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

Morpholine, 4-(1-oxo-2-propenyl)- (acryloyl morpholine)

Evaluation statement

25 September 2023

Draft

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AICIS Evaluation statement

Subject of the evaluation

Morpholine, 4-(1-oxo-2-propenyl)- (acryloyl morpholine)

Chemical in this evaluation

Name	CAS registry number
Morpholine, 4-(1-oxo-2-propenyl)-	5117-12-4

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

The chemical is a UV-curable acrylate monomer used in several applications. Internationally it has reported use in cosmetic and in personal care products functioning as a plasticiser. The reported concentration in nail preparations is 5−25%.

The chemical also is used in several commercial applications including paints and coatings, adhesives and printing inks. Although some of these products may be available to consumers, available data indicate that domestic use is not widespread. However, there is evidence of consumer use as an adhesive for phone and device protectors.

Human health

Summary of health hazards

The identified health hazards are based on the limited data available for the chemical. There are no toxicokinetic studies available. Based on the physico-chemical properties and effects seen in in vivo toxicity studies and human case studies, the chemical is expected to be readily absorbed following oral, dermal and inhalation exposure.

Based on the available data, the chemical:

- has low acute dermal and inhalation toxicity but moderate acute oral toxicity (median lethal dose (LD50) 588 mg/kg body weight (bw))
- is a slight irritant
- is not expected to cause specific adverse effects on fertility/sexual function and foetal development
- is not considered to have genotoxic potential.

The chemical is currently listed on the Hazardous Chemicals Information System (HCIS) with classifications for acute oral toxicity, eye irritation and skin sensitisation. The available data are consistent with these classifications. The chemical has a reported LD50 value of 588 mg/kg bw. The chemical causes irreversible effects on the cornea as reported in a study with rabbits and positive results for sensitisation have also been observed in a guinea pig maximisation test and human patch tests.

Patch testing studies in humans reported a high rate of positive reactions to the chemical. Reactions occurred in workers with previous contact of up to 80% acryloyl morpholine in adhesive products, and also in individuals who experienced non-occupational exposure to adhesive products.

The chemical also has an existing classification for repeated dose toxicity. Effects on the nasal epithelium were observed in inhalation studies in rats. Irritant capacity of the chemical may contribute to effects seen in inhalation studies. The existing classification is supported by the available data. Serious systemic effects were not observed in available oral studies. No dermal repeated dose studies are available.

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

Hazard classifications relevant for worker health and safety

The chemical satisfies 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 and environmental hazards. This is the current classification listed in the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H302: Harmful if swallowed
Specific target organ toxicity (repeat exposure)	STOT Rep. Exp. 2	H373: May cause damage to organs through prolonged or repeated exposure
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

Summary of health risk

Public

Based on the available use information, the chemical may be present in nail products and adhesives at up to 25 and 80% concentration, respectively. Therefore, the public may be exposed to the chemical by:

- incidental skin and eye contact with the chemical during use of products
- inhaling aerosols (if used in products that are aerosolised).

It is expected that once cured, the chemical will be bound within articles/coated surfaces and hence, will not be bioavailable. However, prior to complete curing and during use, users may be exposed to the residual monomer.

Given the chemical is a skin sensitiser, with evidence of skin sensitisation in humans, there is a risk to the public that requires management (see **Proposed means for managing risks** section). Additional risks relating to damage to the eye and upper respiratory tract could arise if the chemical is used in products that are aerosolised. The risk could be managed by including the chemical in the *Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons—SUSMP).*

Workers

During product formulation and packaging, oral, 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 identified acute health effects, local and systemic long-term effects, the chemical could pose a risk to workers. Control measures to minimise oral, 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

Public health

It is recommended that the delegate of the Secretary for Poisons Scheduling lists the chemical in the *Poisons Standard (SUSMP).*

To manage the potential risks associated with the use of the chemical, it is recommended that the entry:

- results in labelling requirements that alert users to avoid contact with skin
- potentially restricts of the use of the chemicals in products intended to be aerosolised or to be used in contact with the eyes.

Consideration should be given to the following:

- respiratory tract irritation potential of the chemical

- potential use of these chemicals in cosmetics including nail enhancement products (such as nail polish and artificial nails) that may be available in Australia at concentrations up to 25%).

