Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

2-Propenoic acid, 2-methoxyethyl ester (2-methoxyethyl acrylate)

Evaluation statement

30 June 2022

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AICIS evaluation statement

Subject of the evaluation

2-Propenoic acid, 2-methoxyethyl ester (2-methoxyethyl acrylate)

Chemical in this evaluation

Name	CAS registry number
2-Propenoic acid, 2-methoxyethyl ester	3121-61-7

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

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

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information on introduction, use or end use of the chemical in Australia. Based on international information the chemical is predominantly used as an intermediate in the manufacture of polymers, and bulk and fine chemicals.

While the chemical is listed in the International Nomenclature Cosmetic Ingredient (INCI) dictionary, with a reported function of use as a film former, no evidence of use in cosmetic products has been identified for the chemical. Future use of the chemical as a cosmetic ingredient is unlikely. In the European Union (EU), as of 1 March 2022, the chemical is banned from use in any cosmetic products marketed for sale or use. The chemical may be present as an impurity in polymers used in cosmetic products (concentrations up to 1500 ppm).

Human health

Summary of health hazards

The critical health effects for risk characterisation of this chemical are:

- systemic acute effects from oral, dermal and inhalation exposure
- local effects including skin sensitisation, skin corrosion, eye damage and respiratory irritation

- reproductive and developmental toxicity.

While no specific toxicokinetic studies are available, the chemical is expected to be bioavailable following oral, dermal and inhalation exposure. Following systemic absorption, the chemical is expected to be hydrolysed to acrylic acid and 2-methoxyethanol. The latter is expected to be subsequently oxidised to methoxyacetic acid.

Based on the available data, the chemical has moderate acute oral (LD50 404 – 818 mg/kg bw), high acute dermal (LD50 252/5 mg/kg bw) and moderate acute inhalation (LC50 2.7 mg/L) toxicity.

Although limited data are available, the evidence suggest that the chemical has the potential to cause skin corrosion, eye damage and irritation or corrosion of the respiratory tract. Based on in vivo local lymph node assay (LLNA) and in silico data, the chemical is considered to be a skin sensitiser. This is consistent with other acrylates of similar molecular weight.

Based on the available data, male reproductive organs appear to be the target organs for systemic toxicity. Other adverse effects reported following repeated oral exposure to the chemical are considered to be caused by the corrosive properties of the chemical.

Based on the available data, the chemical is expected to cause specific adverse effects on fertility and development. In a combined repeated dose and reproductive/developmental toxicity study, lowest observed adverse effect levels (LOAELs) for both reproductive toxicity and developmental toxicity of 40 mg/kg bw/day were reported. Observed effects included:

- histopathological changes in the testes and epididymides
- impairment of the spermatogenetic cycle
- increase in precoital time
- reduced fertility
- no live litters
- decreased viability index.

Similar effects on the male reproductive system and effects on pup viability were observed for the metabolite 2-methoxyethanol (ECHA 2018; NICNAS 2014).

In vitro genotoxicity testing has given some indication of genotoxicity. The chemical did not induce in vitro gene mutations in bacterial cells, but it did induce in vitro chromosomal aberrations and gene mutations in mammalian cells. Sufficient data are not available to confirm whether the chemical is a specific genotoxin in vivo. The chemical was positive in an in vivo mammalian alkaline comet assay. A significant increase in the % tail intensity was observed in the non-glandular stomach; however, the influence of cytotoxicity on this result is uncertain. The chemical has structural alerts for in vivo genotoxicity.

Hazard classifications relevant for work health and safety

The chemical satisfies 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 (UNECE 2017). This does not consider classification of physical hazards and environmental hazards. In addition, the chemical satisfies the criteria for the following non-GHS hazard statements (SWA 2012):

- AUH071 – Corrosive to the respiratory tract

Health hazards	Hazard category	Hazard statement
Acute toxicity (oral)	Acute Tox. 4	H302: Harmful if swallowed
Acute toxicity (dermal)	Acute Tox. 3	H311: Toxic in contact with skin
Acute toxicity (inhalation)	Acute Tox. 3	H331: Toxic if inhaled
Skin irritation/corrosion	Skin Corr. 1	H314: Causes severe skin burns and eye damage
Serious eye damage/ eye irritation	Eye Dam. 1	H318: Causes serious eye damage
Sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Reproductive toxicity	Repr. 1B	H360FD: May damage fertility; May damage the unborn child.

