



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

2-Methoxyethyl methacrylate and 2-ethoxyethyl methacrylate

Evaluation statement

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Draft

DRAFT



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AICIS evaluation statement

Subject of the evaluation

2-Methoxyethyl methacrylate and 2-ethoxyethyl methacrylate

Chemicals in this evaluation

Name	CAS registry number
2-Propenoic acid, 2-methyl-, 2-ethoxyethyl ester	2370-63-0
2-Propenoic acid, 2-methyl-, 2-methoxyethyl ester	6976-93-8

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemicals in this group are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment of all identified industrial uses of these chemicals in Australia.

These chemicals have been evaluated as a group as they are structurally similar, only differing by one methyl group. They are both esters of methacrylic acid (CAS No. 79-41-4), with 2-ethoxyethyl methacrylate being the ester formed from 2-ethoxyethanol (CAS No. 110-80-5) and 2-methoxyethyl methacrylate being the ester formed from 2-methoxyethanol (CAS No. 109-86-4). These chemicals are expected to have similar use patterns, bioavailability and toxicity.

Summary of evaluation

Summary of introduction, use and end use

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

Based on international use information, 2-ethoxyethyl methacrylate (CAS No. 2370-63-0) had reported previous use in nail enhancement products for professional and consumer use at concentrations up to 85%. Recent survey data indicated the chemical is no longer used in these products. Consumer products could include Do-It-Yourself (DIY) at home cosmetic nail kits that are used outside of professional settings although no evidence of use could be identified. No specific information on the cosmetic uses of 2-methoxyethyl methacrylate (CAS No. 6976-93-8) were identified, but given the chemical similarity, both chemicals have potential to have similar uses.

Both chemicals are used as intermediates in chemical synthesis and for the manufacturing of polymers used in cosmetics (including hair products) and food contact materials. While there are identified uses in dental adhesives 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 these chemicals and were supported with read across information from a structurally similar chemical. As these chemicals are methacrylate esters that are expected to hydrolyse in vivo, information on systemic hazards was further supported by the available data for the metabolites 2-ethoxyethanol and 2-methoxyethanol. The systemic toxicity of these chemicals will likely be driven by these metabolites.

Based on the available data these chemicals:

- have low acute and dermal toxicity
- are at most slightly irritating to skin and eyes
- are not considered to have genotoxic potential
- are not expected to be carcinogenic.

Chemicals that contain acrylate and methacrylate groups are often used in nail products and can be skin sensitisers that induce contact allergic dermatitis. Based on the available data, chemicals in this evaluation are not considered likely to be skin sensitisers but may cause cross reactions in individuals who are sensitised to other acrylates and methacrylates in other products.

Based on the read across information from a structurally similar chemical and the metabolites of these chemicals, chemicals are expected to cause adverse effects on fertility and development.

Adverse effects on male reproductive organs, fertility and pup viability have been observed in a study with a structurally related chemical. The metabolites have been shown to cause similar effects in multiple animals after exposure via oral, dermal or inhalation exposure. The effects included: decreased testes weight, atrophy of the testes, decreased sperm motility and changes in sperm morphology. In females, decreased fertility was observed after exposure to 2-ethoxyethanol. Changes in the oestrus cycle and hormone levels and histopathological changes in the ovaries were observed after exposure to 2-methoxyethanol.

The adverse effects on development observed after exposure to these metabolites included:

- decreased numbers of litters
- reduced foetal body weight
- reduced pup viability
- changes in neurochemistry and behaviours
- increased incidence of foetal malformations.

The adverse effects on development were independent of maternal toxicity.

No inhalation data are available. Given the relatively low vapour pressures and uses of these chemicals, exposure by inhalation is unlikely.

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

Hazard classifications relevant for worker health and safety

These chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Reproductive toxicity	Repr. 1B	H360FD: May damage fertility and the unborn child

Summary of health risk

Public

Based on the available use information, the public may be exposed to these chemicals:

- by direct application of these chemicals to the nails and from using nail enhancement products (such as artificial nails).
- at concentrations up to 85%.

Although the public could come into contact with articles or coated surfaces containing these chemicals, it is expected that these chemicals will be bound within articles or coated surfaces and hence will not be bioavailable.

When using nail products containing these chemicals, short term small volume skin contact in the immediate vicinity of the fingernail may occur. Exposure is considered more probable for home use of these chemicals compared to the use in salons by trained personnel. The low volatility of these chemicals limits the potential for exposure through vapour inhalation. The risk is highest when products are in a liquid form as they contain monomers that may be bioavailable. If products are not completely set, dried or 'UV-cured', there is an increased risk of absorption of residual monomers through the skin. The risk is lowered after the liquid nail product has hardened or set, as the monomers polymerise, which reduces their bioavailability.

The chemical, 2-ethoxyethyl methacrylate, has historical reported use in nail enhancement products at high concentrations. No specific information on the cosmetic uses of 2-methoxyethyl methacrylate were identified, but given the chemical similarity, both chemicals have potential to have similar uses.

