Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

2-Propenoic acid, 2-methyl-, 2-ethylhexyl ester (ethylhexyl methacrylate)

Evaluation statement

14 December 2023

Table of contents

Contents

AICIS evaluation statement

Subject of the evaluation

2-Propenoic acid, 2-methyl-, 2-ethylhexyl ester (ethylhexyl methacrylate)

Chemical in this evaluation

Name	CAS registry number
2-propenoic acid, 2-methyl-, 2-ethylhexyl ester	688-84-6

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation statement is a human health risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of the chemical in Australia.

Based on international use information, ethylhexyl methacrylate has potential cosmetic use with reported function of use as an artificial nail builder. No significant evidence of use in cosmetic products has been specifically identified for the chemical in individual products. Other methacrylates have reported use in nail enhancement products at concentrations from 2 to 85%. Consumer uses may include Do-It-Yourself (DIY) at home cosmetic nail products that are used outside of professional settings.

The chemical has reported commercial uses including in paints and coatings, adhesives and construction products. Although some of these products may be available to consumers, available data indicate that domestic use is not widespread.

The chemical has site limited use as:

- an intermediate in the manufacturing of chemicals
- a common methacrylate monomer in polymerisation for resins (used in windscreen repair kits), copolymers, plastics and food contact applications.

While there are identified uses in dental adhesives and bone cement for fixing prosthetic devices in orthopaedic surgery as reported overseas, these are considered non-industrial uses in Australia.

Human health

Summary of health hazards

The identified health hazards are based on the available data for the chemical. The chemical is a methacrylate ester that rapidly hydrolyses in vivo to its corresponding alcohol. Information on systemic effects was further supported by the available data for the metabolite 2-ethylhexanol (CAS No. 104-76-7). The systemic toxicity of the chemical will likely be driven by this metabolite.

Based on the available data, the chemical:

- has low acute oral, inhalation, and dermal toxicity
- is a slight skin and eye irritant
- is not expected to cause serious systemic health effects following repeated exposure
- is not expected to be carcinogenic
- is not considered to have genotoxic potential.

Chemicals that contain acrylate and methacrylate groups are often used in nail products and may be skin sensitisers. Based on the weight of evidence from available in vivo, in silico and human data, ethylhexyl methacrylate is not considered to be a potent sensitiser. However, it may cause cross reactions in individuals who are sensitised to other acrylates and methacrylates in other products.

Based on the available data, the chemical is not expected to cause significant adverse effects on fertility for reproduction and/or development. Although some effects were observed at high doses in studies in rats, these are considered secondary to maternal toxicity. The developmental effects observed for the metabolite, 2-ethylhexanol, were not observed in any studies on the chemical, indicating that the metabolite may not be bioavailable systemically at doses that are high enough to be toxicologically relevant.

For further details of the health hazard information see **Supporting Information**.

Hazard classifications relevant for worker health and safety

The chemical does not satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for worker health and safety. However, the chemical is covered by the generic entry '*monoalkyl or monoaryl or monoalkyaryl esters of methacrylic acid'* in the Hazardous Chemicals Information System.

This evaluation does not consider classification of physical hazards and environmental hazards.

Summary of health risk

Public

Based on the available use information, the chemical has potential use in nail enhancement products at high concentrations and in some domestic products. Overall use in these products does not appear to be widespread. Although the public could come into contact with articles/coated surfaces containing these chemicals, it is expected that these chemicals will be bound within articles/coated surfaces and hence will not be bioavailable.

Based on the available hazard information the chemical is not considered to be a potent sensitiser and systemic effects have not been identified. The chemicals may cause cross reactions in individuals who are sensitised to other acrylates and methacrylates in other products. Overall, there are no identified risks to the public specific to the chemical that require management.

Workers

Beauticians and/or nail technicians who frequently apply nail enhancement products to consumers in professional settings are likely to have a higher risk of repeated exposure to the chemical via the dermal route. There may be risk of inhalation exposure including from dust particles containing the chemical when filing, buffing, or removing nails. However, adverse effects arising from this type of exposure would not be due to the intrinsic hazard properties of the chemical.

During product formulation and packaging, dermal 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 local health effects (potential for cross skin sensitisation), the chemical could pose a risk to workers. Control measures to minimise dermal exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section). Control measures implemented due to the proposed classifications are expected to be sufficient to protect workers from any potential reproductive & developmental health effects.

Proposed means for managing risk

Workers

Information relating to safe introduction and use

The information in this statement should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risks arising from dermal exposure to these chemicals include, but are not limited to:

- minimising manual processes and work tasks through automating processes

- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using this hazardous chemical depends on the physical form and how the chemical is used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

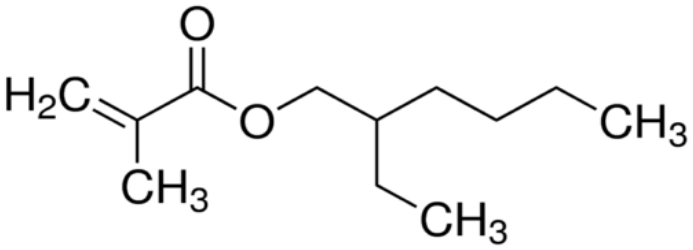
The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

Chemical name	2-propenoic acid, 2-methyl-, 2-ethylhexyl ester
CAS No.	688-84-6
Synonyms	ethylhexyl methacrylate (INCI) 2-ethylhexyl methacrylate 2-EHMA
Molecular formula	C12H22O2
Molecular weight (g/mol)	198.30
SMILES	C(COC(=O)C(=C)C)(CCCC)CC
Chemical description	Clear, colourless sweet liquid at 20°C and 101.3 kPa with an ester-like odour.
Structural formula	

Relevant physical and chemical properties

Ethylhexyl methacrylate has the following physical and chemical properties (OECD 2004; REACH n.d.; US NLM n.d.).

Physical form	Clear, colourless sweet liquid at 20 °C and 101.3 kPa with an ester-like odour.
Melting point	≤50 °C at 101.3 kPa
Boiling point	227.6 °C
Vapour pressure	0.065 hPa at 20 °C
Water solubility	0.0016 g/L at 25 °C
Henry's law constant (estimated)	1.10E-09 atm-m^3/mole at 25 °C
log K_{ow}	4.95 at 20 °C to 5.59 at 25 °C

Introduction and use

Australia

No information is available on introduction and industrial use of the chemicals in Australia.