Summary of health risk

Public

Based on the available international use information it is unlikely that the public will be significantly exposed to the chemical. The public may be exposed to the chemical at low concentrations as an impurity (<0.15%) in cosmetics. Although the public could come into contact with articles or coated surfaces containing the chemical after polymerisation, it is expected that the chemical will be bound within articles and coated surfaces, and hence will not be bioavailable. Therefore, there are no identified risks to the public that require management. However, if information becomes available indicating the chemicals have more widespread consumer use, further risk management may be required.

Workers

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 the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

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

Proposed means for managing risk

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 (PCBU) 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 exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent the chemical 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 the chemical.

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

These control measures may need to be supplemented with health monitoring for any worker who is at significant risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health.

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

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

Conclusions

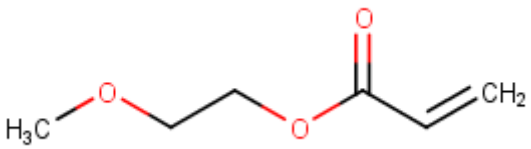
The conclusions of this evaluation are based on the information described in this statement.

Considering the proposed means of managing risks, the Executive Director is 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 and the proposed means of managing the risks identified during this evaluation are implemented.

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

Supporting information

Chemical identity

Chemical name	2-propenoic acid, 2-methoxyethyl ester
CAS No.	3121-61-7
Synonyms	2-methoxyethyl acrylate methoxyethyl acrylate (INCI) acrylic acid, 2-methoxyethyl ester 2-methoxyethyl prop-2-enoate ethylene glycol monomethyl ether acrylate 2-MEA
Structural formula	
Molecular formula	C6H10O3
Molecular weight (g/mol)	130.14
SMILES	COCCOC(=O)C=C

Relevant physical and chemical properties

Physical form	Colourless, transparent liquid.
Melting point	A liquid at room temperature (measured at 20°C).
Boiling point	164°C
Vapour pressure	281 Pa at 25°C
Water solubility	144 g/L at 20°C (measured at a pH of 5.3)
log K_{ow}	0.9

Introduction and use

Australia

No specific Australian introduction, use, or end use information has been identified for the chemical.

International

Based on the available information the chemical has predominant site limited use as an intermediate in the manufacture of polymers and bulk and fine chemicals (ECHA 2017; REACH).

The chemical has reported commercial use (REACH; SPIN) in:

- printing and reproduction of recorded media
- paints lacquers and varnishes.

It is unclear whether this use is for the chemical or polymers manufactured from the polymer.

No consumer uses were reported under the EU REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) Regulation or in a North American consumer product information database (DeLima Associates). Consumer preparations were identified in the Substances and Preparations in Nordic countries (SPIN) database. However, it should be noted that SPIN does not distinguish between direct use of the chemical and use of the materials that are produced from chemical reactions involving the chemical.

The chemical is listed in the INCI Dictionary, with a reported function of use as a film former (Personal Care Products Council). However, the chemical was not identified as being used in cosmetic products in the United States of America or in the EWG Skin Deep database (EWG, De Lima Associates; Personal Care Products Council). In the European Union (EU), as of 1 March 2022, the chemical is banned from use in any cosmetic products marketed for sale or use.

It is noted that polymers manufactured from the chemical have reported use in cosmetics, with functions of film formers and hair fixatives (Personal Care Products Council). Residual acrylic acid (representative of acrylate monomers) concentrations in polymers are reported to be typically between 10 and 1000 ppm, with an upper limit of 1500 ppm (CIR 2019).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for this chemical.

Public

No specific controls are currently available for this chemical.

Workers

The chemical is not listed on the HCIS and no specific exposure standards are available in Australia (Safe Work Australia).

International regulatory status

Exposure standards

No specific exposure standards have been identified.