These chemicals have the potential to cause systemic long term effects on reproduction and development following dermal application. Using a worst-case scenario model, the dose from a typical application of a product containing 2-ethoxyethyl methacrylate was determined to be 2.2 mg/kg bw/day. Using the lowest available no adverse effect level (NOAEL) for developmental toxicity of the metabolite 2-ethoxyethanol, the margin of exposure (MOE) for the use of the chemical in nail enhancement products is 18. The MOE value estimates the likelihood that an adverse health effect will occur under the conditions of exposure. Using interspecies and intraspecies assessment factors of 10, the acceptable MOE for an NOAEL-based assessment is greater than or equal to 100. Despite uncertainties due to a lack of

specific data on these chemicals, the calculated MOE of 18 is significantly less than 100 and indicates a potential health risk to the public if used in these products.

However, based on more recent data, these chemicals are unlikely to be in use in products available to the public. Therefore, there are no identified risks to the public that require management. If additional information become available indicating consumer use of these chemicals in Australia, further evaluation of these chemicals may be required.

Workers

Beauticians and/or nail technicians who frequently apply nail enhancement products to consumers are likely to have a higher risk of repeated exposure to these chemicals through the dermal route. There may be risk of inhalation exposure including dust particles containing these chemicals when filing, buffing, or removing nails, but this would not be due to the intrinsic hazard properties of these chemicals.

During product formulation and packaging, dermal, 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 these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Beauticians and/or nail technicians who frequently apply nail enhancement products to consumers are likely to have a higher risk of repeated exposure to these chemicals through the dermal route. There may be risk of inhalation exposure including dust particles containing these chemicals when filing, buffing, or removing nails, but this would not be due to the intrinsic hazard properties of these chemicals.

Given the critical systemic long term health effects and potential for cross 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**).

Proposed means for managing risk

Inventory Listing

To manage the risks to public health from the introduction and use of these chemicals, the Inventory listing should be varied under *Section 86* of the *Industrial Chemicals (IC) Act 2019*.

Term of listing	Details
Specific requirements to provide information to the Executive Director under <i>Section 101</i> of the <i>IC Act</i>	<p>Obligations to provide information apply. You must tell the Executive Director the volume of introduction, use and end use of the chemical within 20 working days if:</p> <ul style="list-style-type: none">the chemical is being introduced for consumer end use except uses in articles

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, 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 risk arising from dermal exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- 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 these chemicals.

Measures required to eliminate, or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to these chemicals, 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. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

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 conclusions of this evaluation are based on the information described in this statement.

Considering the identified uses and proposed means of managing risks, the Executive Director proposes to be satisfied that the identified human health risks can be managed within existing risk management frameworks.

This is provided that:

- all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory
- the proposed means of managing the risks identified during this evaluation are implemented.

However, risk conclusions for the public were driven by the fact that these chemicals are not expected to be currently used in products available to the public. Given that these chemicals cause adverse effects on fertility and development and risk estimates based on historical uses in cosmetic products indicated a risk to the public, it is important that the introduction and use of the chemical in Australia are known so that the risks can be appropriately managed. Therefore, a variation to the term of the listing for these chemicals, to add a specific requirement to provide information, is necessary to manage the risks from introduction of these chemicals (see **Proposed means of managing risk**).

Note: Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.

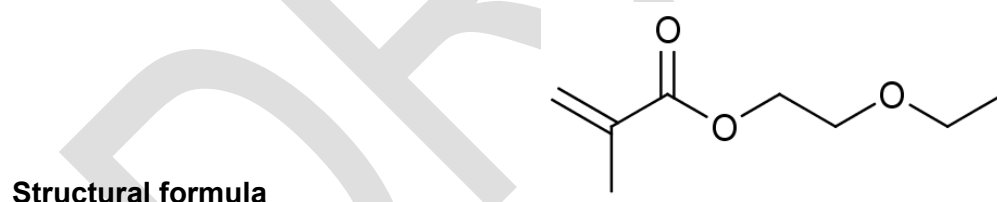
Supporting information

Grouping rationale

These chemicals were evaluated as a group as they are structurally similar, only differing by one methyl group. They are both esters of methacrylic acid (CAS No. 79-41-4), with 2-ethoxyethyl methacrylate being the ester formed from 2-ethoxyethanol (CAS No. 110-80-5) and 2-methoxyethyl methacrylate being the ester formed from 2-methoxyethanol (CAS No. 109-86-4). These chemicals are expected to have similar use patterns, bioavailability and toxicity.