International

The following international uses have been identified through:

- European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH n.d.) dossiers
- the Organisation for Economic Cooperation and Development (OECD) Screening information data set International Assessment Report SIAR (OECD 2004)
- Chemwatch (Galleria Chemica)
- Substances and Preparations in Nordic countries (SPIN) database
- European Commission Cosmetic Ingredients and Substances (CosIng) database (EC n.d.)
- the Good Scents Company (TGSC n.d.)
- the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary (US Personal Care Products Council (n.d.)
- the US Environmental Protection Agency Chemical Data Reporting (CDR) (US EPA 2020)
- the United States National Library of Medicine (NLM n.d.)
- publicly available information including Safety Data Sheets (SDSs).

Internationally, the chemical has reported cosmetic use in film-forming and artificial nail building applications. However, no specific concentrations in products are reported for the chemical. Reports indicate the chemical is unlikely to be used as a flavour or fragrance agent (TGSC n.d.).

Artificial Nail Builders are chemical ingredients that are defined under INCI as follows: "*used in nail enhancement products to build, elongate or extend the nail. They consist of various monomers, polymers, polymerisation catalysts, stabilisers and promoters which, during application to the nail, are converted to polymers that upon drying form a hard structure that resembles the natural nail plate. Some ingredients that function as Artificial Nail Builders may also have other functions, such as film formers, in other product categories*" (US Personal Care Products Council n.d.).

Methacrylate ester monomers in general have cosmetic uses as artificial nail builders in nail enhancement products. The concentrations of methacrylates containing monomers in nail enhancement products can range from 2–85% (CIR 2005). Where methacrylate ester monomers are used as secondary monomers, the typical concentrations are in the range 10–15% (Danish EPA 2008).

In products, the chemical acts as a monomer which can react with each other, and other ingredients to form a hard polymer coating on the nail. These nail products can be air dried or set more rapidly using ultraviolet (UV) light treatments. The chemical is not expected to be present in significant amounts after polymerisation (low levels of residual monomer). Whilst UV light treatments are traditionally found in professional settings, there is an increased prevalence of DIY nail kits that might contain the chemical, targeted for consumers without professional experience (Gatica-Ortega et al. 2017; Gatica-Ortega et al. 2018; Lee et al.

2015; MPA 2012; MPA 2019a; MPA 2019b). No DIY products containing the chemical could be identified through internet searches.

The chemical has reported commercial uses, including:

- in adhesives and binding agents
- as a cleaning and washing agent
- in paints, lacquers and varnishes (e.g. automotive coatings and floor polishes)
- in solvents
- in construction materials.

Some of the commercial uses may also be used in domestic applications. There were no active products for the chemicals in North American consumer product databases (DeLima Associates). There was a discontinued automotive care product for 'Trim and Detail' adhesives kits, where the chemical is available in the product (as a liquid) at concentrations between 5 to 10% (DeLima Associates (n.d.)). The REACH registration dossier for the chemical identified uses by professional users only. A use in consumer paints and coatings was reported under the US Environmental Protection Agency's Chemical Data Reporting (CDR) under the Toxic Substances Control Act (US EPA 2020). However, the function was reported as monomer. Consumer preparations for the chemical were identified in SPIN. However, it should be noted that SPIN does not distinguish between direct use of the chemical and use of the materials that are produced from chemical reactions involving the chemical.

The chemical has reported site limited use as an intermediate in the manufacture of chemicals including as a common methacrylate monomer in polymerisation for resins (including use in windscreen repair kits), copolymers and polymer plastics including food contact applications (REACH n.d.; OECD 2004).

The chemical has reported non-industrial uses, including in dental adhesives and bone cement for fixing prosthetic devices in orthopaedic surgery (OECD 2004).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

The metabolite, 2-ethylhexanol (CAS No. 104-76-7) is listed under 'Octyl alcohols' in Appendix B, *Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons)* (SUSMP) (TGA 2023).

Note: Appendix B, Clause 3 substances are considered not to require control by scheduling for any use due to low toxicity (TGA 2023).

Workers

Ethylhexyl methacrylate (CAS No. 688-84-6) is not individually listed on the HCIS (SWA n.d.).

The chemical is covered by the generic entry in the Hazardous Chemical Information System HCIS (SWA n.d.) with the following hazard category and statements for human health under the group entry of '*monoalkyl or monoaryl or monoalkyaryl esters of methacrylic acid with the exception of those specified elsewhere in this database'*:

Health hazards	Hazard category	Hazard statement
Eye irritation	Eye Irrit. 2	H319: Causes serious eye irritation
Specific target organ toxicity (single exposure)	STOT Single Exp. 3	H335: May cause respiratory irritation
Skin irritation	Skin Irrit. 2	H315: Causes skin irritation

The classifications are subject to the following notes:

'Note A: (The name of the substance should appear on the label in the form of one of the designations given in this spreadsheet. Use is sometimes made of a general description such as '... compounds' or '... salts'. In this case, the supplier should state the correct name on the label.)'

Note 8: '(The tables in schedule 6 of the WHS regulations replace some tables in the GHS, this may affect the cut off concentrations for this chemical.)'

No specific exposure standards are available for this chemical (SWA n.d.).

International regulatory status

Exposure standards

No specific exposure standards are currently available for this chemical.

European Union

The chemical is listed under the '*Switzerland Annex 10 of the Ordinance of the Federal Department of Home Affairs (FDHA) on materials and articles intended to come into contact with foodstuffs (List of permitted substances for the production of packaging inks, and related requirements - Table 1: List of substances*)' (Chemwatch n.d.).

OECD

The chemical is identified in the US EPA High Production Volume Program Chemical List (Chemwatch n.d.).

Ethylhexyl methacrylate is listed as an OECD High Production Volume (HPV) chemical. It is produced in volumes greater than 1000 tonnes per year in at least one member country of the OECD.

The chemical was assessed under the group category '*Short chain alkyl methacrylates'* and a Screening Information Data Sheet (SIDS) Initial Assessment Report (SIAR) was published (OECD 2004).

The chemical group category was considered to possess properties indicating a hazard for human health (skin sensitisation, skin and eye irritation). Based on data presented by the Sponsor countries (Japan and United States of America (USA)), exposure to humans is anticipated to be low. Therefore, these chemicals were considered to be currently a low priority for further evaluation. It was concluded that countries may choose to investigate any exposure scenarios that were not presented by the Sponsor countries.