Workers

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 oral, dermal, ocular and inhalation exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come in 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 the chemical is used. These control measures may need to be supplemented with:

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

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

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

Conclusions

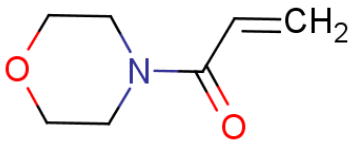
The conclusions of this evaluation are based on the information described in this statement.

Considering the proposed means of managing risks, the Executive Director proposes to be satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory 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	morpholine, 4-(1-oxo-2-propenyl)-
CAS No.	5117-12-4
Synonyms	1-(4-morpholinyl)-2-propen-1-one 2-propen-1-one, 1-(4-morpholinyl)- 4-(1-oxo-2-propenyl)morpholine morpholine, 4-acryloyl ACMO acryloyl morpholine (INCI)
Molecular formula	C7H11NO2
Molecular weight (g/mol)	141.17
SMILES	O=C(C=C)N1CCOCC1
Chemical description	Monofunctional UV-curable monomer
Structural formula	

Relevant physical and chemical properties

Physical form	Colourless liquid
Melting point	-8 °C at 760 mm Hg
Boiling point	Decomposition at 158.5 °C
Vapour pressure	1.03 Pa at 25 °C
Water solubility	Readily water soluble at 20 °C
log K_{ow}	-0.46 at 21 °C

Introduction and use

Australia

No specific Australian use, import, or manufacturing information has been identified for the chemical.

International

Limited information is available on the introduction, use and end use of acryloyl morpholine internationally. The following uses were identified from:

- the European Union Registration, Evaluation and Authorisation of Chemicals (REACH n.d.-a; REACH n.d.-b)
- Galleria chemica (Chemwatch n.d.)
- United States Environmental Protection Agency Chemical Data Reporting (CDR) (US EPA 2012, USEPA CDR) 2016, US EPA 2020)
- INCIpedia (Personal Care Products Council n.d).

The chemical has reported cosmetic uses in personal care products (REACH n.d.-a) The chemical is included in the INCI database as a cosmetic ingredient functioning as a plasticiser (Personal Care Products Council n.d.). Published safety data sheets (SDS) indicate the chemical has use in nail and manicure products, with concentrations of up to 25% reported,

The chemical has reported commercial uses, including in:

- inks, toners and colourant products
- paints, lacquers and coatings
- adhesive and sealant products.

Some of the commercial uses may also be used in domestic applications. There were no identified products containing the chemical in North American consumer product databases (DeLima Associates). The REACH registration dossier identified uses by professional users only. Only commercial uses were reported under the US Chemical Data Reporting (CDR) under the Toxic Substances Control Act (US EPA, 2012; US EPA 2016; US EPA 2020).

Adhesive products (concentration 20% to 80%) used to attach protective cases of smart devices were identified. The products were reported to be available for both professional and consumer use (Gatica-Ortega et al. 2022; Herreros-Montejano et al. 2022).

The chemical has reported site limited uses, including:

- in plastic and polymer manufacture
- as diluent or thinner in ultraviolet curable (UV) resins.

The chemical is also listed in the Food Contact Chemicals database for use in printing inks (FCCdb n.d.).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

No specific controls are currently available for the chemical.

Workers

The chemical is listed in the HCIS (Safe Work Australia, SWA n.d.) with the following hazard category and statements for human health:

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H302: Harmful if swallowed
Specific target organ toxicity (repeat exposure)	STOT Rep. Exp. 2	H373: May cause damage to organs through prolonged or repeated exposure
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

No exposure standards are available for the chemical in Australia (SWA).

International regulatory status

No specific controls or exposure standards are currently available for the chemical. The chemical is currently listed in the Prio Database as a priority risk reduction substance due to skin sensitisation characteristics (Swedish Chemicals Agency n.d.)

Health hazard information

Toxicokinetics

Information on toxicokinetics of the chemical is not available. Absorption via the oral route is expected to be high based on the observed effects in in vivo studies using this route. Similarly, dermal absorption is expected to occur based on results from skin sensitisation studies and observations in humans. As the chemical is readily water soluble and has a low log K_{ow} (-0.46) it is likely to distribute in water soluble compartments and be excreted via the urinary system, rather than accumulate in fatty tissues.

Acute toxicity

Oral

The chemical is classified as hazardous in the HCIS (Safe Work Australia SWA n.d.) for Acute Toxicity – Category 4 (Harmful if swallowed). The data are consistent with this classification.

