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

Tetrahydrofurfuryl acrylate and tetrahydrofurfuryl methacrylate

Evaluation statement

14 December 2023

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AICIS evaluation statement

Subject of the evaluation

Tetrahydrofurfuryl acrylate and tetrahydrofurfuryl methacrylate

Chemicals in this evaluation

Name	CAS registry number
2-Propenoic acid, (tetrahydro-2-furanyl)methyl ester	2399-48-6
2-Propenoic acid, 2-methyl-, (tetrahydro-2-furanyl)methyl ester	2455-24-5

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

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

Chemicals in this evaluation have an acrylate or methacrylate group attached to a tetrahydrofurfuryl alkoxy group. They have been assessed together as they have a common metabolite (tetrahydrofurfuryl alcohol, CAS No. 97-99-4) and are expected to have similar critical health effects. The previous assessment of the metabolite should be read in conjunction with this evaluation statement (NICNAS 2018).

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, tetrahydrofurfuryl methacrylate has cosmetic use in nail enhancement products for professional and consumer use at a maximum concentration of 38.2% (range for other methacrylate and acrylate compounds: 2–85%). Consumer uses include Do-It-Yourself (DIY) at home cosmetic nail products that are used outside of professional settings.

The chemicals have reported commercial uses, including in:

- inks and toners
- paints, lacquers and coatings

- adhesive and sealant products
- construction materials.

Some of the commercial uses may also be used in domestic applications. However available information indicates that domestic use is not widespread. The chemicals have site limited use as chemical intermediates in chemical synthesis and for the manufacturing of polymers.

While there are 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 the chemicals. As these chemicals are (meth)acrylate esters that are expected to hydrolyse in vivo, the hazard information for systemic effects was further supported by data available for the metabolite, tetrahydrofurfuryl alcohol. The systemic toxicity of the chemicals will likely be driven by this metabolite.

Based on the available data:

- tetrahydrofurfuryl methacrylate has low acute oral toxicity
- tetrahydrofurfuryl methacrylate is a slight skin and eye irritant
- the chemicals are not expected to cause serious systemic health effects (apart from reproductive effects) following repeated exposure
- the chemicals are not expected to have genotoxic potential.

Methacrylates can be metabolised by ester hydrolysis in various tissues or by conjugation with glutathione (GSH). Hydrolysis of acrylate esters, which is catalysed by carboxylesterases, results in the formation of acrylic acid and alcohol. Similarly, tetrahydrofurfuryl (meth)acrylate can be hydrolysed to (meth)acrylic acid and tetrahydrofurfuryl alcohol.

Based on the available data, tetrahydrofurfuryl acrylate has moderate acute oral toxicity (median lethal dose (LD50)=928 mg/kg body weight (bw) in rats).

Tetrahydrofurfuryl acrylate is corrosive. In 2 dermal irritation studies in rabbits using this chemical, visible necrosis of the skin was observed following ≤4-hour exposure. Corrosive effects were not observed at sites with 3 minute and 1-hour exposures.

Tetrahydrofurfuryl acrylate is reported to cause serious eye irritation effects (mean corneal opacity ≥1, in at least 2 out of 3 animals) in eye irritation studies in rabbits, which were not reversible within the observation period. Although the observation period did not extend to 21 days, corrosive chemicals are also considered to cause irreversible effects in the eyes.

Based on the available human, in vitro and in silico data, the chemicals are considered to be skin sensitisers. Tetrahydrofurfuryl methacrylate was reported to have positive results in the following in vitro tests: direct peptide reactivity assay (DPRA), keratinocyte activation test (LuSens assay) and human histiocytic lymphoma cell line U937 activation test. Several retrospective studies conducted in different countries overseas reported a high rate of positive patch test results (up to 79.5%) following exposure to tetrahydrofurfuryl methacrylate. Most of the reactions were from people with high exposures including

professional nail salon workers or consumers using nail products. Although limited data are available for tetrahydrofurfuryl acrylate, positive patch test results have been reported in small case studies.

Based on the read across information for the tetrahydrofurfuryl methacrylate and the metabolite tetrahydrofurfuryl alcohol, the chemicals are expected to cause specific adverse effects on fertility and development. In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in SD rats treated orally with tetrahydrofurfuryl methacrylate, a no observed adverse effect level (NOAEL) of 120 mg/kg bw/day was reported for female reproductive toxicity and offspring developmental toxicity. Observed effects on fertility (delayed parturition) and developmental toxicity (early resorptions and litter loss) were similar for tetrahydrofurfuryl methacrylate and the metabolite tetrahydrofurfuryl alcohol, indicating that the metabolite is likely to cause the adverse effects.

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) (UNECE 2017) for hazard classes relevant for worker health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

The classification for acute oral toxicity, skin corrosion and eye irritation apply only to tetrahydrofurfuryl acrylate.

Health hazards	Hazard category	Hazard statement
Acute toxicity – oral	Acute Tox. 4	H302: Harmful if swallowed
Skin corrosion/irritation	Skin Corr. 1C	H314: Causes severe skin burns and eye damage
Serious eye damage/Eye irritation	Eye Damage 1	H318: Causes serious eye damage
Skin sensitisation	Skin Sens.1	H317: May cause an allergic skin reaction
Reproductive toxicity	Repr. 1B	H360Df: May damage the unborn child; Suspected of damaging fertility

Summary of health risk

Public

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

- at concentrations from 2−85% (maximum concentration of tetrahydrofurfuryl methacrylate: 38.2%) in nail enhancement products
- by direct application of these chemicals to the nails and from using nail enhancement products (such as nail polish and artificial nails)
- from incidental skin and eye contact if used in domestic products.

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

The critical health effects for these chemicals are skin sensitisation, and the potential systemic long-term effects (reproductive and developmental toxicity). While tetrahydrofurfuryl acrylate has local hazards (skin corrosion and serious eye damage), uses in consumer products have not been identified for this chemical.