United States of America

There is no regulation in the USA that specifically prohibits the use of methyl methacrylate monomer in cosmetic products. In the 1970s, the US Food and Drug Administration (FDA) received complaints of injury including contact dermatitis associated with the use of artificial nails containing methyl methacrylate monomer. Based on their investigations, the US FDA removed products containing 100% methyl methacrylate monomer from the market through court proceedings, resulting in a preliminary injunction against one firm, as well as seizure actions and voluntary recalls (US FDA 2022).

The Cosmetic Ingredient Review (CIR) Expert Panel determined that certain methacrylates (ethylhexyl methacrylate unspecified) are safe as used in nail enhancement products when skin contact is avoided. They recommended that products containing these ingredients should be accompanied with directions to avoid skin contact due to the sensitising potential of methacrylates (CIR 2005). The panel reconsidered this conclusion in 2021–2022 and concluded that this assessment remains valid, as no new toxicity data warrants re-evaluation of the chemicals (CIR 2022).

The chemical is also listed in the '*US FDA Indirect Food Additives - Substances for use as Components of Coatings - Resinous and polymeric coatings for polyolefin films 21CFR 175-320*' under the substance category of '(i) Resins and polymers: Vinylidene chloride copolymerized with one or more of the following: Methacrylic acid and its methyl, ethyl, propyl, butyl, or octyl esters' (Chemwatch n.d.).

Human exposure

Public

Consumers who use DIY nail products are at risk of dermal exposure to the chemical. When applying the nail product to the fingernails or toenails, the skin around the nails may be inadvertently exposed and dermal absorption may occur. Application of the nail product on to the nails is not expected to penetrate the nail plate and reach the skin under the nail because the chemical is expected to polymerise within minutes of application. For similar methacrylate esters, a set time of 3.15 minutes for tetrahydrofurfuryl methacrylate (CAS No. 2455-24-5) was reported, where the chemical is expected to fully polymerise (set), and not be bioavailable. Similarly, for ethoxyethyl methacrylate (CAS No. 2370-63-0) a set time of approximately 5 minutes was reported. It is expected that 50% of the product will polymerise, and after 1 hour, less than 1% of the residual chemical would be available (CIR 2005).

The main route of exposure is expected to be dermal. Inhalation exposure may occur from dust particles produced from filing the nails. However, this may not lead to inhalation exposure as the chemical will have polymerised. The chemical is not expected to be volatile due to its low vapour pressure.

Health hazard information

The chemical is expected to metabolise to methacrylic acid (CAS No. 79-41-4) and 2-ethylhexanol (CAS No. 104-76-7) in the human body (see **Toxicokinetics** section). Both metabolites have been previously assessed under our former scheme, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2013; NICNAS 2018). These previous assessment reports should be read in conjunction with this evaluation.

Based on available data on the metabolites, methacrylic acid does not cause significant systemic toxicity and the systemic toxicity of the chemical will likely be driven by the metabolite 2-ethylhexanol. Data for 2-ethylhexanol has been used to support findings related to systemic toxicity.

Toxicokinetics

Based on a non-guideline metabolism (in vivo and in vitro) experimental study in male Wistar rats, alkyl-methacrylate esters are rapidly absorbed and hydrolysed at extremely high rates to methacrylic acid by high capacity, ubiquitous carboxylesterases. Further to this, the removal of the hydrolysis product, methacrylic acid, is reported to be very rapid (minutes). The half-life for the chemical was reported to be 23.8 minutes, where 99.9% of the chemical was removed by first-pass metabolism in the liver. It was concluded that short chain alkyl-methacrylate esters are very rapidly metabolised by non-specific carboxylesterases to methacrylic acid (CAS No. 79-41-4) and the structurally corresponding alcohol in several tissues. The half-life for disappearance of the parent esters from the body is in the order of minutes. Methacrylic acid and the corresponding alcohol metabolite, 2-ethylhexanol (CAS No. 104-76-7) are thus expected to be subsequently cleared predominantly via the liver (by their respective pathways) (OECD 2004; REACH n.d.).

Based on an in vitro skin absorption study conducted similarly to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 428, the absorption of the chemical was evaluated through Wistar rat and human epidermis in an in vitro system. The rate of absorption of the chemical across the epidermis was measured following the application of 100 µL/cm² of the chemical to the epidermal surface. The mean rate of absorption through rat and human epidermis was 234 and 7.72 µg/cm^2-h. The total amount of chemical that was absorbed during the time of exposure was 7.8 (over 30 hours) and 0.551% (over 24 hours). No measure of the metabolism during skin absorption was reported as the epidermal layer was only used (REACH n.d.).

Methacrylates can be metabolised via 2 pathways: by ester hydrolysis (esterases) in various tissues (the main metabolic pathway) and by conjugation with GSH (only occurs at very high tissue concentrations of methacrylates). The former has been demonstrated for methacrylates in vitro and in vivo (formation of mercapturic acid) (Greim et al. 1995).

Acute toxicity

Oral

Based on the data available, the chemical has low acute oral toxicity.

In a good laboratory practice (GLP) compliant acute oral toxicity study conducted in accordance with OECD TG 401, Sprague Dawley (SD) rats (5/sex/dose) were administered (gavage) a single dose of the chemical at 0, 500, 1000 or 2000 mg/kg body weight (bw) in both sexes. The median lethal dose (LD50) was reported to be >2000 mg/kg bw (both

sexes). No significant treatment related effects on clinical parameters including body weight changes, mortality and gross pathology findings at necroscopy were reported post 14 day observation period for both sexes. Although soft faeces were reported in animals across all dose groups, the effects were considered to be attributed to corn oil that was used as a vehicle. Depression of body weight gain was also reported on the second day in both sexes (OECD 2004; REACH n.d.).

In a non-guideline acute oral toxicity study (GLP compliance unspecified), Wistar rats (5/sex/dose) were administered (gavage) a single dose of the chemical of 10.0, 12.6, 15.9, and 20.0 mL/kg bw (equivalent conversions to mg/kg bw are unspecified) in both sexes. Treatment related clinical effects (24 hours post-treatment) included signs of reduced activity, impairment of coordination, exophthalmos, and piloerection. However, changes to body weight were reported to return to normal within the observation period. Mortality during the post 14 day observation was reported in 1/10, 1/10, 3/10 and 6/10 rats at the respective doses. Gross pathology findings at necroscopy included reddening of mucous membranes in the stomach and the intestine. The LD50 was reported to be >2000 mg/kg bw (equivalent to LD50 of 16465 mg/kg bw based on 20.0 mL/kg bw) (OECD 2004; REACH n.d.).