Chemical identity

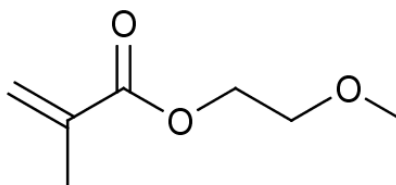
Chemical name	2-Propenoic acid, 2-methyl-, 2-ethoxyethyl ester
CAS No.	2370-63-0
Synonyms	2-ethoxyethyl methacrylate ethoxyethyl methacrylate (INCI) methacrylic acid, 2-ethoxyethyl ester
Molecular formula	C ₈ H ₁₄ O ₃
Molecular weight (g/mol)	158.20
SMILES	<chem>O=C(OCCOCC)C(=C)C</chem>
Chemical Description	-



Chemical name	2-Propenoic acid, 2-methyl-, 2-methoxyethyl ester
CAS No.	6976-93-8
Synonyms	2-methoxyethyl methacrylate methoxyethyl methacrylate methacrylic acid, 2-methoxyethyl ester
Molecular formula	C ₇ H ₁₂ O ₃
Molecular weight (g/mol)	144.17

SMILESO=C(OCCOC)C(=C)C**Chemical Description**

-

**Structural formula:**

Relevant physical and chemical properties

Measured physical and chemical property data for these chemicals were identified from the European Union Registration, Evaluation and Authorisation of Chemicals dossiers (REACH n.d.-a, REACH n.d.-b).

Chemical	2-ethoxyethyl methacrylate	2-methoxyethyl methacrylate
Physical form	Colourless liquid at 20 °C	Colourless liquid at 20 °C
Melting point	None	None
Boiling point	>185 °C (decomposition)	175 °C
Vapour pressure	9.6 Pa at 20 °C	22.3 Pa at 20 °C
Water solubility	17.05 g/L at 20 °C	31.33 g/L at 20 °C
Density	0.96 g/cm ³ at 20 °C	0.99 g/cm ³ at 20 °C
log K_{ow}	1.8 at 23 °C	1.3 at 23 °C

Introduction and use

Australia

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

International

Based on international information, the main uses of these chemicals are cosmetic and site limited, in nail enhancement products and as chemical intermediates in polymerisation, respectively.

The chemical, 2-ethoxyethyl methacrylate is listed on the International Nomenclature Cosmetic Ingredient (INCI) database with the reported function of “artificial nail builders” (Personal Care Products Council n.d.).

Artificial Nail Builders are chemical ingredients 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” (Personal Care Products Council n.d.). 2-Ethoxyethyl methacrylate had previous reported use in nail enhancement products at a maximum reported concentration of 85%. More recent survey data from the United States of America indicate that the chemical is not being used in these products (CIR 2022). No specific information on the cosmetic uses of 2-methoxyethyl methacrylate was identified, but given the chemical similarity, both chemicals have potential to have similar uses.

Methacrylates are used in liquid nail enhancement (or “artificial nail”) products for use by the general public and professional workers. In such products, these chemicals function as monomers which can react with each other, or other ingredients, to form a hard polymer coating on the nail. These nail products can be air dried or set more rapidly using UV light treatments. Whilst UV light treatments are traditionally found in professional settings, there is an increased prevalence of DIY nail kits designed for at home use by the general public, without professional experience or guidance (Le et al. 2015; Gatica-Ortega et al. 2018, MPA 2012). No DIY products containing these chemicals could be identified through internet searches.

No domestic or commercial uses were identified for these chemicals.

Both chemicals have site limited use in chemical manufacturing (REACH n.d.-a.; REACH n.d.-b). As both chemicals contain methacrylate groups, they are used as monomers in polymerisation. These chemicals are not expected to be present in significant amounts after polymerisation. Some polymerised products containing these monomers are used in cosmetic uses in hair fixatives (Fiume et al. 2017) and in food-contact materials.

These chemicals have non-industrial uses in dental adhesives.

Existing Australian regulatory controls

Public

No specific controls are currently available for these chemicals.

The primary metabolites 2-ethoxyethanol and 2-methoxyethanol are listed in the *Poisons Standard - the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 7.

Schedule 7:

“2-ETHOXYETHANOL and its acetates **except** in preparations containing 0.5% or less of 2-ethoxyethanol.”

“2-METHOXYETHANOL and its acetates **except** in preparations containing 0.5% or less of 2-methoxyethanol.”

Schedule 7 chemicals are described as: “Dangerous poisons – Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.” (TGA 2023).

Workers

These chemicals are not listed on the HCIS, and no specific exposure standards are available in Australia (SWA n.d.).

International regulatory status

Exposure standards

The following temporary emergency exposure limits (TEELs) have been recommended by the United States Department of Energy for 2-ethoxyethyl methacrylate (Chemwatch n.d.):

- 7900 mg/m³ (TEEL-3)
- 1300 mg/m³ (TEEL-2)
- 120 mg/m³ (TEEL-1)

The Romanian occupational exposure limits for 2-ethoxyethyl methacrylate are 200 mg/m³ for, and 100 mg/m³, for short term exposures and 8-hour exposures, respectively (Chemwatch n.d.).

No exposure standards were available for 2-methoxyethyl methacrylate.

United States of America

The Cosmetic Ingredient Review (CIR) Expert Panel concluded that 2-ethoxyethyl methacrylate is safe for use in nail enhancement products where skin contact is avoided. They noted that products 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 these chemicals (CIR 2022).