When using nail products containing the 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 the chemicals compared to the use in salons by trained personnel. The low volatility of the 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 chemicals have the potential to cause systemic long term effects on reproduction and development following dermal application. Using a worst case scenario model, the margin of exposure (MOE) for the use of the chemicals in nail enhancement products was >100, indicating that the chemicals are unlikely to pose a risk of adverse systemic effects at concentrations up to 38.2%. If the chemicals are used at higher concentrations there could be a risk of adverse effects.

The Cosmetic Ingredient Review (CIR) concluded that the chemicals 'are safe to use in nail enhancement products when skin contact is avoided. Products containing these ingredients should be accompanied with directions to avoid skin contact, because of the sensitising potential of methacrylates' (CIR 2005). The chemicals have been demonstrated to elicit sensitisation in humans with reactions associated with use in nail products. A large amount of data show that a significant number of individuals are sensitised to tetrahydrofurfuryl methacrylate. Elicitation of skin sensitisation has already been observed at low concentrations (0.2%, 70 µg/cm^2). There are currently no labelling requirements for products containing the chemicals. Therefore, the evidence indicates that there is a risk to the public that requires management (see **Proposed means for managing risks** section).

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 the chemicals through the dermal route. There may be risk of inhalation exposure including dust particles containing the chemicals when filing, buffing or removing nails, but this would not be due to the intrinsic hazard properties of the chemicals.

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

Given the critical systemic long term and local health effects, the chemicals could pose a risk to workers. Control measures to minimise ocular, dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risk** section).

Proposed means for managing risk

Public health

Recommendation to Department of Health and Aged Care

It is recommended that the delegate of the Secretary for Poisons Scheduling lists the chemicals in the *Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons)* (SUSMP).

It is recommended that to manage the potential risk associated with the use of these chemicals the entry:

- restricts the concentration of these chemicals in cosmetics
- results in labelling requirement that provide warning statements and safety directions relating to skin sensitisation.

Consideration should be given to the following:

- the skin sensitisation potential based on human data and evidence of cross-sensitisation
- elicitation of skin sensitisation has been observed at low concentrations (0.2%, 70 µg/cm^2)
- the potential use of these chemicals in cosmetics including professional nail enhancement products (such as nail polish and artificial nails) that may be available in Australia at high concentrations up to 85% (maximum concentration of tetrahydrofurfuryl methacrylate: 38.2%) (CIR 2005) (based on overseas exposure data)
- the increasing trend of DIY at home cosmetic nail products used outside of professional settings at unspecified concentrations
- the high risk when products are in their liquid monomer form. If products are not ‘ultraviolet (UV)-cured’ (set/dried) correctly there is an increased risk of absorption through skin due to the bioavailable residual monomer
- the metabolite, tetrahydrofurfuryl alcohol (excluding its derivatives), is listed in Schedule 6 of the *Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons)* (SUSMP) (TGA 2023). Based on metabolism to this chemical, the chemicals may pose a risk related to reproductive and developmental effects if used in high concentrations (>40%)
- the chemical may also be used in therapeutic products.

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) updates 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 ocular, dermal and inhalation exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent these chemicals from entering the breathing zone of any worker
- 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.

Model codes of practice, available from the SWA 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 chemicals can be managed.

Note:

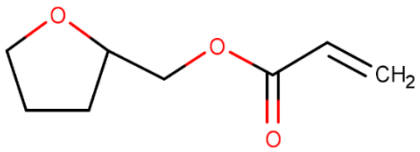
1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Grouping rationale

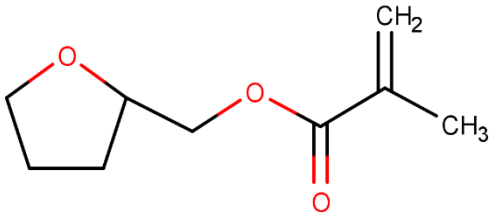
The chemicals in this evaluation have an acrylate or methacrylate group attached to a tetrahydrofurfuryl alkoxy group. They have been assessed together as they have a common metabolite (tetrahydrofurfuryl alcohol, CAS No. 97-99-4) and are expected to have similar critical health effects. The chemicals are expected to have similar use patterns, bioavailability and toxicity.

Chemical identity

Chemical name	2-Propenoic acid, (tetrahydro-2-furanyl)methyl ester
CAS No.	2399-48-6
Synonyms	tetrahydrofurfuryl acrylate oxolan-2-ylmethyl prop-2-enoate 2-propenoic acid, tetrahydrofurfuryl ester
Molecular formula	C8H12O3
Molecular weight (g/mol)	156.18
SMILES	O=C(OCC1OCCC1)C=C
Chemical description	-
Structural formula	

Chemical name	2-Propenoic acid, 2-methyl-, (tetrahydro-2-furanyl)methyl ester
CAS No.	2455-24-5
Synonyms	tetrahydrofurfuryl methacrylate (INCI) methacrylic acid tetrahydrofurfuryl ester
Molecular formula	C9H14O3
Molecular weight (g/mol)	170.21
SMILES	O=C(OCC1OCCC1)C(=C)C
Chemical description	-

Structural formula:



Relevant physical and chemical properties

Measured physical and chemical property data for the chemicals were identified from the European Union Registration, Evaluation and Authorisation of Chemicals dossiers (REACH n.d.-a, REACH n.d.-b) and the US cosmetic ingredient review (CIR 2005).

Chemical	tetrahydrofurfuryl acrylate	tetrahydrofurfuryl methacrylate
Physical form	liquid	colourless to slightly yellowish liquid at 20°C and 1013 hPa
Boiling point	206.5 °C	222°C at 1020 hPa
Vapour pressure	119 Pa at 25°C	27 Pa at 20°C
Water solubility	79.1 g/L at 20°C	19 g/L at 20°C
log K_{ow}	0.81	1.88

Introduction and use

Australia

No specific Australian information on introduction, use and end use has been identified for the chemicals.