In a GLP compliant acute oral toxicity study, conducted in accordance with OECD TG 401, Sprague Dawley (SD) rats (5/sex/dose) were treated with a single dose of the chemical via oral gavage at doses of 400, 500, 640 or 1000 mg/kg bw. Deaths occurred in the 500 mg/kg bw and higher dose groups in males and in 640 mg/kg bw and higher dose group in females. Upon macroscopic examination, pallor of kidneys, spleen and liver was observed in animals that died during the study. The LD50 was calculated to be 588 mg/kg bw (REACH n.d.-a).

Dermal

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

In an acute dermal toxicity study, conducted according to OECD TG 402, the chemical was applied to SD rats (5/sex/dose) under occlusive conditions at concentrations of 1260, 2000 or 3200 mg/kg bw (no vehicle) for 24 hours. There were reductions in body weight of animals on day 8, particularly in higher dose groups. Deaths of 2 animals occurred during the 14 day observation period in the 2000 mg/kg bw female group. Macroscopic examination revealed pallor of the liver in animals that died during the study. The LD50 was determined to be >2000 mg/kg bw for SD rats in this study (REACH n.d.-a).

Inhalation

Based on the limited data, the chemical has low acute inhalation toxicity.

In an acute inhalation toxicity study conducted in accordance with OECD TG 403, SD rats (5/sex/dose) were exposed to acryloyl morpholine as an aerosol, mass median aerodynamic diameter of up to 3.2 µm, via nose-only inhalation for 4 hours. Concentrations tested were 2.3 and 5.28 mg/L. No deaths occurred in any of the treated animals during the 14 day post exposure period. A median lethal concentration (LC50) value of >5.28 mg/L was determined. Sub-lethal effects included tremors and increased respiratory movements immediately following exposure, and a slight decrease in body weight on day 3 post exposure. There was no gross pathology upon post-mortem examination (REACH n.d.-a).

In a study with few details reported (guidelines followed or method of exposure not specified), mortality was observed in rats exposed to 1.13 mg/L chemical. The LC50 from this study was <1 mg/L. The information provided in this study is not sufficient for classification for acute inhalation toxicity of the chemical.

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is at most slightly irritating to skin.

In an in vivo skin irritation study conducted similar to OECD TG 404, intact and abraded skins of 6 New Zealand White (NZW) rabbits were treated with 0.5 mL of the undiluted chemical under occlusive conditions for 24 hours. At 24 hours there was very slight erythema at 6 intact sites and 5 abraded sites treated with the chemical. The mean score for erythema was 0.45 which was resolved by 72 hours. No oedema was observed at any time point. No further details were provided (REACH n.d.-a).

In an additional skin irritation study, the intact and abraded skin of 6 NZW rabbits were treated with the chemical under occlusive conditions for 24 hours. Mean erythema scores for intact and abraded skin were 0.5, and 0.8, respectively. There was no observable oedema at treated sites on either intact or abraded skin. All erythema was resolved within 72 hours (REACH n.d.-a).

Eye irritation

The chemical is classified as hazardous in the HCIS (Safe Work Australia SWA n.d.) as ‘Serious eye damage - Category 1’ (Causes serious eye damage). The data are consistent with this classification.

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, 0.1 mg of the chemical was instilled into 1 eye each of 3 NZW rabbits. The eyes were observed at 1, 24, 48, 72 hours, 4, 7, 14 and 21 days after instillation. Mean scores for animal 1 were: corneal opacity 2.3/4, iritis 1/2, conjunctival redness 1.7/3 and chemosis 1.7/4. Mean scores for animal 2 were: corneal opacity 1.3/4, iritis 0/2, conjunctival redness 1/3 and chemosis 0.3/4. Mean scores for animal 3 were: corneal opacity 0.6/4, iritis 0/2, conjunctival redness 1.7/3 and chemosis 1/4. The corneal opacity effects were not reversible even after 21 days. All other effects were reversible within 7–14 days (REACH n.d.-a).

Similar effects were observed in an additional study conducted under the same conditions but with irrigation of the eyes for 4 or 30 seconds after instillation of the chemical into the conjunctival sac. In the experiments which utilised irrigation, effects were seen in all animals. Effects were reversible within 7 to 14 days, but the rinsing of the chemical did not reduce the irritation potential of the chemical (REACH n.d.-a).