Human exposure

Public

Consumers who use DIY nail products are at risk of dermal exposure to the 2-ethoxyethyl methacrylate when applying the nail products to the fingernails or toenails.

The chemical may be absorbed through the skin around the nails if the skin becomes exposed to the nail product through inadvertent skin contact (Gatica-Ortega et al. 2018). Application of the nail product onto the nails is not expected to result in penetrating the nail

plate and reaching the skin under the nail because the chemical is expected to polymerise within minutes of application.

The main route of exposure is expected to be dermal, which is the focus of this quantitative risk assessment. Inhalation exposure may occur from dust particles produced from filing the nails; however, this scenario is not included in this assessment as these chemicals will have polymerised. These chemicals are not expected to be volatile due to their low vapour pressure.

The exposure to the chemical in artificial nails depends on a number of factors. Values for typical use patterns for liquid artificial nail products, were obtained from published sources. For the purposes of public exposure assessment, Australian use patterns for these products are assumed to be similar to those internationally.

In calculating exposure estimates the following values and assumptions were used:

- A worst-case scenario of 100% dermal absorption (DA) rate was applied as the skin around the nail plate may be inadvertently exposed to the chemical. The dermal absorption may be lower as the polymerisation of the chemical would reduce the amount absorbed through the skin.
- A lifetime average body weight (BW) of 70 kg (enHealth 2012).
- The amount of liquid artificial nail product applied per day was assumed to be 2 g/day (2000 mg/day).
- The skin around the nails has a surface area of about 4 cm², corresponding to about 9% of the total area of nails and skin and thereby contributing to the systemic dose. A typical application of liquid artificial nails contains 2000 mg of product. Therefore, it is estimated that the amount (A) of nail product in direct contact with skin is 9% x 2000 mg/day = 180 mg/day (Danish EPA 2008).
- Concentration (C) of 85% based on the maximum reported concentration of 2-ethoxyethyl methacrylate in nail enhancement products (CIR 2005).
- A retention factor (RF) of 1 used as the product is applied to nails and not removed or washed off immediately (Danish EPA 2008).

A daily systemic exposure of 2.2 mg/kg bw/day was calculated using ConsExpo Web (RIVM n.d.) (see Table 1).

Table 1 – Daily systemic exposure to artificial nail products (dermal exposure)

Type of product	A (mg/day)	C (%)	RF (unitless)	DA (%)	Daily systemic exposure (mg/kg bw/day)
Liquid artificial nails	180	85	1	100	2.2

Daily systemic exposure = (A × C × RF × DA)/BW
 (A = amount applied; C = chemical concentration; RF = retention factor; DA = dermal absorption; BW = body weight)

The above calculation estimates a worst-case scenario daily exposure value for artificial nail products when typical applications of these products are much less frequent (Danish EPA 2008). As the risk of dermal absorption is only present when the product is a liquid the systemic risk can be considered similar to an acute exposure. Based on data for 2-ethoxyethanol methacrylate and other methacrylates, it is expected that 50% of the product will polymerise (or set) between 2-6 minutes, and <1% of the residual chemical will be available after 1 hour (CIR 2002; CIR 2005). The dermal absorption of the chemical is likely

to be lower than 100% as the polymerisation of these chemicals would reduce the amount available to be absorbed through the skin.

Health hazard information

There is limited data available on this group of chemicals. For most endpoints, data are only available for 2-ethoxyethyl methacrylate. Due to their structural similarity, the data for 2-ethoxyethyl methacrylate has been used to evaluate the toxicity of both chemicals in this group.

These chemicals are expected to metabolise as methacrylic acid (CAS No. 79-41-4) and 2-ethoxyethanol (CAS No. 110-80-5) or 2-methoxyethanol (CAS No. 109-86-4). These metabolites have been previously assessed under our former scheme, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2014; 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. The systemic toxicity of the chemical is likely to be driven by the metabolites 2-ethoxyethanol and 2-methoxyethanol. These metabolites have a similar toxicological profile. Additional data on systemic toxicity was drawn from the Australian Industrial Chemicals Introduction Scheme (AICIS) evaluation statement on 2-propenoic acid, 2-methoxyethyl ester (CAS No. 3121-61-7) as the chemical shares the 2-methoxyethanol metabolite with 2-methoxyethyl methacrylate (AICIS 2022).

Toxicokinetics

There are no specific studies on the toxicokinetics of these chemicals.

Based on the log K_{ow} and molecular weights, these chemicals are expected to be absorbed via oral or dermal routes. Significant inhalation exposure and absorption is unlikely due to the relatively low vapour pressures of these chemicals. Due to the relatively low molecular weights of these chemicals, wide distribution throughout the body is expected (REACH n.d.-a; REACH n.d.-b).