International

The following uses were identified from:

- the European Union Registration, Evaluation and Authorisation of Chemicals dossiers (REACH n.d.-a, REACH n.d.-b)
- United States Environmental Protection Agency Chemical Data Reporting (CDR) (US EPA 2012, USEPA 2016, US EPA 2020)
- INCIpedia (Personal Care Products Council n.d)
- Cosmetic Ingredient Reviews (CIR 2005, CIR 2022)
- Substances in preparations in Nordic countries (SPIN) database (SPIN n.d).

Tetrahydrofurfuryl methacrylate is listed in the INCI database with the function of film formers (Personal Care Products Council n.d.). Methacrylate ester monomers, including tetrahydrofurfuryl methacrylate, have cosmetic uses as artificial nail builders in nail enhancement products. The maximum concentration of tetrahydrofurfuryl methacrylate in nail enhancement products is 38.2% (CIR 2005; CIR 2022). Tetrahydrofurfuryl acrylate is not listed in the INCI database but use in personal care products (concentration up to 30%) was reported in the United States of America (US CDR 2016).

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 chemicals act as monomers 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 curing treatments, where 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 or guidance (Lee et al. 2015; Gatica-Ortega et al. 2018; MPA 2012).

The chemicals have reported commercial uses, including in:

- inks and toners
- paints, lacquers and coatings
- adhesive and sealant products
- 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). Two discontinued adhesive products (concentration up to 55%) were reported for tetrahydrofurfuryl methacrylate. The REACH registration dossiers for the chemicals identified uses by professional users only. The majority of uses reported under the US Chemical Data Reporting (CDR) under the Toxic Substances Control Act were commercial. There was one reported consumer use in ink and toner in 2012 (US EPA, 2012, US EPA 2016, US EPA 2020). Consumer preparations for the chemicals 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.

Both chemicals have site limited use in chemical manufacturing (REACH n.d.-a.; REACH n.d.-b, SPIN n.d.). As both chemicals contain (meth)acrylate groups, they are used as monomers in polymerisation. The chemicals are not expected to be present in significant amounts after polymerisation.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No specific controls are currently available for these chemicals.

The metabolite, tetrahydrofurfuryl alcohol (excluding its derivatives), is listed in Schedule 6 of the *Poisons Standard (SUSMP)* (TGA 2023).

‘Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.’

Workers

These chemicals are not listed on Safe Work Australia’s HCIS and no specific exposure standards are available (SWA n.d.).

International regulatory status

Exposure standards

No specific exposure standards are currently available for these chemicals.

European Union

European Chemicals Agency (ECHA) is proposing further regulatory risk management action, including restrictions for tetrahydrofurfuryl acrylate and tetrahydrofurfuryl methacrylate due to their potential to form the metabolite, tetrahydrofurfuryl alcohol, which has a reproductive toxicity hazard profile (ECHA 2022).

United States of America

The Cosmetic Ingredient Review (CIR) Expert Panel concluded that tetrahydrofurfuryl 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 warrant re-evaluation of the chemicals (CIR 2022).

Human exposure

Public

Consumers who use DIY nail products are at risk of dermal exposure to tetrahydrofurfuryl methacrylate when applying the nail product on fingernails or toenails. The skin around the nails may be inadvertently exposed to the chemical (Gatica-Ortega et al. 2018). Significant exposure by oral or inhalation routes is not expected with typical use of these products.

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 the chemicals will have polymerised. The chemicals are not expected to be volatile due to their low vapour pressure.

The exposure to the chemical in artificial nails depends on several factors. Values on typical use patterns for specific nail products, i.e. for liquid artificial nails, were derived from published sources. For this public exposure assessment, Australian use patterns for nail products are assumed to be similar to those overseas. In calculating exposure estimates the following assumptions and values were applied:

- 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 retention factor of 1 is used as the product is applied to nails and not removed or washed off immediately (Danish EPA 2008).
- A lifetime average body weight (BW) of 70 kg was used (enHealth 2012).
- The amount of liquid artificial nail product applied per day was assumed to be 2 g/day or 2000 mg/day.
- The skin around the nails has a surface area of about 4 cm^2, 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) is based on the maximum reported concentrations in nail enhancement products (38.2%; CIR 2022). A daily systemic exposure of 0.98 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	Amount (mg/day)	C (%)	RF (unitless)	DA (%)	Daily systemic exposure* (mg/kg bw/day)
Liquid artificial nails	180	38.2	1	100	0.98

*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). Based on data for tetrahydrofurfuryl 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 lower than 100% as the polymerisation of the chemicals would reduce the amount available to be absorbed through the skin.

Health hazard information

The chemicals are expected to metabolise to tetrahydrofurfuryl alcohol (CAS No. 97-99-4) and methacrylic acid (CAS No. 79-41-4) or acrylic acid (CAS No. 79-10-7) in the human body (See **Toxicokinetics** section). These metabolites have been previously assessed under our former scheme, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2013; NICNAS 2014; NICNAS 2018). These previous assessment reports should be read in conjunction with this evaluation.

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

Toxicokinetics

(Meth)acrylates can be metabolised via two pathways: by ester hydrolysis (esterases) in various tissues; and by conjugation with GSH which has been demonstrated for acrylates and methacrylates in vitro and in vivo (formation of mercapturic acid) (Greim et al. 1995). Hydrolysis of (meth)acrylate esters, which is catalysed by carboxylesterases, results in the formation of (meth)acrylic acid and alcohol (McCarthy and Witz 1997). It is expected that tetrahydrofurfuryl (meth)acrylate would be hydrolysed to (meth)acrylic acid and tetrahydrofurfuryl alcohol.

For ethylacrylates, it has been demonstrated that, while the GSH conjugation is the main metabolic pathway after administration of low doses, hydrolysis of the ester becomes the predominant pathway at higher dose levels (Greim et al. 1995).