European Union

The chemical is listed in Annex II of the EU Cosmetic Product Regulation 1223/2009/EC, as amended by Regulation (EU) 2021/1902. The chemical is listed as a prohibited substance due to its classification in the EU as carcinogenic, mutagenic, or toxic for reproduction (EU 2021).

Chemicals listed in Annex II are banned from use in any cosmetic products marketed for sale or use in the EU. This listing became effective on 1 March 2022, for this chemical.

Health hazard information

Toxicokinetics

While no specific toxicokinetic studies are available for the chemical, it is expected to be bioavailable following oral, dermal and inhalation exposure based on its molecular weight and log K_{ow} value. This is supported by observations of effects following all routes of exposure.

Read across information suggests that after systemic absorption, the chemical is expected to readily hydrolyse to form 2-methoxyethanol (CAS No. 109-86-4) and acrylic acid (CAS No. 79-10-7) by enzymatic cleavage of the ester bond (ECHA 2017; OECD 2019; REACH). The chemical 2-methoxyethanol is expected to be subsequently oxidised to methoxyacetic acid (ECHA 2017; NICNAS 2014a). Consistent with this, the rat liver S9 metabolism simulator of the Organisation for Economic Cooperation and Development (OECD) quantitative structure activity relationship (QSAR) Toolbox, predicted the formation of 2-methoxyethanol and methoxyacetic acid, as well as other metabolites (OECD QSAR Toolbox version 4.2).

Acute toxicity

Oral

Based on the available data, the chemical has moderate acute oral toxicity, which warrants hazard classification. Oral median lethal dose (LD50) values were reported to be in the range 404 – 818 mg/kg bw.

In an acute oral toxicity study similar to OECD Test Guideline (TG) 401, the chemical was administered via gavage to Sprague Dawley (SD) rats (5 animals/sex/dose) at 252.0, 353.5, 505.0, 555.5 or 606.0 mg/kg bw (ECHA 2017; REACH). No mortality was observed at the lowest dose, in either males or females. All animals were reported to be deceased at the highest dose. No clinical signs of toxicity were reported. Necropsies were conducted on deceased animals only, with cases of pulmonary haemorrhage reported in animals from all relevant dose groups. A calculated LD50 value of 404 mg/kg bw was reported in this study.

In an acute oral toxicity study conducted similar to OECD TG 401, the chemical was administered via gavage, to male Wistar rats (5 animals/dose) at 505, 1010 or 2020 mg/kg bw (ECHA 2017; REACH). No mortality was observed at the lowest dose, with 'sluggish behaviour' reported as the only observation. Mortalities were reported in the mid-dose group (n=4) and the high dose group (n=5), occurring on day one of exposure to the chemical. At necropsy, congestion in the lungs and abdominal viscera was reported across all dose groups. An oral LD50 of 818 mg/kg bw was calculated in this study.

Dermal

Based on the limited available data, the chemical has moderate acute dermal toxicity. The dermal LD50 was reported to be 252.5 mg/kg bw. Although the study did not strictly follow an OECD TG, there is sufficient evidence to warrant hazard classification.

In an acute dermal toxicity study conducted in 1968, similar to OECD TG 402, the chemical was applied to the clipped trunk of rabbits (4 animals/dose; strain and sex of animals not specified) at 126.25, 252.5 or 505 mg/kg/bw (as reported), under occlusive dressing, for 24 hours (REACH). The entire trunk of the rabbit was then wrapped in impervious vinylite (a thermoplastic vinyl resin) covering. No clinical signs of toxicity were reported. All high dose group animals died, 2 mortalities were reported in the mid-dose group, and no mortality was observed at the lowest dose. Mottled liver was the only finding reported at necropsy. Based on the reported details, it is unclear whether skin irritation was observed in treated animals, or at which dose level this occurred. No corrosive effects on the skin were reported.

Inhalation

Based on the limited available data, acute inhalation exposure to 2-methoxyethyl acrylate vapour, is expected to cause moderate toxicity. The inhalation median lethal concentration (LC50) value was reported to be 2.7 mg/L. Although the study did not strictly follow an OECD TG, there is sufficient evidence to warrant hazard classification.