In a range of non-GLP compliant non-guideline acute oral toxicity studies in rats and mice, LD50s of 2152 to >12800 mg/kg bw were reported. No further study details were available (OECD 2004; REACH n.d.).

Dermal

Based on the available data, and low dermal absorption expected in humans (see **Toxicokinetics** section), the chemical is considered to have low acute dermal toxicity.

In a limited non-guideline acute dermal toxicity study in guinea pigs (unspecified strain), an LD50 of 17620 mg/kg bw (based on 20.0 mL/kg bw) was reported. No further study details are available (OECD 2004; REACH n.d.).

Inhalation

Based on the limited available data, the chemical is considered to have low acute inhalation toxicity.

In a non-GLP compliant, limited non-guideline acute inhalation toxicity study in rats, a Lethal Concentration (LC0) was reported to be >14 ppm after 6 hours of exposure. No mortality was reported. No further study details are available (OECD 2004; REACH n.d.).

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is not expected to be irritating to the skin, although slight irritation cannot be excluded. The data do not meet the classification criteria for skin irritation. Although the chemical is captured by the generic entry '*monoalkyl or monoaryl or monoalkyaryl esters of methacrylic acid'* in the HCIS (see **Existing Australian regulatory controls** section), there is insufficient evidence to support a recommendation to amend this.

In a non GLP-compliant, in vivo skin irritation study conducted in 6 New Zealand white (NZW) rabbits (sex not specified), an undiluted 0.5 mL aliquot of the chemical was applied to

abraded (scarified) and intact (shaved) skin for 24 hours, under occlusion. Observations were recorded at 24, 48 and 72 hours after patch removal. The following mean scores for all 6 animals were reported for observations at 24, 48 and 72 hours: 1.66 for erythema, and 0.9 for oedema for shaved skin; and 1.6 for erythema, and 2.1 for oedema scarified skin (maximum score out of 4). At 24 hours post application on abraded (scarified) and intact (shaved) skin, well defined erythema was observed in 5/6 animals. At 72 hours post application 3/6 animals had well defined erythema; and 3/6 had very slight erythema. Slight oedema was reported 24 hours post application in all 6/6 animals (where very slight oedema was observed in 2/6 of these animals). These effects (oedema) were reported to be completely reversible within 72 hours in 5/6 animals except 1/6 animals with very slight oedema. A primary irritation index of 3.1 was reported (OECD 2004; REACH n.d.).

In a similar non GLP compliant in vivo skin irritation study, an undiluted 0.5 mL aliquot of the chemical was applied to abraded (scarified) and intact (shaved) skin of 6 NZW rabbits (sex not specified), for 24 hours, under occlusion. Observations were recorded at 24 and 72 hours after patch removal. The following mean scores for all 6 animals were reported for observations at 24 and 72 hours: 1.9 for erythema, and 2.2 for oedema for shaved skin; and 1.9 for erythema, and 2.1 for oedema abraded skin (maximum score out of 4). Signs of irritation include barely perceptible to moderate reddening and swelling of the skin at 24 hours post application (where reactions continued to 72 hours). It was reported that the chemical induced well defined to moderate erythema which was not reversible 72 hours post exposure. Very slight to moderate oedema was reported over the 72 hours observation period. A general increase in turgor, discolouration and induration were also reported. A primary irritation index of 4.04 was reported (OECD 2004; REACH n.d.).

In a GLP compliant in vitro skin irritation study reported to be conducted according to OECD TG 439 (in vitro reconstructed human epidermis (RHE) test method for skin irritation. The chemical (100% concentration; no vehicle), was applied topically to a 3 dimensional RHE human skin model (EpiDerm™) for 1 hour. A mean tissue viability of 95% was reported for the chemical in this study, and it was determined to be not irritating to the skin (REACH n.d.).

Short chain alkyl-methacrylate esters are generally reported to be considered slightly irritating to the skin of rabbits when applied under semi-occlusive conditions for short durations, with moderate irritation developing with more effective occlusion and prolonged contact. However, it was acknowledged there was a high degree of variability between skin irritancy data due to differing protocols used and physico-chemical properties of the respective methacrylate esters (OECD 2004).

Eye irritation

Based on the available data, the chemical is expected to be at most slightly irritating to the eyes. The data do not meet the classification criteria for eye irritation. Although the chemical is covered by the generic entry '*monoalkyl or monoaryl or monoalkyaryl esters of methacrylic acid'* in the HCIS (see **Existing Australian regulatory controls** section), there is insufficient evidence to support a recommendation to amend this.

In a non-GLP compliant in vivo eye irritation study, a single application of 0.1 mL of the undiluted chemical was instilled into the conjunctival sac of the left eye of 6 NZW rabbits (sex not specified) and left unrinsed. The right eye was left untreated and served as a control. Observations were made at 24, 48 and 72 hours and up to 7 days after installation. The following mean scores (for all 6 animals) were reported at 24, 48 and 72 hours: corneal opacity 0/4, iritis 0/2, conjunctival redness 0/3, and chemosis 0/4. Except for initial

conjunctival redness, no treatment related effects were reported, and the chemical was considered to not be irritating to the eye (OECD 2004; REACH n.d.).

In another non-GLP compliant in vivo eye irritation study, a single application of 0.1 mL of the undiluted chemical was instilled into the conjunctival sac of the left eye of 6 female NZW rabbits and left unrinsed. Observations were made at 24, 48 and 72 hours and up to 7 days after installation. The following mean scores were reported at 24, 48 and 72 hours for all 6 animals: corneal opacity 0/4, iritis 0/2, conjunctival redness 0.33/3, and chemosis 0.11/4 (OECD 2004; REACH n.d.).

It was reported that short chain alkyl-methacrylate esters have decreasing eye irritancy across the category from ethyl methacrylate (EMA) which is expected to produce slight to moderate eye irritation, as compared to ethylhexyl methacrylate (the chemical). The chemical is expected (at worst) to produce slight irritation. However, it was acknowledged there was a high degree of variability between eye irritancy data to establish a clear trend (OECD 2004).