In the case of methacrylates, ester hydrolysis is the main metabolic pathway while GSH conjugation plays a minor role in their metabolism, and only occurs at very high tissue concentrations of methacrylates (Greim et al. 1995).

Tetrahydrofurfuryl alcohol is converted to an aldehyde (as an intermediate) and then to a carboxylic acid (Zarnt et al. 1997). Following oral administration of ^{14}C-labelled furfuryl

alcohol in male Fischer 344 rats, the liver and kidneys contained the highest levels of radioactivity, and the brain had the lowest. The majority of the administered furfuryl alcohol (83–88%) was excreted in the urine within 24 hours of dosing, and 4% was excreted in the faeces (Nomeir et al. 1992).

Acute toxicity

Oral

Based on the available data, tetrahydrofurfuryl acrylate has moderate acute oral toxicity (LD50 in rats was 928 mg/kg bw), warranting classification (see **Hazard classifications relevant for worker health and safety** section). Tetrahydrofurfuryl methacrylate has low acute oral toxicity (LD50 in rats was 3945 and 4000 mg/kg bw).

In a non-GLP compliant acute oral toxicity study conducted in accordance with the Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 401, Wistar rats (5/sex/dose) were treated with a single dose of tetrahydrofurfuryl acrylate at doses of 600, 1000, 2000 or 5000 mg/kg bw in both sexes. The LD50 was 928 mg/kg bw (both sexes). Reported sublethal signs of toxicity included sedation, abdominal position, curved body position, ruffled fur, exophthalmos and emaciation. Gross pathological observations included stomach filled with the chemical, discolouration of the small intestine, and fluid filled abdominal cavity (REACH n.d.-a).

In a non-GLP compliant acute oral toxicity study conducted similarly to OECD TG 401, SD rats (5/sex/dose) were treated with a single dose of tetrahydrofurfuryl methacrylate at doses of 2500, 3750, 5630 or 8440 mg/kg bw in both sexes. The LD50 was 3945 mg/kg bw. Reported sublethal signs of toxicity included decreased motor activity and respiratory rate in all animals, haematuria, griping, diarrhoea and lachrymose. Gross pathological observations included hepatic discolouration and necrosis, haemorrhages in the urinary bladder, gastrointestinal tract, pancreas, kidneys and thymus, and discolouration and necrosis of the spleen (REACH n.d.-b).

In a non-GLP compliant acute oral toxicity study conducted in accordance with OECD TG 401, Wistar rats (3/sex/dose) were treated with a single dose of tetrahydrofurfuryl methacrylate at doses of 1000, 3000 or 5000 mg/kg bw in both sexes. The LD50 was 4000 mg/kg bw. Reported sublethal signs of toxicity included sedation, dyspnoea, curved body position and ruffled fur (REACH n.d.-b).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion/Irritation

Skin irritation

Based on the available data, tetrahydrofurfuryl acrylate is expected to be corrosive to the skin, warranting hazard classification (see **Hazard classifications relevant for worker**

health and safety section). Sufficient data are available to sub-categorise. Tetrahydrofurfuryl methacrylate is a slight skin irritant.

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 New Zealand White (NZW) rabbits were treated with tetrahydrofurfuryl acrylate for 3 minutes, 1 and 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours, day 7 and 14 after patch removal. The following mean scores for individual animals were reported for animals exposed for 4 hours: 2, 4 and 2 for animal 1, 2 and 3, respectively, for erythema, and 1.67, 2.33 and 2.67 for animal 1, 2 and 3, respectively, for oedema. Brown areas and eschar (necrosis) were also observed in one animal. In one animal, well defined to severe erythema was observed from 24 hours to day 7 after patch removal, as well as severe oedema 1 hour after patch removal. The erythema and oedema were all reversible by day 14. No evidence of corrosion or severe irritation was noted at sites exposed for 3 minutes and 1 hour (REACH n.d.-a).

In a GLP compliant skin irritation study conducted similarly to OECD TG 404, 3 NZW rabbits were treated with tetrahydrofurfuryl acrylate for 4 hours under occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours after patch removal. The following mean scores were reported for observations at 24, 48 and 72 hours: 4 for erythema, and 3.2 for oedema. Destruction of the treated skin (deep necrosis) was observed in all animals. Animals were sacrificed after 72 hours of observation (REACH n.d.-a).

In a non-guideline skin irritation study, 6 NZW rabbits were treated with tetrahydrofurfuryl methacrylate for 24 hours under occlusive conditions. Observations were recorded at 24, 48 and only up to 72 hours after patch removal. The following mean scores for individual animals were reported: 0.5, 0, 0, 1, 0 and 0 for animals 1, 2, 3, 4, 5 and 6, respectively, for erythema, and 0 for all 6 animals for oedema. Signs of irritation include very slight erythema which was reversible in one animal within 72 hours. However, slight skin irritation for the other animal was still present at 72 hours (REACH n.d.-b).

Eye irritation

Corrosive chemicals are also considered to cause irreversible effects in the eyes. Based on the available data, tetrahydrofurfuryl acrylate causes serious eye damage, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section). Tetrahydrofurfuryl methacrylate causes slight eye irritation.

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, tetrahydrofurfuryl acrylate was instilled into one eye each of 3 NZW rabbits. The eyes were washed out after 24 hours and observed at 1, 24, 48 and 72 hours. The animals were sacrificed 72 hours after administration of the chemical. The following mean scores were reported at 24, 48 and 72 hours: corneal opacity 2/4, iritis 0.8/2, conjunctival redness 3/3, and chemosis 2.8/4. The observed effects were not reversible within 72 hours (REACH n.d.-a).