In an acute inhalation toxicity study conducted in 1968, similar to OECD TG 403, male Wistar rats (n=6) were exposed to the chemical as a vapour by inhalation (whole body exposure), at 1.4, 2.7 or 5.4 mg/L, for 4 hours (ECHA 2017; REACH). Clinical signs of toxicity were reported to include laboured breathing and gasping, and swollen abdomen. Irritation of the eyes, nose and extremities were also reported. No mortality was observed at the lowest dose, 3 mortalities were reported in the mid dose group, and all high dose group animals were deceased. At necropsy, congestion in the lungs and abdominal viscera was reported across all dose groups. Rats that died had slight haemorrhage in the lungs and blood in the intestines, while 2 out of 3 rats exposed to 2.7 mg/L that survived, had areas of focal consolidation scattered throughout the lungs.

Corrosion/Irritation

Skin irritation

There is very limited reliable data available to evaluate the skin irritation properties of the chemical. Three specific skin irritation studies of the chemical are available, with varying results reported. However, none of these studies were conducted strictly according to an OECD TG.

While corrosive effects were not observed in all instances, the evidence indicates that the chemical has the potential to cause skin corrosion, warranting hazard classification. It is not possible to determine a classification subcategory based on the available data.

In a skin irritation study similar to OECD TG 404 (with deviations), 1.0 mL of the chemical was applied under occlusive dressing, to the shaved skin of 6 New Zealand White (NZW) rabbits, for 4 hours (ECHA 2017; REACH). Observations were recorded at 4 and 48 hours after patch removal. Skin corrosion was reported in 5 of 6 animals, 48 hours after patch removal. No corrosive effects were reported in animals 4 hours after patch removal. No irritation scores were reported and no further details on the corrosive effects are available. Deviations from the OECD TG for this study included application of 1.0 mL of the chemical instead of 0.5 mL, and observations only recorded at 4 and 48 hours, with the study ending after 48 hours.

In skin irritation study similar to OECD TG 404 (with deviations), 0.5 mL of the chemical was applied under occlusive dressing, to both intact and abraded skin of 6 NZW rabbits for 24 hours (ECHA 2017; REACH). Observations were recorded at 24 and 72 hours after patch removal (a 48 hour observation point was not included). Mean irritation scores of 3.0 and 3.2 for erythema and 3.0 and 2.5 for oedema, were reported at 24 and 72 hours, respectively. Individual mean scores were not provided, and reversibility of effects was not assessed. No difference between intact and abraded skin was reported. Deviations from the OECD TG for this study included a test exposure period of 24 hours instead of 4 hours, and observations only recorded at 24 and 72 hours, with the study ending after 72 hours.

In a skin irritation study of low reliability, 0.01 mL of the chemical was applied to the abdomen (non-occlusive) of 5 rabbits (sex and strain not specified) for 24 hours (ECHA 2017; REACH). Observations were recorded immediately after treatment. Very slight irritation was reported in one animal and slight irritation was reported in 4 animals. No further details are available.

No corrosive effects on the skin were reported for rabbits following exposure to the chemical in an acute dermal toxicity study. Based on the reported details, it is unclear whether skin irritation was observed in treated animals, or at which dose level this occurred (see **Acute toxicity – dermal** section).

Oral exposures studies suggest that the chemical may be corrosive to the gastrointestinal tract following ingestion (see **Acute toxicity – oral** section).

Eye irritation

Based on the limited available data, the chemical is considered to cause serious eye damage.

In an eye irritation study similar to OECD TG 405 (with deviations), 0.1 mL of the chemical was instilled into one eye each of 6 NZW rabbits, with eyes not washed out after application, and 3 NZW rabbits with eyes washed out 30 seconds after application. Observations were conducted at 24, 48 and 72 hours, and at 4 and 7 days after exposure. The following mean values of the scores at 24, 48 and 72 hours were reported for animals with unwashed and washed eyes, respectively: 1.7 and 1 for corneal opacity (out of a maximum 4), 0.2 and 0 for iritis (out of a maximum 2), 2.7 and 1.8 for conjunctival redness (out of a maximum 3), and 3.9 and 3.22 for chemosis (out of a maximum 4).