Both chemicals are methacrylate esters that are expected to be hydrolysed by non-specific carboxylesterase enzymes in vivo (ECHA 2017). As carboxylesterases are ubiquitous in humans, hydrolysis is expected to occur within minutes. Ester hydrolysis produces the metabolites methacrylic acid (CAS No. 79-41-4), 2-ethoxyethanol (CAS No. 110-80-5) and 2-methoxyethanol (CAS No. 109-86-4) (REACH n.d.-a; REACH n.d.-b). These metabolites distribute widely around the body, including in a developing foetus. The concentrations of these chemicals in the developing foetus can be greater than that of the dam (NICNAS 2014).

These alcohols can undergo further biotransformation to ethoxyacetic acid (CAS No. 627-03-2), ethylene glycol (CAS No. 107-21-1) and methoxyacetic acid (CAS No. 625-45-6), which are believed to be responsible for the adverse effects associated with these chemicals (NICNAS 2014). Other minor metabolic pathways include glutathione conjugation, sulfonation and glucuronidation of the alcohol and its downstream metabolites (ECHA 2017; REACH n.d.-a).

Given this rapid metabolism, the metabolites 2-ethoxyethanol and 2-methoxyethanol are presumed to be responsible for any of the systemic effects observed after exposure to 2-ethoxyethyl methacrylate and 2-methoxyethyl methacrylate, respectively.

Acute toxicity

Oral

Based on the available data, these chemicals have low acute oral toxicity.

In a good laboratory practice (GLP) compliant acute oral toxicity study conducted in accordance with the Organisation for Economic Cooperation and Development Test Guideline (OECD TG) 401, Sprague Dawley (SD) rats (5/sex/dose) were treated with a single dose of 2-ethoxyethyl methacrylate. The median lethal dose (LD50) was >2000 mg/kg bw. No clinical signs of toxicity were reported (REACH n.d.-a).

In a non-GLP compliant acute oral toxicity study conducted similar to OECD TG 401, CFLP mice (5/sex/dose) were treated with a single dose of 2-ethoxyethyl methacrylate. The LD50 was >8200 mg/kg bw. Reported sublethal signs of toxicity included lethargy and piloerection (REACH n.d.-a).

In a non-GLP compliant acute oral toxicity study, albino Alderley Park rats (number of animals/sex/dose not specified) were treated with a single dose of 2-ethoxyethyl methacrylate. The LD50 was >5000 mg/kg bw. Reported sublethal signs of toxicity included sensitivity to touch and hunched posture (REACH n.d.-a).

In a GLP compliant acute oral toxicity study conducted according to OECD TG 401, SD rats (5/sex/dose) were treated with a single dose of 2-methoxyethyl methacrylate. The LD50 was >2000 mg/kg bw. Reported sublethal signs of toxicity included hunched posture, lethargy and piloerection (REACH n.d.-b).

Dermal

Based on the available data, these chemicals have low acute dermal toxicity.

In a GLP compliant acute dermal toxicity study conducted in accordance with OECD TG 402, SD rats (5/sex/dose) were treated with a single dose of the 2-ethoxyethyl methacrylate. The median lethal dose was >2000 mg/kg. No clinical signs of toxicity were reported (REACH n.d.-a).

Inhalation

No data are available.

Corrosion/Irritation

Skin irritation

Based on the available data, these chemicals are expected to be at most slightly irritating to skin.

In a GLP compliant skin irritation study conducted according to OECD TG 404, 3 New Zealand white (NZW) rabbits (sex not specified) were treated with 2-ethoxyethyl methacrylate for 4 hours under semi-occlusive conditions. The following mean scores for individual animals were reported for observations at 24, 48 and 72 hours: 1, 1.67 and 2 for erythema and 0, 0 and 0 for oedema, respectively (maximum score of 4). Signs of irritation

included very slight to moderate cutaneous reactions and skin dryness. The erythema were reversible in all animals within 4 or 5 days (REACH n.d.-a).

In a skin irritation study conducted in accordance with the US Federal Hazardous Substances Act (FHSA) guideline 16 CFR 1500.41, 6 rabbits (sex and strain not specified) were treated with 2-ethoxyethyl methacrylate for 24 hours under occlusive conditions on intact and abraded skin. Observations were recorded at 24 and 72 hours after patch removal. Very slight oedema (score 1, maximum score of 4) was observed in 5/6 animals at 24 and 72 h. Very slight erythema was observed in 4 of these animals at 72 hours. No information on reversibility was available (REACH n.d.-a). Whilst this study deviates from OECD guidelines, the slight erythema is consistent with the other reported study.

Eye irritation

Based on the available data, these chemicals are expected to be at most slightly irritating to eyes.

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, 2-ethoxyethyl methacrylate was instilled into 1 eye each of 3 NZW rabbits (sex not specified). The eyes were observed at 1, 24, 48 and 72 hours. The following mean scores were reported at 24, 48 and 72 hours in each animal: corneal opacity 0/4, iritis 0/2, conjunctival redness 0/3 and chemosis 0/4. Conjunctival redness was observed in the 2/3 animals after 1 hour but was fully resolved within 24 hours (REACH n.d.-a).