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, tetrahydrofurfuryl acrylate was instilled into one eye each of 3 NZW rabbits. The eyes were washed out after 24 hours and observed at 1, 24, 48 and 72 hours and day 7. The following mean scores were reported at 24, 48 and 72 hours: corneal opacity 2.1/4, iritis 1/2, conjunctival redness 2.5/3, and chemosis 3.7/4. The observed effects of corneal opacity, conjunctival redness and chemosis were not reversible within day 7 (REACH n.d.-a).

In a non-guideline eye irritation study, tetrahydrofurfuryl methacrylate was instilled into one eye each of 6 NZW rabbits. Observations were made at 24, 48 and 72 hours. The following

mean scores were reported at 24, 48 and 72 hours: corneal opacity 0/4 and iritis 0/2. The following mean scores for individual animals for conjunctival redness were: 0.33, 0, 0.33, 1, 1.33 and 0.33 (out of 3) for animals 1, 2, 3, 4, 5 and 6, respectively. The following mean scores were reported at 24, 48 and 72 hours for chemosis: 0/4 (for animal 1, 2, 3 and 6) and 0.67/4 (for animal 4 and 5). All the observed effects were completely reversible within 4 days (REACH n.d.-b).

Sensitisation

Skin sensitisation

Based on the available human, in vitro and in silico data, the chemicals are considered to be skin sensitisers, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section). Skin sensitisation has been observed in several patch test studies in humans However, high frequency responses were typically observed in persons exposed occupationally (high exposures). Overall data are not sufficient to sub-categorise. Although limited data are available for tetrahydrofurfuryl acrylate positive patch test results have been reported in small case studies.

In vitro

Positive results were reported, for tetrahydrofurfuryl methacrylate, from one in chemico and two in vitro cell based assays that address specific key events of the Adverse Outcome Pathway (AOP) for skin sensitisation. Based on the “2 out of 3” defined approach (OECD Guideline 497) the chemical is predicted to be a skin sensitiser, warranting classification. However, it is not possible to determine potency sub-categorisation based on the in-vitro data.

The chemical was reported as positive in the first key event assay of the AOP for skin sensitisation, in the in chemico direct peptide reactivity assay (DPRA) conducted in accordance with OECD TG 442C. Mean cysteine and lysine depletion by the chemical was 30%, indicating moderate peptide binding (ECHA 2022; REACH n.d.-b)

The chemical was reported as positive in the second key event assay of the AOP for skin sensitisation, an in vitro skin keratinocyte activation test (LuSens assay) conducted in accordance with OECD TG 442D at concentrations up to 383.33 µg/mL. The chemical induced a significant luciferase activity as fold induction remained >1.5, indicating keratinocyte activation (ECHA 2022; REACH n.d.-b).

The chemical was reported as positive in the third key event assay of the AOP for skin sensitisation in a non-guideline human histiocytic lymphoma cell line U937 activation test similar to OECD 442E. The cell line U937 is used as a surrogate for dendritic cells, where immune cell activation is quantified by measuring increased expression of the cell surface marker CD86 using fluorescent antibodies. The cells were treated with the chemical at concentrations from 79.18 to 1266.87 µg/mL for 48 hours. A test substance is predicted to have dendritic cell activating potential when the CD86 marker expression exceeds the threshold of 1.2 with respect to vehicle treated cells at any tested non-cytotoxic (cell viability ≥70%) concentration in 2 independent experiments. Increased expression of CD86 above 1.2 was observed at concentrations from 158.36 to 633.44 µg/mL (in experiment 1), and from 79.18 to 158.36 µg/mL (in experiment 2) where the cell viability was >70%, indicating a positive result (ECHA 2022; REACH n.d.-b).

In silico

The mechanistic and endpoint specific profiling functionality of the OECD Quantitative Structure Activity Relationship (QSAR) Toolbox v4.6 (OECD 2023) were used to determine the presence of potential structural alerts for skin sensitisation. The chemicals have positive structural alerts for protein binding.

QSAR modelling using OASIS TIMES (optimized approach based on structural indices set–tissue metabolism simulator) predicted that tetrahydrofurfuryl acrylate was a skin sensitiser based on the alert for “Michael type addition on conjugated systems with electron withdrawing groups”. The autoxidation metabolites of tetrahydrofurfuryl acrylate were predicted to be non-sensitisers. Tetrahydrofurfuryl methacrylate and its autoxidation metabolites were predicted to be negative for skin sensitisation.

The expert rule based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (version 6.0.1) gave skin sensitisation alerts for both chemicals due to the presence alpha,beta-unsaturated esters (Lhasa Limited). Alpha beta-unsaturated esters are electrophilic groups that can undergo Michael additions with nucleophiles on proteins on the skin. The predicted effective concentrations producing a stimulation index of 3 (EC3s) in a local lymph node assay (LLNA) were 16 and 18% for tetrahydrofurfuryl acrylate and tetrahydrofurfuryl methacrylate, respectively, indicating that the chemicals are weak sensitisers.

Observation in humans

Positive patch test results following tetrahydrofurfuryl methacrylate exposure were reported in 31 out of 39 (79.5%) patients tested in Spain between January 2013 to June 2016 (patch test concentration 2% in petrolatum). The patients were diagnosed with allergic contact dermatitis that was caused by the nail polish that they used when working as beauticians or for personal use. Tetrahydrofurfuryl methacrylate was one of the frequently identified (30.7%) methacrylate ingredients in nail polish products used (Gatica-Ortega et al. 2017).

Four hundred and forty patients with a history of exposure to (meth)acrylates from work, artificial nails or limb prosthesis were identified in a retrospective study of patch tests conducted during the period of January 1983 to March 1998. Five of the patients (out of 147 tested (3.4%) with tetrahydrofurfuryl methacrylate) had positive reactions to tetrahydrofurfuryl methacrylate (patch test concentration 2% (w/w)) (Tucker and Beck 1999).