Sensitisation

Skin sensitisation

The chemical is classified as hazardous in the HCIS (Safe Work Australia SWA n.d.) as ‘Skin sensitisation – Category 1; H317 (May cause an allergic skin reaction)’. Data are consistent with this classification. Although the chemical was negative in a local lymph node assay

(LLNA) and Buehler test, positive results have been observed in a guinea pig maximisation test (GPMT) and human patch tests (see **observation in humans**).

In a GLP compliant GPMT, equivalent to OECD TG 406, intradermal induction was performed on female Dunkin Hartley (DH) guinea pigs (10/group; 5/control) using 5% of the chemical in water and topical induction with 30% of the chemical. The animals were challenged with 25% of the chemical in water. Reactions were reported in 60% of the animals. The chemical was reported to be sensitising in this study, meeting criteria for a Category 1 skin sensitiser based on GHS criteria (REACH n.d.-a).

In an in vivo skin sensitisation study conducted in accordance with OECD TG 406 (Buehler test), female DH guinea pigs were first induced (10/group) with 100% concentration of the chemical. The animals were then challenged with 100% of the chemical. None of the treated animals showed skin reactions. The chemical was reported to be non-sensitising in this study (REACH n.d.-a).

In an LLNA performed in accordance with OECD TG 429, female CBA mice (4/group) received topical applications of 0 (vehicle only), 5, 10 or 25% of the chemical in acetone/olive oil (4:1 v/v). The reported stimulation indices (SI) were 1.32, 1.48, and 1.38 for concentrations of 5, 10 and 25%, respectively. The estimated concentration to produce a 3-fold increase in lymphocyte proliferation (EC3) was not calculated in the study because no SI value was >3 (REACH n.d.-a).

The expert rule based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (Lhasa Limited n.d.) identified alerting groups (alpha,beta-unsaturated amide) indicating that the alerts may interact with proteins in the skin through a Michael addition mechanism. DEREK Nexus also predicted an EC3 value (0.097%) for the chemical which indicate its strong skin sensitisation potential.

Respiratory sensitisation

No data are available to evaluate respiratory sensitisation.

Observation in humans

Seven individuals with occupational allergic contact dermatitis arising from use of UV-curable adhesive associated with smartphone screen protector application kits were patch tested with the acryloyl morpholine. The chemical was applied for 48 hours under occlusive conditions at concentrations of 0.05, 0.5, 0.16% in petrolatum. Reactions were observed in 6/7 subjects, 1 individual had a flare up reaction at an alternative site to the patch tested area on day 3. Acryloyl morpholine was detected at up to 80% concentration in samples of adhesive product provided by the users. Concentration in the adhesive was different in samples purchased at different times (ranging from approximately 20% to 80%). In additional testing of 25 control eczema patients with no identified prior exposure to the chemical, 3 individuals had positive reactions to patch testing. One of the individuals had a history of sensitisation to multiple acrylates. The chemical was considered to be a sensitiser (Herreros-Montejano et al. 2022).

In an additional study by the same authors, 3 patients were identified to have suspected allergic contact dermatitis arising from contact with adhesive product used to attach protective screens to their smart watches (Gatica-Ortega et al. 2022). Two of the individuals underwent patch testing with acryloyl morpholine at 0.05, 0.5, 0.16 % in petrolatum. Positive reactions were observed at all concentrations in both individuals and also to samples of the adhesive used on their smart watch screens.

Repeat dose toxicity

The chemical is classified as hazardous in the HCIS (Safe Work Australia SWA n.d.) as 'Specific target organ toxicity repeated exposure (STOT RE) – Category 2'. Available data from inhalation studies are consistent with this classification. Observed effects occurred predominately in higher dose groups and may be due to irritant effects of the chemical on the olfactory epithelium. Serious systemic effects were not observed in available oral studies. No dermal repeated dose studies are available.

Oral

Based on the limited data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure.

In a 28 day study, conducted in accordance with OECD TG 407, SD rats (5/sex/dose) were administered the chemical once daily by gavage at 0 (vehicle), 4.5, 15 or 50 mg/kg bw/day, for 28 days. Increased liver weights were observed for females receiving 50 mg/kg bw/day, which reached statistical significance. In 2 of the animals, enlargement of hepatocytes was observed during histopathological examination correlating with the increased liver weight. This change was considered adaptive in the high dose group due to metabolism of the chemical. The no observed adverse effect level (NOAEL) was reported to be 50 mg/kg bw/day and the NOEL was 15 mg/kg bw/day as no effects were observed in the lower dose groups for either sex (REACH n.d.-a).