In a pre-GLP eye irritation study, 2-ethoxyethyl methacrylate was instilled into 1 eye each of 3 NZW rabbits (sex not specified). The eyes were observed at 2, 24, 48 and 72 hours, and at 4 and 7 days post dosing. In 2/3 animals, no signs of eye irritation were observed. Conjunctival redness was observed in the third animal with mean score 0.67/3 and was fully resolved after 72 hours (REACH n.d.-a).

Sensitisation

Skin sensitisation

Based on the available data, including mixed results from Quantitative Structure-Activity Relationship (QSAR) modelling, these chemicals are not considered likely to be skin sensitisers. However, chemicals that contain acrylate and methacrylate groups are often used in nail products and can be skin sensitisers that induce contact allergic dermatitis. Chemicals in this evaluation may cause cross reactions in individuals who are sensitised to other acrylates and methacrylates in other products (CIR 2005).

In a GLP compliant guinea pig maximisation test (GPMT) conducted according to OECD TG 406, intradermal induction was performed on 10 female Dunkin Hartley guinea pigs using 10% 2-ethoxyethyl methacrylate in paraffin oil. The chemical at 100% was used for epicutaneous topical induction and challenge. After challenge, no reactions were reported in the animals (REACH n.d.-a).

In a non-GLP GPMT (Polak method), intradermal induction was performed on Hartley guinea pigs (number of animals and sex not specified) using 0.2% 2-ethoxyethyl methacrylate in ethanol:saline (1:4), in Freund's complete adjuvant (FCA). The animals were challenged with 5% 2-ethoxyethyl methacrylate in acetone:olive oil (4:1) using an open skin test on day 7, and then weekly for 12 weeks. No reactions were reported in the animals (Parker and Turk 1983).

In a non-guideline ear-flank dermal sensitisation test, topical induction was performed on Alderley Park, albino strain guinea pigs using 10% 2-ethoxyethyl methacrylate in *N,N*-dimethylformamide. The animals were challenged with 2-ethoxyethyl methacrylate at 0.1%, 1% or 10% in *N,N*-dimethylformamide. After challenge, no reactions were reported in the animals (REACH n.d.-a).

In silico data

Mixed results for skin sensitisation were found for both chemicals in several in silico models.

The mechanistic and endpoint specific profiling functionality of the OECD QSAR Toolbox and OASIS TIMES (optimized approach based on structural indices set–tissue metabolism simulator) predictions indicated that both chemicals and their metabolites were non-sensitisers (OASIS LMC n.d.; OECD 2020).

ChemTunes-ToxGPS (MN-AM n.d.) predicted that both chemicals had the potential for skin sensitisation and were likely to be weak skin sensitisers. The predictions were within the applicability domain of the model.

The expert rule based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (version 6.0.1) gave alerts for skin sensitisation due to the presence alpha,beta-unsaturated esters (Lhasa Limited n.d.-a). Alpha beta-unsaturated esters are electrophilic groups that can undergo Michael additions with nucleophiles on proteins on the skin. The predicted effective concentration producing a stimulation index of 3 (EC3s) in a local lymph node assay (LLNA) were 17% and 15% for 2-ethoxyethyl methacrylate and 2-methoxyethyl methacrylate respectively (weak sensitisers).

Respiratory sensitisation

No data are available for these chemicals. Given the relatively low vapour pressures and uses of these chemicals, exposure by inhalation is unlikely. There are concerns that low molecular weight (<C8) methacrylates are potential respiratory sensitisers (ECHA 2023), but there is insufficient data to evaluate these chemicals.

The endpoint specific profiling functionality of the OECD QSAR Toolbox (OECD 2020) was used to determine the presence of potential structural alerts for respiratory sensitisation. These chemicals have positive structural alerts for respiratory sensitisation.

Observation in humans

There are concerns about chemicals containing methacrylate groups causing allergic contact dermatitis (see **Summary of health risk**). However, there is limited sensitisation data for these chemicals in humans.

In 11 patients with occupational allergic contact dermatitis from acrylates and methacrylates, one patient had a positive reaction after patch testing with 2-ethoxyethyl methacrylate. The occupation of this patient was a carpenter who frequently worked with wood paints and glues (Tosti et al. 1993). Whilst there is no information about the specific chemicals which the worker had used, the positive patch test suggests that cross sensitisation is possible in humans.

Repeat dose toxicity

No oral, dermal or inhalation repeat dose toxicity data are available for these chemicals. Based on the read across information from a study on the structurally similar chemical and studies on the metabolites, the target organ for repeat dose toxicity is the male reproductive system (see **Reproductive and Development Toxicity**) and haematopoietic systems. The doses at which effects on the haematopoietic system are likely to occur are not sufficient to warrant classification.

