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

2-Propenamide, 2-methyl- (methacrylamide)

Evaluation statement

22 December 2022

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AICIS evaluation statement

Subject of the evaluation

2-Propenamide, 2-methyl- (methacrylamide)

Chemical in this evaluation

Name	CAS registry number
2-Propenamide, 2-methyl-	79-39-0

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 in Australia.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use or end use of the chemical in Australia. Based on international information, the chemical is predominantly used as an intermediate in the synthesis of polymerised compounds, including textile finishing agents, paper finishing agents, coating agents and condensing agents. Typical residual monomer contents are 0.001% to 0.01%.

The chemical has reported potential commercial and domestic uses including adhesives and paints and coatings. It is likely that this relates to the use of the polymers and available evidence indicates that any domestic use is not widespread.

Human health

Summary of health hazards

Critical health effects for risk characterisation are neurotoxic effects following single and repeated exposure. The chemical also causes reversible eye irritation.

Neurotoxic effects and effects in the peripheral nervous system have been observed in animals following single and repeated dose toxicity studies. In a 28 day oral study decreased grip strength, staggering gait, ataxia, decreased muscle tone and degeneration of sciatic nerve fibres were observed at 300 mg/kg body weight (bw)/day. In a 12 month study in rats

and mice reduction in rotarod performance and peripheral neuropathy were observed at doses ≥19.5 mg/kg bw/day (rats) and ≥49.6 mg/kg bw/day (mice). Reversible effects on grip strength were observed in a repeated dose dermal toxicity study. No effects have been observed following inhalation exposure. Neurotoxic effects in offspring have been noted in animal studies following exposure via lactation.

The structurally related chemical acrylamide is well established as being neurotoxic. Similar effects for grip strength and histopathological observations in the peripheral nervous system are observed for both chemicals. However, effects for acrylamide are observed at much lower doses than acrylamide in both acute and repeated dose toxicity studies.

Based on the available data, the chemical may have potential to cause developmental toxicity (decreased foetal weight and viability) at doses greater than 100 mg/kg bw/day following repeated exposure. Developmental effects were not consistently seen in all studies and these effects are generally seen at higher doses than those causing neurotoxicity. No effects on fertility were observed in any study.

The chemical is harmful following acute oral exposure (LD50 1223–950 mg/kg bw in rats). In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, the chemical was determined to be mildly irritating to the eyes based on corneal opacity (score of 1) that was fully reversible in 7 days.

Based on the available data the chemical is:

- slightly irritating to the skin
- not considered to be a potent sensitiser
- not expected to have genotoxic potential.

No reliable data are available to evaluate carcinogenicity for the chemical.

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 does not consider classification of physical and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute Toxicity	Acute Tox. 4	H302: Harmful if swallowed
Eye Irritation	Eye Irrit. 2B	H320: Causes eye irritation
Specific Target Organ Toxicity – Single Exposure	STOT SE 2	H371: May cause damage to organs (peripheral nervous system)
Specific Target Organ Toxicity – Repeated Exposure	STOT RE 2	H373: May cause damage to organs through prolonged or repeated exposure (peripheral nervous system)
Effects on or via lactation	Effect on or via lactation	H362: May cause harm to breast-fed children.

Summary of health risk

Public

Based on the available use information it is unlikely that the public will be significantly exposed to the chemical.

There may be exposure of the general public to the chemical if present in domestic products such as paints and coatings. However, this use is not expected to be widespread. In addition, exposure to do it yourself (DIY) products is incidental and normal precautions to avoid prolonged contact are expected.

Although the public may come in contact with food contact articles and coated surfaces containing low levels of the chemical as a residual monomer, it is expected that the chemical will be bound within the article and hence, will not be bioavailable. The chemical has been identified as not migrating in detectable quantities.

Overall, there are no identified risks to the public that require management.

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, 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 local and systemic acute and long term 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). Control measures implemented due to the singe and repeated exposure hazard classifications are expected to be sufficient to protect workers from any potential reprotoxic effects.

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 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.

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.

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.

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

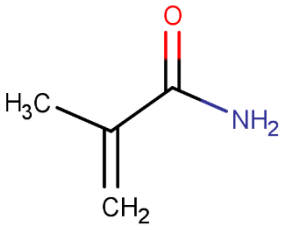
The conclusions of this evaluation are based on the information described in the statement.

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-propenamide, 2-methyl-
CAS No.	79-39-0
Synonyms	methacrylamide 2-methylacrylamide 2-methylpropenamide
Structural formula	
Molecular formula	C4H7NO
Molecular weight (g/mol)	85.10
SMILES	O=C(N)C(=C)C
Chemical description	-

Relevant physical and chemical properties

The chemical is a combustible solid at 20 °C and 101.3 kPa. It is colourless, odourless powder with high water solubility (100 g/L at 25 °C) and low vapour pressure (1.3×10^{-5} kPa at 25 °C) (OECD 2002; Sigma-Aldrich SDS).