In a combined repeat dose toxicity and reproductive/developmental toxicity study (OECD TG 408 and OECD TG 422), (see **Reproductive and development toxicity**) CD rats (10 /sex/dose) were administered the chemical by gavage once daily at 0 (vehicle), 5, 20, or 75 mg/kg bw/day for 90 days. Control animals received the vehicle (water). In high dose animals, there was reduced food uptake and lower bodyweight gain that was more apparent in males, particularly towards the end of the study. No other treatment related effects were noted. An NOEL of 20 mg/kg bw/day was established based on reduced body weight (REACH n.d.-a).

Inhalation

In a short term dose-finding inhalation study, Crl:CD BR rats (5/sex/dose) were exposed to the chemical via snout only inhalation for 6 hours daily, 5 days/week for 2 weeks at mean exposure levels of 0 (vehicle = air), 0.1, 0.3 or 1.0 mg/L.

Exaggerated breathing was evident for all high dose animals during 3 days of exposure. One high dose animal was seen to suffer convulsions, whole body tremors and sensitivity to touch on day 3. Occasional loss hind leg function and whole body tremors were evident for 2 males on day 3. A general poor condition was also evident for all high dose rats. A red discharge from snout was seen post-exposure on days 10–12 for a proportion of intermediate dose rats. A high dose female was found dead in its cage prior to exposure on day 4. The remaining high dose rats were sacrificed on day 4.

Atrophy/disorganisation and hyperplasia of olfactory epithelium were seen in all rats exposed to 0.3 or 0.1 mg/L, with evidence of a dose-dependent relationship in severity. Several rats exposed to 0.3 mg/L also showed erosion of olfactory epithelium, and one showed respiratory metaplasia of olfactory epithelium. Dilated ducts of Bowman's glands were seen in occasional rats exposed to 0.3 or 0.1 mg/L. Increased incidences and severity of cortical

tubules with hyaline droplets were noted in males exposed to 0.3 or 0.1 mg/L, compared with controls.

An NOEL was not established in this study. It was concluded that the changes seen in rats exposed at 0.1 mg/L were sufficiently mild and that this exposure level could be used as the high exposure level for a subsequent 13 week inhalation study.

In the 13 week repeat dose inhalation study (OECD TG 413), CD rats (10/sex/dose) were exposed to the chemical (aerosol) via snout only inhalation for 6 hours daily, at mean exposure levels of 0 (vehicle = air), 0.0124, 0.0297 or 0.1238 mg/L for 5 days/week.

There were statistically significant decreases in bodyweight gain and food consumption across all dose groups which reached statistical significance for males in the 0.1238 mg/L dose group. Statistically significant reduced white blood cells were evident in treated females.

Histopathological examinations indicated effects on the respiratory epithelium that were more apparent for males, and olfactory effects that were slightly more prominent for females. Across all dose groups for both sexes, there were effects on the olfactory epithelium, with hyperplasia, vacuolation, disorganisation, dilated ducts and atrophy of Bowman's glands observed.

In the high dose groups (0.1238 mg/mL), there was increased incidence of inflammatory cells in the nasal epithelium for both males and females, and in the respiratory epithelium for females. In males, epithelial hyperplasia, goblet cell hyperplasia and pseudogland formation in the respiratory epithelium and squamous metaplasia of the transitional epithelium were noted. In females, an increased incidence of inflammatory cells in the lamina propria of the respiratory epithelium was observed .

In addition, changes in the olfactory epithelium, namely, epithelial hyperplasia, disorganisation, vacuolation, dilated ducts and atrophy of Bowman's glands, were noted in both sexes at all three exposure levels. Males of the high dose group had increased incidences of hyperplasia in the respiratory epithelium, goblet cell hyperplasia and pseudo-gland formation. Three males displayed squamous metaplasia, 1 occurring in the respiratory epithelium, and 2 occurring in the transitional epithelium. In the testes, increased incidence of minimal focal testicular seminiferous tubular atrophy was recorded at all exposure levels.

The lowest observed adverse event concentration (LOAEC) was reported as 0.0124 mg/L air due to the effects on the upper respiratory tract.