Oral

In a combined repeat dose and reproductive developmental oral dose study, Wistar rats were dosed with the structurally similar chemical 2-propenoic acid, 2-methoxyethyl ester (CAS No. 3121-61-7) at doses of 40, 100 or 150 mg/kg bw/day. Rats exposed to ≥ 100 mg/kg bw/day of the chemical exhibited hunched posture, increased salivation, piloerection and pale or lean appearance. Changes in blood chemistry, including decreased mean corpuscular volumes (MCV) and decreased mean corpuscular haemoglobin (MCH) levels, were reported in all dose groups. The reported histopathological effects on the stomach were inflammation, haemorrhage, hyperplasia of non-glandular epithelium and degeneration of glandular epithelium. In the liver, hepatocellular necrosis was observed at 150 mg/kg bw/day. Histopathological changes in the thymus in both sexes, and the testes and epididymides in males were observed at all dose levels (AICIS 2022). These effects are expected to occur at higher doses for this group of chemicals in this evaluation, as the structurally similar chemical was acutely toxic.

Several repeat dose oral toxicity studies of the metabolites 2-ethoxyethanol and 2-methoxyethanol have been reported in rats, mice, rabbits and dogs. The reported adverse effects were:

- reduced weight and histopathological changes in the thymus and testes
- increased haemosiderin deposits and isolated haematopoietic foci in the spleen
- decreased haemoglobin levels and haematocrit values
- reduced white blood cell and platelet counts.

These effects are observed following short exposure periods (3–10 days) (NICNAS 2014). These effects are consistent with those observed for 2-propenoic acid, 2-methoxyethyl ester.

Dermal

In a 28 day dermal study in rats with 2-methoxyethanol, effects in the testes and haematological parameters were observed at doses of 1000 mg/kg bw/day. An NOAEL of 100 mg/kg bw/day was reported. Similar effects were observed in a 13 week dermal study in guinea pigs at doses of 1000 mg/kg bw/day (NICNAS 2014).

Inhalation

Repeat dose inhalation toxicity studies on 2-ethoxyethanol and 2-methoxyethanol have been performed in rats, rabbits, and dogs. Adverse effects were observed in the thymus, testes, blood and haematopoietic systems and were similar to those found in repeat dose oral toxicity studies. The lowest reported no observed adverse effect concentration (NOAEC) for 2-ethoxyethanol was 390 mg/m³ in rabbits. The reported NOAEC, not including reproductive or developmental effects, for 2-methoxyethanol was 93 mg/m³ in rabbits (NICNAS 2014).

Genotoxicity

The available data from in vitro genotoxicity studies and QSAR models indicate that these chemicals do not induce point mutations in bacteria. Based on data for the structurally similar chemical and in silico alerts, these chemicals may be clastogenic. The metabolites 2-ethoxyethanol and 2-methoxyethanol are not considered to be genotoxic, and have “at most, weak genotoxic potential” (NICNAS 2014).

Negative results were reported for 2-ethoxyethyl methacrylate in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and TA102 with and without metabolic activation at concentrations up to 5000 µg/plate (REACH n.d.-a).

There is no experimental data to evaluate the clastogenic potential of these chemicals. Whilst it has been observed that the structurally similar chemical 2-propenoic acid, 2-methoxyethyl ester induced chromosomal aberrations in a single in vivo study, the data were not sufficient to warrant classification (AICIS 2022).

In silico data

There were no structural alerts for in vitro mutagenicity (Ames test) using DEREK Nexus, QSAR Toolbox, OASIS TIMES or ChemTunes·ToxGPS (OECD 2020; OASIS LMC n.d.; MN-AM n.d.).

An alert for chromosome damage by alpha,beta-unsaturated esters was found using DEREK Nexus, relating to models of in vitro chromosome aberration and L5178Y TK+/- assay activity (Lhasa Limited-a). The alert was considered plausible. The related system Sarah Nexus (version 3.0.0) predicted that the in vitro mutagenicity endpoint for both chemicals was negative, with 79% confidence in the prediction for 2-ethoxyethyl methacrylate and 72% confidence in the prediction for 2-methoxyethyl methacrylate (Lhasa Limited-b).

OASIS TIMES gave positive predictions for in vitro chromosomal aberrations. The predictions were within the applicability domain of the mutagenicity models and based on alerts for alpha,beta-unsaturated carboxylic acids and esters. However, ChemTunes·ToxGPS was uncertain about the prediction of these chemicals in an in vitro chromosomal aberration test. The predictions were within the applicability domain of the models.

Carcinogenicity

No data are available for these chemicals. The metabolites 2-ethoxyethanol and 2-methoxyethanol, are not expected to be carcinogenic (NICNAS 2014).

In addition, no QSAR alerts for carcinogenicity were found using OECD QSAR Toolbox or DEREK Nexus (OECD 2020; Lhasa Limited n.d.-a).

Reproductive and development toxicity

No reproductive or developmental toxicity data are available for these chemicals. Based on the read across information from a structurally similar chemical and the expected metabolites (see **Toxicokinetics**), the chemical is expected to cause specific adverse effects on fertility and development. There is sufficient evidence on the similar chemical and the metabolites in multiple animals to warrant hazard classification.