Introduction and use

Australia

No specific Australian industrial use, import or manufacturer information were identified for the chemical.

International

The chemical is mainly used as a monomer in the manufacture of intermediates or polymers for (OECD 2002; REACH; SPIN):

- plastic materials and resins
- textile, leather and fur products

- paper finishing products
- paint and coating products.

The chemical has reported commercial uses as a component of (OECD 2002; REACH; SPIN):

- adhesives, binding agents, fillers and sealants
- paints, lacquers and varnishes.

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). No consumer uses were reported under the US Chemical Data Reporting (CDR) under the Toxic Substances Control Act (US EPA 2016). SPIN lists uses considered to be domestic (paints, lacquers/varnishes, adhesives, binding agents), 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. No consumer uses are registered under REACH. The chemical is included in the INCI database as a reference for the definition of other INCI Names and might not be a marketed cosmetic ingredient (Personal care council).

The residual monomer content in polymers is expected to be. 0.5% or less. Typical residual monomer contents are 0.001% to 0.01%. Migration of residual unpolymerised methacrylamide from polymer articles is very low, as typified by migration into food simulants under EU food regulations for plastic materials (OECD 2002). The chemical has been identified as not migrating in detectable quantities.

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

No specific controls are currently available for the chemical.

International regulatory status

Exposure standards

No specific exposure standards were identified.

European Union

The chemical is listed in:

- Plastics Food Contact Materials (FCM) and Articles Regulation No 10/2011, Annex I – Union list of authorised substances. Methacrylamide has a specific migration limit (SML) of not detectable (ND).

United States of America

The chemical is regulated for use as a component of food contact substances under the US FDA List of Indirect Additives Used in Food Contact Substances (US FDA 2018) with the following limitation:

- plastic articles intended for repeated-use food contact: the polymers used in these plastics must not contain more than 5% w/w of total polymer units derived from the chemical.

Health hazard information

Toxicokinetics

Based on its toxicity and excretion profile (OECD 2002; REACH), the chemical is expected to be absorbed, distributed widely to the tissues and rapidly excreted following oral and dermal exposure.

Distribution was highest to liver, then blood, kidney and lung 24-hour after in intravenous injection of ^{14}C-methacrylamide (15% in water) in rabbits. Excretion is mainly via urine (up to 86%) and minimal via exhaled $^{14}CO_2$ (1%). After intraperitoneal (i.p.) administration of ^{14}C-methacrylamide to male ddY mice, radioactivity was determined in different organs 3 minutes after dosing. Levels were highest in the kidney then liver and blood.

Skin absorption of 14C-methacrylamide was studied in male Japanese white rabbits, male Wistar rats and male ddY mice. After dermal exposure of the chemical (5−15% solution) for 15–30 min the percentage of the administered dose detected in the urine after 24 hours was up to 52% in rabbits, and up to 5.7% in rats. Urinary excretion was not determined in mice. The majority of the radioactivity remained at the application site. Organ levels were highest in the liver (rabbits) and kidney (rats and mice).

In an in vitro study, metabolism of methacrylamide was considered dependent on a cytochrome P-450 based on its 2-fold reaction induction by phenobarbital.

Acute toxicity

Oral

Based on the available data, the chemical has moderate acute oral toxicity with reported median lethal doses (LD50) of less than 2000 mg/kg bw in rats. In addition, based on the neurotoxic effects at 1315–1739 mg/kg bw, the chemical can be presumed to have the potential to be harmful to human health (nervous system) following single exposure. These values warrant hazard classification under GHS (see **Hazard classifications relevant for worker health and safety** section).

In a number of animal studies, reported LD50 values were 1223–1950 mg/kg bw in rats, 451–567 mg/kg bw in mice, 100–1000 mg/kg bw in cats, and 1865 mg/kg bw in rabbits (OECD 2002).

Following are 2 key studies for acute oral toxicity of the chemical that were conducted according to good laboratory practice (GLP) and OECD Test Guideline (TG) 401:

In the first study, Crj:CD rats (5/sex/dose) were administered the chemical by oral gavage at doses of 0, 1315, 1512, 1739 or 2000 mg/kg bw. The LD50 values were 1789 and 1774 mg/kg bw for males and females, respectively. Clinical signs in both sexes included tremors at ≥1315 mg/kg bw, staggering gait, salivation, irritability, soiled perioral fur, sitting position and orange yellow urine at ≥1512 mg/kg bw. Histopathological findings included small testes and degeneration of epididymides at 1512 mg/kg bw, degeneration of the sciatic nerve fibres in males (1512 mg/kg bw) and females (1739 mg/kg bw), and necrosis of neurocytes in the cerebellum in both sexes at 1315 mg/kg bw (OECD 2002; REACH).

