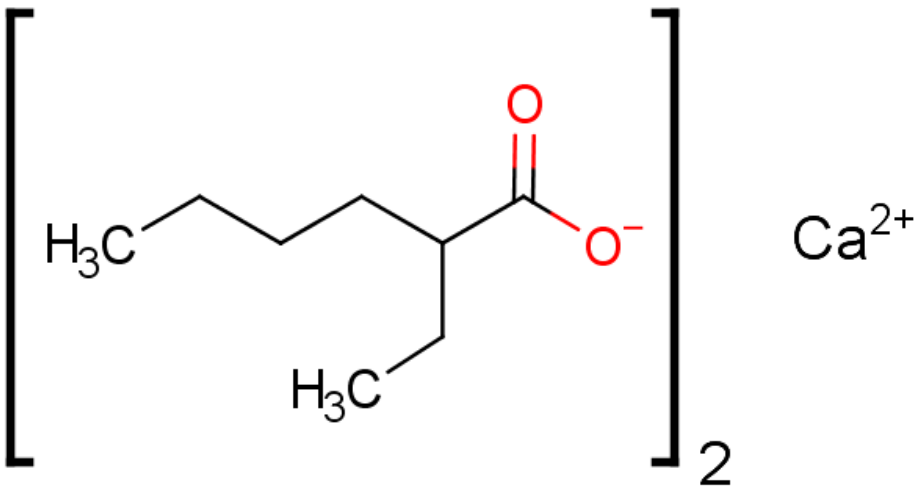
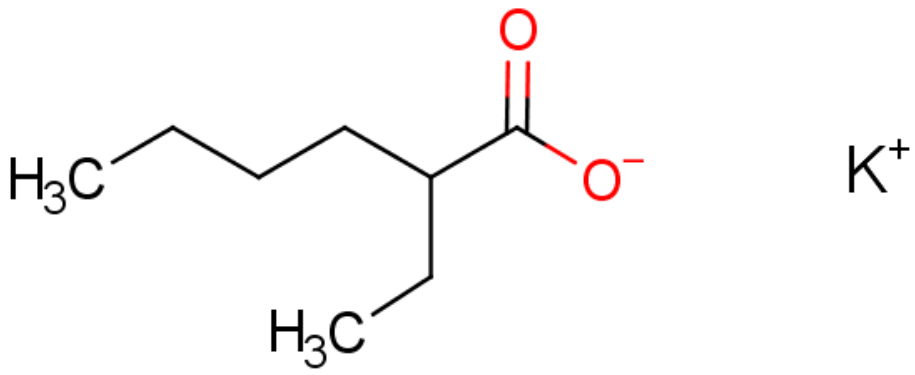
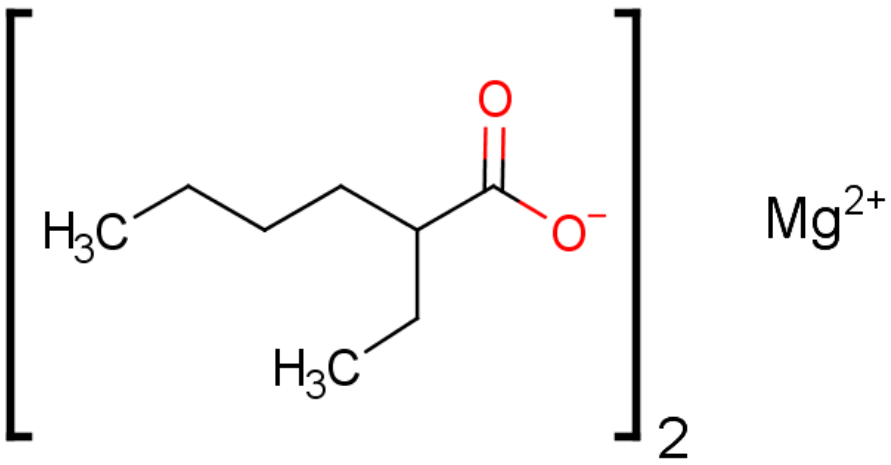
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Hexanoic acid, 2-ethyl-, calcium salt** 2-ethylhexanoic acid, calcium salt calcium 2-ethylhexanoate calcium bis(2-ethylhexanoate)
CAS Number	136-51-6
Structural Formula	
Molecular Formula	C8H16O2.1/2Ca
Molecular Weight	326.487

Chemical Name in the Inventory and Synonyms	**Hexanoic acid, 2-ethyl-, potassium salt** 2-ethylhexanoic acid, potassium salt potassium 2-ethylhexanoate
CAS Number	3164-85-0
Structural Formula	
Molecular Formula	C8H16O2.K
Molecular Weight	182.303

Chemical Name in the Inventory and Synonyms	**Hexanoic acid, 2-ethyl-, magnesium salt** 2-ethylhexanoic acid, magnesium salt magnesium 2-ethylhexanoate
CAS Number	15602-15-0
Structural Formula	
Molecular Formula	C8H16O2.1/2Mg
Molecular Weight	310.714

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