The structurally similar chemical, 2-propenoic acid, 2-methoxyethyl ester (CAS No. 3121-61-7), is classified as hazardous as a Category 1B reproductive toxicant with hazard statements “May damage fertility” and “May damage the unborn child” in the HCIS (SWA n.d.). In a guideline reproductive/developmental toxicity screening study (see **Repeat dose toxicity**), there were histopathological changes in the testes and epididymides, and impairment of the spermatogenic cycle in males at all doses. Sperm degeneration was observed at ≥ 100 mg/kg/day. In both sexes, histopathological changes in the thymus, increased precoital time and reduced fertility was reported at all doses. Pups born from the 40 mg/kg/day group had a significantly decreased viability index and no live litters were observed in the other dose groups. The lowest observed adverse effect levels (LOAELs) for both reproductive toxicity and developmental toxicity were 40 mg/kg/day (lowest dose tested) (AICIS 2022). The toxicological effects noted for 2-propenoic acid, 2-methoxyethyl ester are similar to those reported for 2-methoxyethanol, indicating that the metabolite is likely responsible for reproductive and developmental toxicity.

The metabolites 2-ethoxyethanol and 2-methoxyethanol are classified as hazardous as Category 1B reproductive toxicants with risk phrases “May damage fertility” and “May damage the unborn child” in the HCIS (SWA n.d.). Once absorbed, these metabolites are widely distributed throughout the body, including in the developing foetus (NICNAS 2014).

Both metabolites caused adverse effects to the male reproductive system in multiple animal species following exposure by all routes. These effects included decreased testes weight, atrophy of the testes, decreased sperm motility and changes in sperm morphology (NICNAS 2014). An NOAEL for toxicity to reproduction after oral exposure to 2-ethoxyethanol was 93 mg/kg bw/day in both rats and dogs in 13 week studies (REACH n.d.-c). The adverse effects after oral exposure to 2-methoxyethanol were generally seen at lower doses, with a reported NOAEL of 11 mg/kg bw/day in a one generation study in rats (REACH n.d.-d). Rabbits were generally more sensitive to these adverse effects and mice were less sensitive (WHO 2010).

In female rats, exposure to 100 mg/kg bw/day 2-methoxyethanol caused changes in the oestrus cycle and hormone levels, while histopathological changes in the ovaries were observed at a dose of 300 mg/kg bw/day. Similar effects on oestrus cycle were reported in rats exposed to 2-ethoxyethanol in drinking water at doses of 804 mg/kg bw/day for 13 weeks (WHO 2010).

The adverse effects on development caused by these metabolites were typically seen at lower doses than the effects on reproduction and in the absence of maternal toxicity. These effects included:

- decreased numbers of litters
- reduced foetal body weight
- reduced pup viability
- changes in neurochemistry and behaviour
- increased incidence of foetal malformations (NICNAS 2014).

The cardiovascular system, kidney and skeletal systems were the primary targets of developmental toxicity for both metabolites.

The NOAEL for developmental toxicity after oral exposure to 2-ethoxyethanol was 23 mg/kg bw/day in rats based on increased early and late prenatal deaths and skeletal variations in higher dose groups (ECHA 2008). An NOAEL for developmental toxicity from a one generation study in rats exposed to 2-methoxyethanol in drinking water was 11 mg/kg bw/day, based on a reduction in live pups per litter in higher dose groups (REACH

n.d.-d). In a similar study, an NOAEL could not be established as reduced foetal weights were observed in the lowest dose group (16 mg/kg bw/day). Malformations in pups were observed in the group dosed with 31 mg/kg bw/day 2-methoxyethanol (WHO 2010).

Human health risk characterisation

Critical health effects

The critical effects for risk characterisation are systemic effects on reproduction and development.

Public risk

A Margin of Exposure (MOE) methodology was used to characterise the risk to human health associated with systemic exposure to 2-ethoxyethyl methacrylate. The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB 2003).

The MOE risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, a MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

The starting points for risk characterisation are external exposure levels estimated based on reported maximum international use concentrations (See **Human exposure**). As the critical health effects for the chemical are reproductive and developmental effects and there are no studies on the chemical, the NOAEL was chosen based on the metabolite 2-ethoxyethanol. The lowest NOAEL for developmental effects reported for 2-ethoxyethanol is 23 mg/kg bw/day (see **Reproductive and Development Toxicity**), which corresponds to an NOAEL of 40 mg/kg bw/day for 2-ethoxyethyl methacrylate (based on molecular weights).

The MOE methodology was used to characterise the public health risks from exposure to the chemical through artificial nail products. The worst-case scenario dose from the chemical via dermal exposure was determined to be 2.2 mg/kg bw/day (See **Human exposure**; Table 1). Based on this value the calculated MOE is 18.

Whilst there is no evidence of the use of 2-methoxyethyl methacrylate in nail products, the lowest NOAEL for developmental effects for its metabolite, 2-methoxyethanol is 11 mg/kg bw/day (see **Reproductive and Development Toxicity**). This would result in a lower MOE and greater risk to the public should it be used in artificial nail products.

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