Respiratory irritation

The limited available data indicate the chemical is not expected to be a respiratory irritant. Although the chemical is captured by the generic entry '*monoalkyl or monoaryl or monoalkyaryl esters of methacrylic acid'* in the HCIS (see **Existing Australian regulatory controls** section), there is insufficient evidence to support a recommendation to amend this.

While inhalation of the chemical as a vapour is not expected due to its low vapour pressure, under normal conditions of use (see **Relevant physical and chemical properties** section), respiratory irritation was reported in structurally related short-chain alkyl-methacrylate esters (such as ethyl methacrylate (EMA)). This finding was based on 6hour acute inhalation studies where lesions in the olfactory region of the nasal cavity were observed at 200 ppm.

It was reported that larger esters (such as butyl methacrylate (BMA)) are not expected to be respiratory irritants. A clear trend exists across the short chain alkyl methacrylate category such that a no observed adverse effect concentration (NOAEC) or lowest observed adverse effect concentration (LOAEC) for olfactory nasal lesions is expected to increase with increasing ester size (OECD 2004; REACH n.d.).

Sensitisation

Skin sensitisation

Based on the weight of evidence from available in vivo animal, in silico and human data, the chemical is not considered to be a potent sensitiser. Although ≥ 30% sensitisation rate has been reported in 2 non-guideline guinea pig maximisation tests (GPMT), the chemical was negative in 3 other studies including a guideline LLNA and GPMT study. No positive reactions have been observed in patch tests in humans and in silico predictions mostly indicate no or weak sensitisation potential.

However, chemicals that contain acrylate and methacrylate moieties are often used in nail products and can be skin sensitisers that induce contact allergic dermatitis. The chemicals in this evaluation may cause cross reactions in individuals who are sensitised to other acrylates and methacrylates in other products (CIR 2005).

In vivo

In a GLP compliant local lymph node (LLNA) assay conducted according to OECD TG 429, 5 females/dose CBA/CaOlaHsd mice received topical application of the chemical (in acetone/olive oil (4:1 v/v); purity of 99.23%) at concentrations of 25, 50 or 100% (w/v). The reported stimulation indices (SI) were, 1.53, 2.66, and 2.85 for concentrations of 25, 50 or 100%, respectively. The concentration to produce a 3 fold increase in lymphocyte proliferation (EC3) was not calculated as a clear dose response was reported, where the maximum concentration (100%) used in the study only produced an S.I. of 2.85. It was also reported on day 4 of the animals treated with the top 2 doses of the chemical, exhibited signs of skin irritation (erythema) on the ear post exposure but slowly resolved by days 5 and 6. The chemical was reported to not be a skin sensitiser (REACH n.d.).

In a guideline GLP guinea pig maximisation test (GPMT) according to OECD TG 406, intradermal induction was performed on Dunkin Hartley 20 female guinea pigs using 1% of the chemical in distilled water. The chemical (undiluted) was used for topical induction. The animals were challenged with 75% (in distilled water) and undiluted chemical. After challenge, no positive reactions were observed (OECD 2004; REACH n.d.).

In a non-guideline guinea pig maximisation test (GPMT), intradermal induction was performed on 12 female SSC:AL guinea pigs using 25% of the chemical in soybean oil. The chemical (undiluted) was used for topical induction. The animals were challenged with 25% (in petrolatum). A second experiment was performed with 20 animals with induction at 5% and challenge at 3%. After challenge and induction at 25%, positive reactions were reported in 2/12 animals. 48 hours post exposure after challenge. No positive reactions were observed in the second study (OECD 2004; REACH n.d.).

In a non-guideline GPMT, intradermal induction was performed on 10 female Dunkin Hartley (DH) guinea pigs using 5% of the chemical in paraffin oil. The chemical (undiluted) was used for topical induction and challenged 2 weeks with 33% after topical induction under occlusion. After challenge, positive reactions included mild or well-defined erythema reported in 3/10 animals 48 hours post-exposure after challenge. Treatment related effects included slight oedema in 2/10 animals at 72 hours (OECD 2004; REACH n.d.).

In another non-compliant GPMT, a sensitisation rate of 40% in 10 female DH guinea pigs was reported following intradermal and topical induction and challenge at 0.1M (OECD 2004; REACH n.d.).

It was reported short-chain alkyl-methacrylate esters have equivocal results in adjuvant studies in guinea pigs and may be regarded at worst, weak contact sensitisers. EMA and butyl methacrylate (BMA) have been reported to cross react with other methacrylate esters, but not with acrylate esters. Cross reactivity with other methacrylate esters has been reported. However, cross reactivity with common acrylates (i.e., between methacrylates and acrylates) was not reported. As in animals, methacrylate esters can cross react with other methacrylates but not with acrylates in humans (OCED 2004).

In silico

Mixed results for skin sensitisation were found for the chemical in several in silico models.

The chemical did not contain key protein binding alerts for skin sensitisation based on its structure using the mechanistic and endpoint-specific profilers of the OECD Quantitative Structure Activity Relationship (QSAR) Toolbox v4.6 (OECD QSAR 2023) and OASIS TIMES.

The expert rule based systems, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (version 6.0.1) and METEOR Nexus (version 3.1.0), were used to estimate the skin sensitisation potential of the chemical and its simulated metabolites (Lhasa Limited). Alerts for skin sensitisation by alpha, beta-unsaturated esters were reported. Alpha, beta-unsaturated esters are electrophilic groups that are known to undergo Michael additions with nucleophiles. Therefore, they are likely to interact with skin proteins by such a mechanism. A predicted EC3 value (LLNA) was not available as the chemical and phase 1 and 2 metabolites were reported to be non-sensitisers (or at worst, weak sensitiser) in comparison to similar structures.

Respiratory sensitisation

No data are available for this chemical. The chemical structure presented a structural alert (Michael Addition > Polarised alkenes > Methacrylates) for respiratory sensitisation as profiled by the OECD QSAR Toolbox v4.6 (OECD QSAR 2023). Given the relatively low vapour pressure and uses of the chemical, exposure through the inhalation route is unlikely.

There are concerns that low molecular weight (<C8) methacrylates are potential respiratory sensitisers. However, there is insufficient data to classify this chemical (ECHA 2023).. It was reported that there was no evidence that exposure to short chain alkyl-methacrylate esters is associated with respiratory allergy (OECD 2004).

Observation in humans

In human patch tests, 3–10% of the chemical (in olive oil) was dermally applied to the skin of 17 patients (with contact dermatitis and other skin conditions) under occlusive conditions over 48 hours. No evidence of sensitisation was reported (OECD 2004).