In the second study, Wistar rats (5/sex/dose) were administered the chemical by oral gavage at doses of 1000, 2000 or 3000 mg/kg bw (controls not specified). The LD50 values were 1938 and1653 mg/kg bw for males and females, respectively. Clinical signs in both sexes included sedation at ≥1000 mg/kg bw, and ataxia, ventral/curved or latero-abdominal body position at ≥2000 mg/kg bw. Ruffled fur was observed in males (1000 mg/kg bw) and females (2000 mg/kg bw) (OECD 2002; REACH).

Neurotoxic effects were reported following single exposure in several non-guideline studies in rats, mice and cats (OECD 2002).

Dermal

Insufficient data are available to evaluate this endpoint.

In a non-guideline acute dermal toxicity study, the chemical (10% or 20%) was applied onto the abdominal skin of rats (10 animals) for 4 hours. No mortalities were observed or clinical signs of toxicity, and the author concluded that the LD50 was >1600 mg/kg bw (OECD 2002; REACH). It is noted that the OECD TG 402 for acute dermal toxicity requires occlusive application of the chemical at 100% and 24 hour exposure.

Inhalation

Insufficient data are available to evaluate this endpoint.

No mortalities or clinical signs of toxicity were observed after exposure to methacrylate (as dust) at 0, 12, 60 or 300 mg/m^3 in rats (5/dose) for 6 hours/day, 7 days/week (OECD 2002; REACH) (see **Repeated Dose Toxicity – Inhalation**).

Corrosion/Irritation

Skin irritation

Based on the available data the chemical may cause slight skin irritation.

In a GLP-compliant skin irritation study conducted in accordance with OECD TG 404, 3 New Zealand White (NZW) rabbits were treated with the chemical for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48, 72 hours after patch removal. Slight erythema and oedema (score 1/4) were observed in all animals 1 hour after patch removal. The effects had resolved by 24 hours (OECD 2002; REACH).

In a GLP-compliant skin irritation study conducted in accordance with OECD TG 404, 3 NZW rabbits were treated with the chemical for 4 hours under semi-occlusive conditions. Observations were recorded at 24, 48, 72 hours and 7 days after patch removal. The following mean scores for individual animals were reported: 2, 0.33 and 1 for erythema and 0,0 and 0 for oedema. All effects were reversible within 7 days (OECD 2002; REACH).

Eye irritation

Based on the available data the chemical is expected to cause reversible eye irritation, which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section).

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, the chemical was instilled into 1 eye each of 2 male and 1 female NZW rabbits. The eyes were not washed out. The eyes were observed at 1, 24, 48, 72 hours, 7 days. The following mean scores were reported at 24, 48 and 72 hours: corneal opacity 1/4 (3 animals), iritis 0/2 (2 animals) and 2/2 (1 animal), conjunctival redness 1.67/3 (2 animals) 2/3 (1 animal), chemosis 0.33/4 (2 animals) 0.67/4 (1 animal). The observed effects were reversible in all animals within 7 days (OECD 2002; REACH).

The chemical was reported to be irritating to the eyes in 2 other non-guideline studies prior to 1980. No further information was available (OECD 2002; REACH).

Sensitisation

Skin sensitisation

Based on the weight of evidence of the available data, the chemical is not considered to be a potent skin sensitiser. In the absence of more comprehensive information, hazard classification is not warranted.

In a local lymph node assay conducted in accordance with OECD TG 429, female CBA mice (4/dose) received a topical application of 0, 5, 10 or 25% of the chemical in dimethyl formamide once daily for 3 consecutive days. The reported stimulation indices (SI) were 0.94, 1.03, and 1.60 for concentrations of methacrylamide at 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. The chemical was considered a non-sensitiser (REACH).

The chemical was reported to be non to slightly sensitising in 2 non-guideline guinea pig studies. Induction and challenge concentrations were not clearly reported (OECD 2002).

The structurally related chemical, acrylamide is classified as a skin sensitiser (Safe Work Australia). In a GLP compliant study and GPMT conducted according to OECD TG 406, intradermal induction was performed on 20, female, Dunkin-Hartley guinea pigs using 3.5% acrylamide in water and topical induction with 50% of the chemical. The animals were challenged with 25% of the chemical in water. After challenge, reactions were reported in 85% of the animals. A positive response was found in 40% of the animals in another study using the same protocol (NICNAS 2002).