Of the 6 animals with unwashed eyes, within the 7 day observation period, conjunctival redness was not fully reversible in 3 animals, conjunctival oedema was not reversible in all animals, and corneal opacity was not fully reversible in 5 animals. Effects on the iris were fully reversible within 7 days. In one of the 3 animals with eyes washed at 30 seconds after exposure, conjunctival redness and chemosis were not fully reversible within 7 days. All other effects were reported to be fully reversible.

Although the study observation period did not extend to assess reversibility of effects at 21 days, the lack of reversibility of effects at the end of the 7 day study do not suggest that the effects are expected to reverse, or fully reverse, within 21 days. This evidence is sufficient to meet the criteria for hazard classification.

Respiratory irritation

No data are available on irritation/corrosion on the airway epithelium after exposure to vapours or aerosols of the chemical. Given the high vapour pressure of the chemical and the corrosive properties of the chemical observed in the skin and eye irritation studies, inhalation of vapour could lead to irritation/corrosion of the mucous membranes of the respiratory tract. In an acute inhalation study (see **Acute Toxicity** section) exposure to concentrations where mortalities occurred, caused congestion and slight haemorrhage in the lungs. Overall, there is evidence that the mechanism of toxicity was corrosivity. Therefore, the chemical warrants hazard classification.

Sensitisation

Skin sensitisation

Based on the available data, the chemical is considered to be a skin sensitiser. There is sufficient evidence to warrant hazard classification. Several acrylates and methacrylates are classified for skin sensitisation on the HCIS (SWA).

In a LLNA conducted in accordance with OECD TG 429, female mice (CBA/Ca strain; 4 animals/group) received topical applications of the chemical (in acetone/olive oil) at concentrations of 25 %, 50 % and 100 % (ECHA 2017; REACH). The reported stimulation indices (SI) were 9.20, 12.84 and 11.55, respectively. The EC3 value (concentration producing a three-fold increase in lymphocyte proliferation) could not be established due to all concentrations tested which resulted in reported SI values greater than 3.

In silico

The expert rule-based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (version 6.0.1), was utilised to estimate the skin sensitisation potential of the chemical (Lhasa Limited). An alert for skin sensitisation by alpha,beta-unsaturated esters was reported. Alpha,beta-unsaturated esters are electrophilic compounds that are known to undergo Michael-type conjugate additions with nucleophiles. Therefore, they are likely to interact with skin proteins by such a mechanism. The predicted EC3 in a LLNA for the chemical was 7.4%.

Repeat dose toxicity

Oral

Based on the available data, male reproductive organs appear to be the target organs for systemic toxicity (see **Reproductive and developmental toxicity** section). Effects in the thymus and haematological changes were also observed. Similar effects were observed in studies with the metabolite 2-methoxyethanol (NICNAS 2014). Mortalities observed are considered to be related to acute toxicity. Other adverse effects reported following repeated oral exposure to the chemical are considered to be caused by the corrosive properties of the chemical.

In a combined repeated dose and reproductive/developmental toxicity study, conducted in accordance with OECD TG 422, the chemical was administered by oral gavage to Wistar rats (10 animals/sex/dose) at 40, 100 or 150 (reduced from 250) mg/kg bw/day (ECHA 2017; REACH). Males were treated for 31 to 35 days, which commenced 2 weeks before mating, during mating and up to termination of the study. Females were treated for 42 to 56 days, which commenced 2 weeks before mating, during mating and up to a minimum of 4 days of lactation. The highest dose was reduced from 250 to 150 mg/g bw/day on day 12 of the study onwards, due to severe toxicity.

Clinical signs of toxicity (reported as hunched posture, increased salivation, piloerection and pale or lean appearance), body weight loss and reduced body weight gains were observed in both sexes at doses greater than or equal to (≥) 100 mg/kg bw/day. Prior to reduction in concentration, high mortality (approximately 30%) of parental animals was observed at the beginning of exposure at 250 mg/kg bw/day. It is noted that this was very close to acute oral LD50 of 404 mg/kg bw. One female from the mid dose (100 mg/kg bw/day) group was euthanised on day 21, due to severe toxic effects. No mortality or clinical signs of toxicity were reported at 40 mg/kg bw/day.