Three out of 4 patients with allergic occupational contact dermatitis (attributed to work exposure to acrylates during work with dental protheses) were patch tested with the chemical (1% in petrolatum) under semi-occlusive conditions over 24 hours. No positive reactions to the chemical were reported (OECD 2004; REACH n.d.).

Five patients with dermatitis due to acrylate allergies were patch tested with several acrylates and methacrylates, including the chemical at a concentration of 5% (in olive oil). No positive reactions were reported. No further data were available (OECD 2004; REACH n.d.).

No evidence of skin sensitisation was reported in seven dental technicians with contact dermatitis on their hands (attributed to work exposure to repairing of dental protheses with self-curing acrylic plastics). The technicians were patch tested with 1% of the chemical (in petrolatum) under semi-occlusive conditions over 24 hours (OECD 2004; REACH n.d.).

In an occupational case study, a worker (with a pre-existing skin condition of psoriasis) was exposed to a glue adhesive (consisting of the chemical at <37% and hydroxyethyl methacrylate (<50%)) consisting of several acrylates and methacrylates. It was reported that the worker experienced intermittent scaling of dorsal hands and distal phalanges, including the fingertips, where fissuring extended under the nails. However, a patch test with the chemical was not performed separately (REACH n.d.).

Repeat dose toxicity

Oral

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure. The severity of the adverse effects or doses at which effects were observed is not sufficient to warrant hazard classification.

In a GLP compliant study supporting combined repeated dose/reproductive/developmental oral toxicity study (equivalent to OECD TG 422), male and female SD rats (12/sex/dose) were administered the chemical (by oral gavage in vehicle: corn oil) once daily at doses of 0, 30, 100, 300 or 1000 mg/kg bw/day, 7 days a week (refer to **Reproductive & Developmental Toxicity** section). One female in the highest dose group died. Treatment related effects in the animals of the highest dose group included decreased body weight and food consumption. Transient salivation shortly after administration was observed in animals of both sexes at 30 mg/kg bw/day and above, which may be related to the treatment administration.

Study results indicated that male rats in the 300 and 1000 mg/kg bw/day groups had significantly high absolute and relative kidney weights and increased relative weights of the pituitary gland and liver. The 300 mg/kg bw/day level was considered a lowest observed adverse effect level (LOAEL) for males based on organ weight changes, despite lacking histopathological changes because of corresponding changes at the highest dose of 1000 mg/kg bw/day in serum blood urea nitrogen (BUN) test (kidneys); protein, enzymes and albumin/globulin (A/G) ratio (liver), and haematology parameters (spleen and pituitary). In females at the highest dose the following results were reported at necropsy:

- an atrophied thymus and hypertrophy of bilateral adrenal glands
- significantly high absolute kidney weights
- increased relative weights of thyroid gland, liver and brain
- decreased absolute weights of the pituitary gland and heart.

There was increased relative (but not absolute) kidney weights in females at both 100 and 300 mg/kg bw/day and decreased absolute and relative liver weights in females at 300 mg/kg bw/day. However, these effects were reported to not be dose dependent and were not considered to be related to treatment. The LOAEL for females is considered to be 100 mg/kg bw/day based on organ weight changes in both liver (absolute and relative) and kidneys (relative only). Treatment related microscopic changes were reported in the liver and spleen of males, and in the thymus, spleen and brain of females in the highest dose groups. Histopathological changes included:

- mild focal necrosis of the liver in 2 male rats
- mild decreased extramedullary haematopoiesis in the spleen of 3 male rats and 4 female rats
- mild atrophy of the thymus in 4 female rats,
- softened lesion of the medulla oblongata in 2 female rats at the highest dose.

The no observed adverse effect level (NOAEL) for systemic toxicity for the chemical was 100 mg/kg bw/day in males and 30 mg/kg bw/day in females, based on organ weight changes (OECD 2004; REACH n.d.).

In a GLP compliant 90 day subchronic repeated oral toxicity study (OECD TG 408), Wistar rats of both sexes (15/sex/highest dose group; 10/sex/lower dose groups) were administered the chemical in drinking water daily at 0, 60, 120, or 360 mg/kg bw/day, for 90 days.

Treatment related effects (as compared to controls) included significantly lower body weights in female animals at the highest dose of 360 mg/kg bw/day from day 35 onwards until the end of the administration period and the recovery period. As the lower body weight correlated with the reduced food consumption, it was considered to be related to the administration of the chemical. The high dose group also exhibited adaptive effects including increased potassium levels in both sexes, increased chloride levels and decreased globulin levels in females. The clinical pathology parameters were reported to be transient, returning to the normal range during the recovery period, and not considered adverse as histopathological findings could not be correlated. At 120 and 60 mg/kg bw/day, no treatment related adverse effects were reported for clinical and pathology parameters. An NOAEL of 120 mg/kg bw/day was reported for both sexes based on the lower body weights and changes in blood chemistry parameters (REACH n.d.). However, the change in body weight were correlated with the reduced food consumption, and the blood chemistry parameters returned to normal range. Therefore, the NOAEL is considered to be 360 mg/kg bw/day for both sexes.

The metabolite 2-ethylhexanol is not expected to have specific adverse effects following repeated oral exposure (NICNAS 2013).

Dermal

No data are available for the chemical.

Inhalation

Based on the limited reliable data available, the chemical is not expected to cause specific adverse effects following repeated inhalation exposure.

In a non-GLP compliant non-guideline, subchronic repeat dose inhalation screening study, no clinical signs of toxicity were reported in 8 Alderly Park rats (4/sex/dose) exposed to the chemical (in vapour form) at concentrations of 25 or 60 ppm. The duration of the exposure was reported to be 6 hours/day, 5 days per week, for 3 weeks. No treatment related effects were reported upon gross examination of major organs. However, increased cellularity in the lungs of the rats exposed to the highest concentration upon microscopic examination was reported. A no observed adverse effect concentration (NOAEC) was not established. No further study details are available (OECD 2004; REACH n.d.).

Genotoxicity

Based on the available data, the chemical is not considered to have genotoxic potential. No in vivo studies on the chemical were available. However, vivo studies from structurally related short-chain alkyl-methacrylate esters are available. The metabolite, 2-ethylhexanol is not expected to be genotoxic (NICNAS 2013; NICNAS 2018; SWA n.d.).