In a retrospective study of patch test results from a total of 473 patients tested with the methacrylate series during the period of September 1994 to August 2006, 61 patients were allergic to at least one methacrylate compound. Reactions to tetrahydrofurfuryl methacrylate were detected in 7 patients with allergies to various other methacrylate compounds as well. The patients allergic to tetrahydrofurfuryl methacrylate had used sealants, adhesives, or epoxies during their work as machine assembler, plumber, measurement technician or sewing machine mechanic, but whether these products contained tetrahydrofurfuryl methacrylate is not clear. The reactions to tetrahydrofurfuryl methacrylate were considered by the authors to be due to cross-allergy to other methacrylate compounds (Aalto-Korte et al. 2008).

A retrospective study of patients patch tested in Sweden from January 1995 to December 2004 found that 3 tested positive out of 12 (25%) following exposure to tetrahydrofurfuryl methacrylate. The patients tested with the (meth)acrylates series included workers who had been working in printing with UV-curing paints, the manufacture of acrylate based binders for paints, glass repair, mechanical shop work, and the varnishing of doorsteps, as well as nail

technicians and customers who suspected nail acrylics as the source of the causative ingredient (Teik-Jin Goon et al. 2007).

Positive patch test results following tetrahydrofurfuryl methacrylate exposure were reported in 18.9% (7 positive/37 tested) of patients tested (patch test concentration 2%) in Portugal between January 2006 to April 2013. Positive reactions to the methacrylate compounds were related to contact with artificial acrylic nails (13 technicians, 8 users, and 7 technicians and users), and 2 to their occupation in the industrial production of traffic signs and caravans (Ramos et al. 2014).

An analysis of the patch test results from 114,440 consultations conducted between 2004 and 2013 was obtained from the Information Network of Departments of Dermatology (IVDK) database. The following percentage of positive reactions to tetrahydrofurfuryl methacrylate (patch test concentration 2%) in 4 female groups were reported:

- 0.7% (34 positive/4998 tested) in a group that had contact dermatitis without having used nail materials or did not have an occupation with potential exposure to acrylic nails
- 1.6% (1 positive/61 tested) in a group that had used nail materials and did not have an occupation with potential exposure to acrylic nails
- 5.9% (2 positive/34 tested) in a group that had an occupation with potential exposure to acrylic nails but in whom nail materials were not explicitly mentioned as culprit products
- 13.8% (4 positive/29 tested) in a group that had an occupation with potential exposure to acrylic nails and considered nail materials as causative. In 5 patients that tested positive to tetrahydrofurfuryl methacrylate, there was cross reactivity with 2-hydroxyethyl methacrylate, methyl methacrylate, ethyl acrylate and ethyl methacrylate (Uter and Geier 2015).

A number of patch tests investigating effects relating to exposures in dentistry are available (ECHA 2022). In one key study, patch tests with a calculated dose of 70 µg/cm^2 (0.2% in petrolatum) resulted in 26–48% of dental patients tested positive for tetrahydrofurfuryl methacrylate while about 13% of dental professionals show positive reactions (elicitation) (ECHA 2022).

Patients who had developed allergic contact dermatitis due to contact with acrylates were identified in a retrospective study in Spain between June 1981 to January 2008. Some of the participants were professionals who worked with artificial nails or were end users of such products. One positive patch test for tetrahydrofurfuryl methacrylate (out of 15 patients tested (6.7%)) was found to be a female patient who used artificial nails in her work as a beautician (Roche et al. 2008).

There are case reports of 2 workers in a factory assembling medical device needles who experienced contact dermatitis after a new adhesive had been introduced 2–3 months prior to the onset of their symptoms. They had positive patch test results to tetrahydrofurfuryl acrylate (Moffitt and Sansom 2001). Another case report documented a woman developing contact dermatitis with erythema on the earlobe that was in contact with resin after wearing clip-on earrings. She had positive patch test reactions to tetrahydrofurfuryl acrylate and tetrahydrofurfuryl methacrylate (Suzuki et al. 2020). Another positive patch test to tetrahydrofurfuryl acrylate was reported in a patient with contact dermatitis following use of a medical device (Ulriksdotter et al. 2021).

Respiratory sensitisation

No data are available for these chemicals.

The endpoint specific profiling functionality of the OECD Quantitative Structure Activity Relationship (QSAR) Toolbox v4.6 (OECD 2023) was used to determine the presence of potential structural alerts for respiratory sensitisation. The chemicals have positive structural alerts for respiratory sensitisation.

Given the relatively low vapour pressures 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.

Repeat dose toxicity

No data are available for tetrahydrofurfuryl acrylate. Based on the read across information from the metabolite, tetrahydrofurfuryl alcohol, the chemicals are not expected to cause serious systemic health effects following repeated exposure. No relevant adverse effect with a dose response could be identified in rats dosed orally with tetrahydrofurfuryl methacrylate in concentrations up to 300 mg/kg bw/day. Effects observed for the alcohol in male reproductive organs were not observed in this study but cannot be ruled out at higher doses different exposure routes.

Oral

In a GLP compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422, SD rats (10/sex/dose) were administered tetrahydrofurfuryl methacrylate by gavage once daily at 0, 50, 120 or 300 mg/kg bw/day from 2 weeks before mating for a total of 29 days (males and females), during the mating, gestation and day 3 post-partum periods (see **Reproductive and development toxicity** section). No mortalities or clinical signs of toxicity were observed. A decrease in body weight and body weight gain was observed in the female parental generation (P0) at the high dose (300 mg/kg bw/day). No treatment related systemic adverse effects were reported except for reproductive and developmental toxicity. The reported NOAEL was 300 mg/kg bw/day for the parental generation (REACH n.d.-b).