Genotoxicity

Based on the available data, the chemical is not considered to be genotoxic. In vitro and in vivo studies were mostly reported as negative.

In vitro

- Negative results were reported in a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA 98, 100, 1535, 1537, and 1538 with and without metabolic activation at concentrations up to 5000 µg/plate.

- Positive results were reported in an in vitro mammalian chromosome aberration assay (OECD TG 473) in human lymphocytes at concentrations up to 1250 µg/mL and 312.5 µg/mL with and without metabolic activation, respectively. In an additional test, positive results were reported for concentrations up to 300 µg/mL without metabolic activation, and up to 1000 µg/mL with metabolic activation.

- Negative results were reported in an in vitro mammalian gene mutation assay (OECD TG 490) in mouse lymphoma L5178Y cells with and without metabolic activation at concentrations of 31.25, 62.5, 125, 250, 500, 1000 and 2000 µg/mL.

In vivo

In a GLP compliant mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, CD-1 mice (5/sex/dose) were treated with the chemical via intraperitoneal injection at single doses of 125 or 250 mg/kg bw/day. An additional group of animals (10/sex/dose) were treated with the chemical via intraperitoneal injection at single doses of 500 mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity (REACH n.d.-a).

In a GLP compliant mammalian alkaline comet assay conducted in accordance with OECD TG 489, male SD rats (5/dose) were administered the chemical by oral gavage at doses of 0 (vehicle only), 62.5, 125 and 250 mg/kg bw/day for 2 days at 24 hour intervals. DNA damage in the liver and glandular stomach was not observed. Statistically significant increases in DNA damage were reported in the duodenum, which was not dose dependent. It was noted that the negative control values obtained for the duodenum were below the minimum acceptable limit based on historical data. (REACH n.d.-a).

In silico

No structural alerts for mutagenicity or clastogenicity were observed for the chemical or its metabolites (rat liver S9) using the OECD QSAR Toolbox (version 4.6) (OECD 2023) or OASIS (tissue metabolism simulator) software (version 2.28.1) (OASIS n.d.). No structural alerts for bacterial in vitro mutagenicity were observed for the chemical in the expert rule based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (version 6.0.1). However, an alert for mammalian chromosome aberration was predicted (Lhasa Limited n.d.).

Reproductive and development toxicity

Based on the limited available data, the chemical is not expected to cause specific adverse effects on fertility or development following oral exposure.

In a combined repeat dose and reproductive/developmental toxicity study (OECD TG 408 and OECD TG 422), CD rats (10 /sex/dose) were administered acryloyl morpholine by gavage once daily at 0 (vehicle), 5, 20, or 75 mg/kg bw/day. Control animals received the vehicle (water). All animals of the parent (P) generation were dosed prior to mating (2 weeks and 4 weeks for females and males, respectively) up to 13 weeks for males, or to lactation day 6 for female rats, before necropsy on day 7.

No test substance related changes in mortality, clinical observations, behaviour/physical condition, or food consumption were observed up to the highest tested dose (75 mg/kg bw/day). A reduction in bodyweight gain was observed in males in the 75 mg/kg bw/day

group, which was statistically significant. For females weight gain was lower compared to controls during the 2 week pre-mating period, and slightly lower during gestation up to day 1 of lactation. However, larger increases in body weight gain were subsequently observed on day 7 of lactation.

There were no obvious treatment related effects on fertility or reproductive performance of the P generation animals. All pairings led to successful pregnancy and live litters.

No specific macroscopic alterations or organ weight changes related to the treatment were found at necropsy. Histopathological examinations of selected organs of females (ovaries, uterus, cervix, vagina, pituitary, mammary tissue), did not reveal any treatment related changes at up to the highest tested dose (75 mg/kg bw/day).

There were no adverse findings noted in the development of the offspring (F1) generation (mortality, body weight and gain, or sex ratios of litters) to post natal day 7 pups.

In the repeat dose inhalation study, absolute mean ovary weights were statistically significantly lower in the 0.0297 and 0.1238 mg/L dose groups. There were no effects on testicular weights in any dose group. However, there were slightly increased incidences of seminiferous tubule atrophy in all treated males. See **Repeated dose toxicity**.

Carcinogenicity

No data are available on the carcinogenic effects of the chemical. Metaplasia in the olfactory epithelium was observed in repeat dose inhalation study. However, data is insufficient for carcinogenicity classification.

References

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