In vitro

Negative results were reported in the following in vitro assays (OECD 2004; REACH n.d.):

- bacterial mutation assays (OECD TG 471 and 472) (various *Salmonella typhimurium* strains: TA 1535, TA 1537, TA 98, TA 100, TA 102 and *Escherichia coli* WP2 uvrA) with and without metabolic activation at doses up to 5000 µg/plate
- an in vitro mammalian chromosome aberration assay (OECD TG 473) in human lymphocytes with and without metabolic activation at concentrations up to 1980 µg/mL

- an in vitro mammalian chromosome aberration assay (according to OECD TG 473) in Chinese hamster lung (CHL) cells with and without metabolic activation at concentrations up to 5000 µg/mL
- a mammalian gene mutation assay (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster lung fibroblasts V79 with and without metabolic activation at concentrations up to 2000 µg/mL.

In vivo

Negative in vivo results were reported for structurally related short chain alkyl-methacrylate esters (iso-butyl methacrylate (i-BMA; CAS No. 97-86-9) and n-butyl methacrylate (n-BMA; CAS No. 97-88-1)) conducted according to mammalian in vivo chromosome mutation tests (OECD TG 474) at doses of up to 5000 mg/kg bw using mouse bone marrow cells (OECD 2004).

In silico

The chemical did not contain structural alerts for in vitro mutagenicity (Ames test) based on its structure as profiled (in silico) by DEREK Nexus, OECD QSAR Toolbox v4.6 (OECD QSAR 2023), OASIS TIMES and ChemTunes ToxGPS.

The chemical did contain a DNA binding alert (Michael addition > Polarised Alkenes-Michael addition > Alpha, beta- unsaturated esters) based on its structure for genotoxicity as profiled (in silico) by the OECD QSAR Toolbox v4.6 (OECD QSAR 2023) and DEREK Nexus.

ChemTunes ToxGPS predicted an uncertain result for in vitro chromosomal aberration and a negative result for in vivo micronucleus (predictions were within the applicability domain of the models).

Carcinogenicity

No data are available for the chemical.

The 2 main metabolites of the chemical (see **Toxicokinetics** and **Existing Australian regulatory controls** sections), 2-ethylhexanol and methacrylic acid, are not expected to be carcinogenic (NICNAS 2013; NICNAS 2018).

In addition, the results of carcinogenicity studies conducted on other methacrylates indicated that they are not carcinogenic (CIR 2005).

In silico

The chemical structure did not contain an alert for genotoxic carcinogenicity based on its structure for carcinogenicity as profiled (in silico) by the OECD QSAR Toolbox v4.6 (OCED QSAR 2023) and DEREK Nexus.

Reproductive and development toxicity

Based on the available data, the chemical is not expected to cause significant adverse effects on fertility for reproduction and/or development. Although some effects were observed at high doses these are considered secondary to maternal toxicity. The developmental effects observed for the metabolite (2-ethylhexanol) were not observed in any studies

indicating that the metabolite may not be bioavailable systemically at doses that are high enough to be toxicologically relevant.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening study conducted in accordance with OECD TG 422, the chemical (in vehicle corn oil) was administered daily by oral gavage to SD rats (12/sex/dose) at 0, 30, 100, 300, or 1000 mg/kg bw/day. Male rats were dosed for 49 days; and female rats were dosed from 14 days prior to mating through day 3 of lactation.

All animals apart from one female in the highest dose group survived the study. Decreases in body weight and food consumption were observed in high dose females. There were no adverse effects in dams at any other doses. There were no treatment-related adverse effects in males.

The fertility index was not affected at any of the doses. At the highest dose there were adverse effects on reproductive parameters in females. These included decrease oestrus cycles, prolonged gestation period, decreased number of corpora lutea and implantation sites, and decreased parturition index (77.8%). At this dose, bodyweights of pups and survival during the lactation period was also reduced.

At ≤300 mg/kg bw/day there were no reported effects on the total number of offspring, or the parturition index compared with the control group. Pup survival was reduced on day 0 of lactation at 300 mg/kg bw/day; however, by day 4 survival were not different compared to controls (due to reduced survival in the control group). Furthermore, the observed mean number of pups (13.4) was within the range of newborn F1 in the controls of other OECD TG 422 studies in the same laboratory (13.1–15.2, n=10).

No gross abnormalities were reported in pups at any dose levels. Gross pathology findings at necroscopy included yellowish white nodules in the tail of the right epididymis in one male animal at 300 mg/kg bw/day.

The NOAEL for developmental toxicity is 300 mg/kg bw/day based on reduced parturition index, reduced pup survival, reduced pup bodyweight at 1000 mg/kg bw/day. The NOAEL for female reproductive toxicity is 300 mg/kg bw/day based on decreases in the number of corpora lutea and the number of implantation sites at 1000 mg/kg bw/day. Male reproductive performance was not affected by the chemical (OECD 2004; REACH n.d.).

In a non-GLP compliant, prenatal developmental toxicity study (equivalent to OECD TG 414), NZW rabbits (n=25/group) were administered the chemical at concentrations of 30, 100 and 300 mg/kg bw/day during gestation days (GD) 6–28. No statistically significant treatment related adverse effects were reported on reproductive and developmental parameters. Maternal toxicity was observed at dose level of 300 mg/kg bw/day where treatment related effects included reduced food consumption, absolute weight gain, clinical signs of toxicity and macroscopic findings. Developmental toxicity was observed at the same dose based on slightly higher number of females with post implantation loss (attributed to secondary effects to maternal toxicity) and was not considered an adverse effect (not statistically significant as the mean number of viable foetuses remained unaffected). An NOAEL for maternal and developmental toxicity was reported to be 100 and 300 mg/kg bw/day, respectively (OECD 2004; REACH n.d.).

The metabolite, 2-ethylhexanol (CAS No. 104-76-7) is currently classified under the GHS for reproductive toxicity (category 2). The chemical was reported to cause developmental toxicity, in rats following administration via the oral route (NICNAS 2013). These effects were noted in the absence of signs of marked maternal toxicity and included markedly 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.

Neurotoxicity

In a GLP compliant non-guideline 90 day subchronic oral study, male and female Wistar rats (5/sex/dose (high dose); 10/sex/dose (low and mid dose)) were administered the chemical (by oral gavage in vehicle: CMC (carboxymethyl cellulose)) once daily at doses 0, 60, 120 or 360 mg/kg bw/day, 7 days a week for a total of 90 days. No treatment related effects were reported on parameters for neurotoxicity including functional observational battery and motor activity (REACH n.d.).