In a 90 day repeated dose oral toxicity study conducted similarly to the OECD TG 408, SD rats (20/sex/dose) were treated with tetrahydrofurfuryl alcohol in the diet at dose levels of 35, 69, 339 or 673 mg/kg bw/day (males); 42, 84, 401 or 781 mg/kg bw/day (females). Food consumption and body weights were significantly reduced in a dose dependent manner at ≥69 and ≥401 mg/kg bw/day in male and female rats, respectively. Histopathological changes in the spleen as well as dose related decreases in haemoglobin, leukocytes, platelets, albumin and total protein were reported at ≥339 and 401 mg/kg bw/day in males and females, respectively. Effects on male reproductive organs included significant weight reductions and histopathological findings in the testes, epididymides, seminal vesicles at ≥339 mg/kg bw/day, and in prostates at 673 mg/kg bw/day. The NOAEL values were determined to be 35 mg/kg bw/day in males and 84 mg/kg bw/day in females, based on systemic toxicity reported at higher doses (NICNAS 2018).

In a 28 day repeated dose oral toxicity study (OECD TG 407), Crj:CD(SD) rats (5–10/sex/dose) were treated by gavage with tetrahydrofurfuryl alcohol at dose levels of 0, 10, 40, 150 or600 mg/kg bw/day. High-dose effects on body weights, locomotor activity,

haematological and biochemical parameters, histopathological changes of the spleen, atrophy of thymus and testes were similar to those reported in the 90 day repeated dose and reproductive toxicity studies (see **Reproductive and Developmental Toxicity** section). In this study, necrosis of seminiferous tubules was reported at ≥150 mg/kg bw/day. Therefore, the NOAEL was considered to be 40 mg/kg bw/day (NICNAS 2018).

Dermal

In a 90 day repeated dose dermal toxicity study (OECD TG 411), SD rats (12–17/sex/dose) were treated with tetrahydrofurfuryl alcohol at dose levels of 0, 100, 300 or 1000 mg/kg bw/day. Both male and female rats at 1000 mg/kg bw/day had a significantly lowered weight gain as compared to the controls. Spermatogenic effects of tetrahydrofurfuryl alcohol were reported at ≥300 mg/kg bw/day. The NOAEL values were determined to be 100 mg/kg bw/day in males and 300 mg/kg bw/day in females (NICNAS 2018).

Inhalation

In a 90 day repeated dose inhalation toxicity study (OECD TG 413), SD rats (10–14/sex/dose) were exposed to vapourised tetrahydrofurfuryl alcohol at 0, 50, 150 or 500 ppm, 6 hours/day for 5 days/week. Intermittent whole body spasms and dose related hyperactivity were observed at ≥50 ppm (approximately 0.2 mg/L). Lowered food consumption, reduced body weight gain and prostate weight were seen at ≥150 ppm in males. Other male reproductive effects were also reported at 500 ppm (see **Reproductive and Developmental Toxicity** section). Yellow urogenital matting, salivation and haematological effects occurred at 500 ppm in both sexes. A no observed adverse effect concentration (NOAEC) value could not be determined (NICNAS 2018).

Genotoxicity

Based on the weight of evidence, the chemicals are not considered to have genotoxic potential.

In vitro

Negative results were reported for tetrahydrofurfuryl methacrylate in the following in vitro genotoxicity studies (REACH n.d.-a; REACH n.d.-b):

- a bacterial reverse mutation assay (similar to OECD TG 471) in *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537, and *Escherichia coli* WP2 with and without metabolic activation at concentrations 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 1700 µg/plate
- 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 1720 µg/mL
- an in vitro micronucleus test (OECD TG 487) in human lymphocytes with and without metabolic activation at concentrations up to 1700 µg/mL.

In silico

The mechanistic and endpoint specific profiling functionality of the OECD QSAR Toolbox v4.6 (OECD 2023) were used to determine the presence of potential structural alerts for

genotoxicity. The chemicals have positive structural alerts for DNA binding by OECD, which relates to the alpha, beta unsaturated esters in the structure of the chemicals that may affect DNA alkylation and intercalation.

There were no structural alerts for in vitro mutagenicity (Ames test) using OASIS TIMES. However, the chemicals and one of their simulated S9 metabolites have positive alerts for in vitro chromosome aberration.

An alert for chromosome damage by alpha,beta-unsaturated esters was found for the chemicals using DEREK Nexus, relating to models of in vitro chromosome aberration. The alert was considered plausible. Therefore there were no alerts for in vitro mutagenicity (Ames).

Carcinogenicity

No animal data are available for the chemicals.

The chemicals have structural alerts for carcinogenicity using the mechanistic and endpoint specific profiling functionality of the OECD QSAR Toolbox v4.6 (OECD 2023). The chemicals have positive alerts for oncologic primary classification.

Reproductive and development toxicity

No data are available for tetrahydrofurfuryl acrylate. Based on the read across information from tetrahydrofurfuryl methacrylate and the metabolite, tetrahydrofurfuryl alcohol, the chemicals are expected to cause specific adverse effects on fertility, reproduction and/or development. Observed effects on fertility (delayed parturition) and developmental toxicity (early resorptions and litter loss) were similar for tetrahydrofurfuryl methacrylate and the metabolite tetrahydrofurfuryl alcohol, indicating that the metabolite is likely responsible for reproductive and developmental toxicity. Therefore, there is sufficient evidence to warrant hazard classification for both chemicals.