Changes in blood chemistry were reported at all dose levels in female animals; mean corpuscular volume (MCV) measures were decreased across all treatment groups (statistically significant at 40 and 100 mg/kg bw/day), while mean corpuscular haemoglobin (MCH) measures were significantly decreased across all treatment groups.

Histopathological observations included treatment related effects, specifically in the stomach and liver of both males and females at ≥100 mg/kg bw/day. In the stomach, this included inflammation, haemorrhage, and hyperplasia of non-glandular epithelium, and degeneration of glandular epithelium. In the liver, hepatocellular necrosis was observed, but only at the highest dose.

Histopathological changes in the testes and epididymides of males, and thymus of both males and females at all treatment dose levels, were reported. Changes in blood chemistry were also reported at all dose level. A reported LOAEL for parental toxicity of 40 mg/kg bw was based on these findings.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

In vitro genotoxicity testing has given some indication of genotoxicity. While it was reported not to induce in vitro gene mutations in bacterial cells, it did induce in vitro chromosomal aberrations and gene mutations in mammalian cells. Sufficient data are not available to confirm whether the chemical is a specific genotoxin in vivo. The chemical was reported to be positive in an in vivo mammalian alkaline comet assay based on a significant increase in the % tail intensity observed in cells of the non-glandular stomach. However, the influence of cytotoxicity on this result is uncertain. In vivo genotoxicity structural alerts were identified by in silico analysis of the chemical. It is also noted that the two main metabolites of the chemical (refer to **Toxicokinetics** section), 2-methoxyethanol and acrylic acid were reported to have, at most, weak genotoxic potential (NICNAS 2014a; NICNAS 2014b). As only a single in vivo study is available, of which the results are not unambiguous, the data are not sufficient to classify the chemical.

In vitro

Negative results were reported in the following in vitro gene mutation assays in bacteria (Ames test):

- In a bacterial reverse mutation assay (conducted according to OECD TG 471) in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98, at concentrations of 5 to 5000 µg/plate, with or without metabolic activation.
- In a bacterial reverse mutation assay (similar to OECD TG 471) in *S. typhimurium* strains TA 100, TA 1535, TA 97, and TA 98, at concentrations up to 3333 µg/plate, with or without metabolic activation.

Mostly positive results were reported in the following in vitro mammalian cell assays:

- In an in vitro mammalian gene mutation assay (conducted according to OECD TG 476) in mouse lymphoma L5178Y cells, a dose related increase in the frequency of mutations was reported, with and without metabolic activation, at concentrations up to 40 µg/mL without metabolic activation, and up to 648 µg/mL with metabolic activation.
- In an in vitro mammalian chromosome aberration assay (conducted according to OECD TG 473) in human lymphocyte cells, a statistically significant increase in the frequency of chromosomal aberrations was reported only in the presence of metabolic activation, at doses up to 640 µg/mL. This effect was not observed without metabolic activation, at concentrations up to 40 µg/mL.

In vivo

In an in vivo mammalian alkaline comet assay, conducted in accordance with OECD TG 489, male Wistar rats (7 animals/dose) were administered 2 single treatments of the chemical within 24 hours, by oral gavage, at doses of 120, 240, or 480 mg/kg bw/day. Animals were then euthanised 4 hours after the second dose for tissue analysis.

One animal from the 480 mg/kg bw/day group was deceased within 24 hours after dosing. Clinical signs of toxicity, including hunched posture approximately one hour after each dosing, were reported for all remaining animals at this dose.

Histopathological observations in the glandular and non-glandular stomach at ≥240 mg/kg bw/day were similar to those reported in a study detailed in the **Reproductive and developmental toxicity** section, at comparable dose levels (noting that effects were observed at ≥100 mg/kg bw/day in that study).

The DNA damage (reported as a significant increase in the % tail intensity between the treatment group and control group) was observed in the non-glandular stomach at ≥240 mg/kg bw/day and in the glandular stomach at all dose levels. However, the glandular stomach values were reported to fall within the limited historical control data. No DNA damage was observed in the liver at any dose level.