References

ChemTunes ToxGPS (Version 4.0), [Computer software], Molecular Networks GmbH and Altamira, LLC (MN-AM), accessed 01 September 2023.

Chemwatch (n.d.) Galleria Chemica, Chemwatch website, accessed 01 September 2023.

CIR (Cosmetic Ingredient Review) (2005) *Final Report of the Safety Assessment of Methacrylate Ester Monomers Used in Nail Enhancement Products*, CIR, accessed 01 September 2023.

CIR (Cosmetic Ingredient Review) (2022) *160th Expert Panel Meeting: Memo, Agenda, Minutes*, CIR, accessed 01 September 2023.

Danish EPA (Danish Environmental Protection Agency) (2008) *Survey and safety assessment of Chemical substances in artificial nails and nail hardeners*, DK EPA, accessed 01 September 2023.

DeLima Associates (n.d.) CPID (Consumer Product Information Database), DeLima Associates website, accessed 01 September 2023.

DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (Version 6.0.1), [Computer software], Lhasa Limited website, accessed 01 September 2023.

EC (European Commission) (n.d.) *CosIng*, EC website, accessed 01 September 2023.

ECHA (European Chemicals Agency) (2023) *Assessment of Regulatory Needs for Acrylates and methacrylates with linear or branched aliphatic alcohols, simple acids and salts*, ECHA, accessed 13 July 2023.

Gatica-Ortega ME, Pastor-Nieto MA, Mercader-García P, Silvestre-Salvador JF (2017). 'Allergic contact dermatitis caused by (meth)acrylates in long-lasting nail polish - are we facing a new epidemic in the beauty industry?', *Contact Dermatitis*, 77(6):360-366, doi: 10.1111/cod.12827.

Gatica-Ortega ME, Pastor-Nieto MA, Gil-Redondo R, Martínez-Lorenzo ER, Schöendorff-Ortega C (2018). 'Non-occupational allergic contact dermatitis caused by long-lasting nail polish kits for home use: the tip of the iceberg.' *Contact Dermatitis*. Apr;78(4):261-265. doi: 10.1111/cod.12948

Greim H, Ahlers J, Bias R, Broecker B, Hollander H, Gelbke HP, Jacobi S, Klimisch H-J, Mangelsdorf I, Mayr W, Schon N, Stropp G, Stahnecker P, Vogel R, Weber C, Ziegler-Skylakakis K, Bayer E (1995) 'Assessment of structurally related chemicals: toxicity and ecotoxicity of acrylic acid and acrylic acid alkyl esters (acrylates), methacrylic acid and methacrylic acid alkyl esters (methacrylates)', *Chemosphere,* 31:2637–2659.

MPA (Methacrylate Producers Association) (2012). *The methacrylate producers association's position on use of methacrylic acid and unreacted methacrylate monomers liquid form in artificial nail products* (2012), accessed 01 September 2023.

MPA (Methacrylate Producers Association) (2019a). *Global product safety summary: 2-ethylhexyl methacrylate* (2019), accessed 01 September 2023.

MPA (Methacrylate Producers Association) (2019b). *Global product safety summary: Basic methacrylate category* (2019), accessed 01 September 2023.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2013) *IMAP Single Assessment Report – 1-Hexanol, 2-ethyl-: Human health tier II assessment*, NICNAS, accessed 01 September 2023.

NICNAS (National Industrial Chemicals Notification and Assessment Scheme) (2018) *IMAP Single Assessment Report – 2-Propenoic acid, 2-methyl-: Human health tier II assessment*, NICNAS, accessed 01 September 2023.

OECD (Organisation for Economic Co-operation and Development) (2004). *SIDS Initial Assessment Report (SIAR) on Short chain alkyl methacrylates (CAS No. 688-84-6)*, OECD website, accessed 01 September 2023.

OASIS–TIMES (Optimised Approach based on Structural Indices Set–TIssue MEtabolism Simulator) (Version 2.28.1.6), OASIS LMC (Laboratory of Mathematical Chemistry) [Computer software], LMC, accessed 01 September 2023.

OECD QSAR (Organisation for Economic Co-operation and Development) (2023) *Quantitative Structure-Activity Relationship Toolbox* (Version 4.6) [Computer software], OECD website, accessed 01 September 2023.

REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) (n.d.) *Registered dossier for 2-ethylhexyl methacrylate, CAS No. 688-84-6*, European Chemicals Agency website, accessed 01 September 2023.

RIVM (The Dutch National Institute for Public Health and the Environment) (2012) *Cosmetics Fact Sheet - To assess the risks for the consumer, Updated version for ConsExpo 4, Report 320104001/2006*, RIVM website, accessed 01 September 2023.

SCCS (Scientific Committee on Consumer Safety) (2023) *The SCCS's notes of guidance for the testing of cosmetic substances and their safety evaluation*, 12th revision, European Commission website, accessed 01 September 2023.

SWA (Safe Work Australia) (n.d.) *Hazardous Chemical Information System*, SWA website, accessed 01 September 2023.

SPIN (Substances in Preparation in Nordic Countries) (n.d.). *SPIN Database*, SPIN website, accessed 01 September 2023.

TGA (Therapeutic Goods Administration) (2023) *Standard for the Uniform Scheduling of Medicines and Poisons (Poisons Standard July 2023)*, TGA, accessed 01 September 2023.

TGSC (The Good Scents Company) (n.d.). *Information System on 2-ethyl hexyl methacrylate (CAS No. 688-84-6)*, accessed 01 September 2023.

UNECE (United Nations Economic Commission for Europe) (2017) *Globally Harmonized System of Classification and Labelling of Chemicals (GHS) Seventh Revised Edition*, UNECE, accessed 01 September 2023.

US EPA (United States Environmental Protection Agency Chemical Data Reporting (CDR)) (2020) *Chemical Data Reporting under the Toxic Substances Control Act*, accessed 14 September 2023.

US FDA (United States Food and Drug Administration) (2022) *Cosmetics Safety Q&A: Prohibited Ingredients*, US FDA, accessed 01 September 2023.

US NLM (United States National Library of Medicine) (n.d.) *ChemIDplus Advanced Database*, NLM website, accessed August 2022.

United States (US) Personal Care Products Council (n.d.) *Cosmetic Ingredient Identification Database*, Personal Care Products Council website, accessed 01 September 2023.