In a GLP compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted in accordance with OECD TG 422, SD rats (10/sex/dose) were administered tetrahydrofurfuryl methacrylate by gavage once daily at 0, 50, 120 or 300 mg/kg bw/day from 2 weeks before mating for a total of 29 days (males), during the mating, gestation and day 3 post partum periods (a total of 29 days for females) (see **Repeat dose toxicity – oral** section). On Day 20 post coitum, a decrease in body weight and body weight gain (statistically significant) was observed in the parental females at the high dose (300 mg/kg bw/day) group compared with controls. A slight increase in mean pre-coital interval was observed in the mid (120 mg/kg bw/day) and high dose animals compared to controls. The increase in the mid dose group was related to one parental female which mated 14 days after pairing. Gestation length of the low (50 mg/kg bw/day) and mid dose groups was slightly longer than the control group in which the majority of dams gave birth on day 22 of gestation. Most of low and mid dose dams gave birth on day 23 post coitum. No relevant differences in litter data were noted between the control, the low and the mid-dose groups. High dose dams had more prolonged gestation length (4 dams gave birth on day 25 post-coitum, 2 gave birth on day 24 post coitum and only 1 on day 22 post-coitum) which was statistically significant. The pre-birth loss (~66%) was significantly increased in high dose dams with total resorptions observed in 3 females. A total litter loss was reported for the remaining 7 females with no live pups from day 1 post partum. This increase could be attributable to the prolonged gestation period which caused pup death during or shortly the birth. Decreased litter weights (not statistically significant) were

observed in the low and mid dose groups due to the lower number of pups particularly in the mid dose group. The NOAEL for the parental females and the offspring was 120 mg/kg bw/day based on significant adverse effects on gestation length and loss of litter in the high dose dams. Effects on male reproductive organs or sperm were not observed in this study (ECHA 2022, REACH n.d.-b).

The metabolite, tetrahydrofurfuryl alcohol, is classified as a Category 1B Reproductive toxicant with hazard statement H360Df (May damage the unborn child. Suspected of damaging fertility) in the HCIS (SWA n.d.).

In a reproduction/developmental toxicity screening study (OECD TG 421), Crj:CD(SD)IGS rats (12/sex/dose) were treated by gavage with tetrahydrofurfuryl alcohol at dose levels of 0, 15, 50, 150 or 500 mg/kg bw/day. For parental toxicity, reduced body weight gain, locomotor activity changes and histopathological changes in spleen (capsule inflammation and/or decreased extramedullary haematopoiesis in females) were reported at ≥150 mg/kg bw/day. Reduced weights of body, thymus, testes and epididymides, including histopathological changes such as atrophy of seminiferous tubule, hyperplasia of interstitial cells, cell debris and/or decreased sperm were seen at 500 mg/kg bw/day (NICNAS 2018).

At 150 mg/kg bw/day, although copulation index, fertility index or implantation index were not impaired, other reproductive effects (prolonged gestation length and reduced gestation index) and developmental effects (decreased number of newborn, live birth index, litter size, viability index and live pups on postnatal day 4) were significant. At 500 mg/kg bw/day, there was total embryonic/foetal loss in pregnant females. An NOAEL of 50 mg/kg bw/day was determined for maternal, reproductive and developmental toxicity (NICNAS 2018). Based on the limited information available, it is difficult to decide if separate mechanisms were involved in the foetotoxicity and the delay in the onset of parturition. In particular, it is not known if administration of alcohol had a direct effect on parturition mechanisms, or if the presence of dead foetuses in the uterus resulted in the delay of parturition. If it were the latter, the concern for an adverse effect on sexual function / fertility would be lessened and the predominant concern would be for a developmental effect (ECHA 2012).

In the 90 day repeated oral dose study (see **Repeated Dose Toxicity – Oral** section), reduced testes, epididymis and seminal vesicle weights, including small and/or soft testes, degeneration of seminiferous tubules and interstitial (peritubular) oedema in the testes, and accumulation of cellular debris in the epididymides were seen at ≥339 mg/kg bw/day. Prostate weight was significantly lowered at 673 mg/kg bw/day. An NOAEL of 69 mg/kg bw/day was determined based on male reproductive toxicity at higher doses (NICNAS 2018).

In the 28 day repeated oral dose study (see **Repeated Dose Toxicity – Oral** section), necrosis of the seminiferous epithelium of the testes was noted at ≥150 mg/kg bw/day, and decreased ratio of spermatid:sertoli cells at 600 mg/kg bw/day (NICNAS 2018).

In the 90 day repeated dermal study (see **Repeated Dose Toxicity – Dermal** section), an NOAEL of 100 mg/kg bw/day was determined, based on decreases in sperm motility, sperm number and production rate at ≥300 mg/kg bw/day (NICNAS 2018).

In the 90 day repeated inhalation study (see **Repeated Dose Toxicity – Inhalation** section), reduced weights of prostates at ≥150 ppm, as well as epididymides and seminal vesicles at 500 ppm were reported. At 500 ppm, multifocal atrophy of testes, reduced sperm motility and numbers, as well as a higher incidence of sperm abnormalities were also observed. On this basis, the NOAEC for male reproductive effects was considered to be 50 ppm (approximately 0.2 mg/L) (NICNAS 2018).

Human health risk characterisation

Critical health effects

The critical health effects for risk characterisation are skin sensitisation and the potential reproductive and developmental effects.

Public risk

Skin sensitisation

A quantitative risk assessment for skin sensitisation was not performed because of the lack of animal data on the estimated concentration needed to produce a stimulation index of 3 (EC3) or data from a human repeat insult patch test.

A large amount of data show that a significant number of individuals are sensitised to tetrahydrofurfuryl methacrylate. Public exposure to these chemicals is mainly from nail enhancement products.

Given the increasing exposure to the chemicals and the potential for cross sensitisation, there is insufficient data to determine the levels that induce or elicit sensitisation in humans for the chemicals. However, elicitation of skin sensitisation has already been observed at low concentrations (0.2%, 70 µg/cm^2).

Systemic exposure risk

A Margin of Exposure (MOE) methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. 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 ≥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 international use concentrations (see **Human exposure** section). The NOAEL for tetrahydrofurfuryl methacrylate (120 mg/kg bw/day) for maternal, reproductive and developmental toxicity was derived from a guideline (OECD TG 422) reproduction/developmental toxicity screening study.

The worst case scenario internal dose from the chemicals via dermal exposure was determined to be 0.98 mg/kg bw/day (based on maximum reported concentration 38.2%) (see **Human exposure** section; Table 1). Based on this value, the calculated MOE using the NOAEL (120 mg/kg bw/day) is 122. If the chemical was used at higher concentrations, there could be a risk of adverse effects.

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