The OECD TG states that positive findings in a comet assay may not be due solely to genotoxicity, as target tissue toxicity (tissue damage) may also result in an increase in DNA migration (identified as DNA damage) (OECD 2016). DNA damage was reported in the non-glandular stomach at doses where histopathological observations indicated tissue cell damage (cytotoxicity). However, it was not possible to establish a correlation between the severity of the histopathological findings and the % of tail intensity. Therefore, the chemical cannot be clearly and unambiguously determined to be a specific genotoxin in this study.

In silico

Based on the mechanistic profiling functionality of the OECD QSAR Toolbox, structural alerts for DNA binding (Michael addition) and in vivo micronucleus formation (H-acceptor-path3-H-acceptor) were identified for the chemical (OECD QSAR Toolbox version 4.2). Structural alerts for in vivo mutagenicity (micronucleus formation) and protein binding alerts for chromosomal aberrations were also identified for simulated metabolites (by hydrolysis or S9 metabolism) of the chemical.

The genotoxicity potential of the chemical was predicted using DEREK Nexus (version 6.0.1) (Lhasa Limited). An alert for chromosome damage by alpha,beta-unsaturated esters was reported, relating to in vitro chromosome aberration and L5178Y TK+/- assay activity. The alert was considered plausible. The chemical was considered to be negative for mutagenicity, as no alerts for mutagenicity in vitro (no misclassified or unclassified features) were reported.

QSAR modelling using OASIS TIMES (optimized approach based on structural indices set–tissue metabolism simulator) predicted that the chemical and metabolites induce chromosomal aberrations in vitro and micronucleus formation in vivo (OASIS LMC). The predictions were within the applicability domain of the genotoxicity models and based on alerts for alpha,beta-unsaturated carboxylic acids and esters and dicarbonyl compounds. There were no alerts for in vitro mutagenicity (Ames test).

Carcinogenicity

No data are available specifically for 2-methoxyethyl acrylate. The 2 main metabolites of the chemical (see **Toxicokinetics** section), 2-methoxyethanol and acrylic acid, are not expected to be carcinogenic (NICNAS 2014a; NICNAS 2014b).

Reproductive and development toxicity

Based on the available data, the chemical is expected to cause specific adverse effects on fertility and development. There is sufficient evidence to warrant hazard classification.

In a combined repeated dose and reproductive/developmental toxicity study, conducted in accordance with OECD TG 422, the chemical was administered by oral gavage to Wistar rats (10 animals/sex/dose) at 40, 100 or 150 (reduced from 250) mg/kg bw/day (ECHA 2017; REACH). Males were treated for 31 to 35 days, which commenced 2 weeks before mating, during mating and up to termination of the study. Females were treated for 42 to 56 days, which included 2 weeks before mating, during mating and up to a minimum of 4 days of lactation. The highest dose was reduced from 250 to 150 mg/g bw/day on day 12 of the study onwards, due to severe toxicity. Details from this study are also presented in the **Repeat dose toxicity** section.

Histopathological changes in the testes and epididymides of males, and thymus of both males and females at all treatment dose levels, were also reported. Impairment of the spermatogenetic cycle in testes was observed at all doses with sperm degeneration observed at ≥100 mg/kg bw/day.

A dose related increase in precoital time and reduced fertility was reported at all dose levels. While implantation sites were noted in females from all dose groups, no live litters were observed at ≥100 mg/kg bw/day. A significantly decreased viability index was reported in pups born to females from the 40 mg/kg bw/day group; only 4 out of 9 litters still had live pups at the end of the study period. No significant difference in body weights was reported for pups from the 40 mg/kg bw/day group compared with control group pups. LOAELs for both reproductive toxicity and developmental toxicity of 40 mg/kg bw/day were reported for this study.

While changes in maternal blood chemistry measures were reported at 40 mg/kg bw/day, histopathological changes, clinical signs of toxicity and mortality were observed in parental animals at ≥100 mg/kg bw/day. Therefore, it is considered that the effects on development at 40 mg/kg bw/day are not secondary non-specific consequences of maternal toxicity.

A major metabolite of the chemical, 2-methoxyethanol (see **Toxicokinetics** section), is also classified as a reproductive and developmental toxin (Safe Work Australia). Similar effects on the male reproductive system and effects on pup viability were observed (ECHA 2018; NICNAS 2014a).

References

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