In silico data

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 was utilised to estimate the skin sensitisation potential of the chemical. An alert for skin sensitisation by alpha,beta-unsaturated amides was reported. This alert describes the skin sensitisation of alpha,beta-unsaturated amides which may interact with skin proteins via a Michael addition.

The chemical has structural alerts for protein binding via Michael addition based on the mechanistic profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox v4.5).

Repeat dose toxicity

Oral

Based on the available data, the chemical is expected to have the potential to be harmful to human health (nervous system) following repeated exposure, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section).

In a 28 day repeated dose toxicity study conducted similarly to OECD TG 407 (deviation 7 animals/sex/dose instead of 10), Crj:CD rats were administered the chemical by oral gavage at doses of 0, 30, 100 or 300 mg/kg bw/day. At 300 mg/kg bw/day, decreased body weight gain, food and water consumption were observed in both sexes. Body weight gain was decreased in female rats at 100 mg/kg bw/day. Effects on haematology and blood chemistry included decreases in haematocrit, haemoglobin, alpha1-globulin, alpha2-globulin, alkaline phosphatase (ALP), urea nitrogen, and creatinine and an increase in albumin and platelet. Haemoglobin and mean cell haemoglobin (MHC) were decreased in male rats at 100 mg/kg bw/day. Relative and absolute organ weight of testes were increased at 300 mg/kg bw/day and at the end of recovery period, respectively. Neurotoxicity effects included decreased grip strength in male rats, and staggering gait, ataxia, and decreased muscle tone in both sexes at 300 mg/kg bw/day. These effects were still present at end of recovery period (14 days). Decreased locomotor activity, decrease in body weight, body weight gain, and food and water consumption were noted in males and females at ≥100 and ≥30 mg/kg bw/day, respectively. Associated histopathological findings at 300 mg/kg bw/day included swelling of the axons in the cerebellar peduncle and degeneration of the sciatic nerve fibres. These effects were still present at end of recovery period (14 days). The 28 day no observed adverse effect level (NOAEL) was 30 mg/kg bw/day for male rats, and not determined for female rats in this study (OECD 2002; REACH).

In a 12 month study, male Wistar rats and ddY mice (18–22/dose) were administered the chemical in drinking water at 200, 400, 800 and 1200 ppm equivalent to approximately 4.6, 9.1, 19.5 and 31.6 mg/kg bw/day for rats or 24.3, 49.6, 120 and 220.6 mg/kg bw/day for mice) (OECD 2002; REACH).

The following effects were observed in rats:

- reduction in rotarod performance (50% after week 10), distension of the urinary bladder, atrophy of gastrocnemius muscle, and shrinkage and loss of myelinated fibres of sciatic nerve at ≥19.5 mg/kg bw/day
- peripheral neuropathy (decrease in grip strength and abnormal gait) and paralysis of hindlimb (after week 15) at 31.6 mg/kg bw/day
- increased total cholesterol and phospholipid content at 31.6 mg/kg bw/day.

The reported NOAEL was 9.1 mg/kg bw/day for rats based on reduction in rotarod performance, atrophy of gastrocnemius muscle, and shrinkage and loss of myelinated fibres of sciatic nerve at ≥19.5 mg/kg bw/day.

The following effects were observed in mice:

- reduction in rotarod performance (50% after week 3), distension of the urinary bladder, and atrophy of gastrocnemius muscle at ≥120 mg/kg bw/day
- peripheral neuropathy (decrease in grip strength and abnormal gait) and body weight gain at ≥120 mg/kg/day
- paralysis of hindlimb (after week 10) and shrinkage and loss of myelinated fibres of sciatic nerve at ≥49.6 mg/kg/day.

The reported NOAEL for mice was 24.3 mg/kg bw/day based on hind limb paralysis and myelinated fibres of sciatic nerve at ≥49.6 mg/kg bw/day.

Neurotoxicological signs were reported in several non-guideline repeated dose animal studies in rats, mice, rabbits and cats (OECD 2002).

Dermal

Limited data are available.

In a 5 or 12 week repeated dose dermal toxicity study, NZW rabbits (male/female) were dermally exposed to the chemical at doses of 0, 5 or 50 mg/kg bw/day (12 weeks) or 500 mg/kg bw/day (5 weeks; weeks 6–12 served as a recovery period). Clinical signs of neurotoxicity including splaying of hindlimbs were observed in 15/23 animals at a dose of 500 mg/kg bw/day. These effects were reversible within 20 days after the last dose administered. The NOAEL was reported as 50 mg/kg bw/day in this study (OECD 2002; REACH).

In a 4 week repeated dose dermal toxicity study, male rabbits were dermally exposed to the chemical at doses of 0, 700 or 800 mg/kg bw/day 21 times (8 hours/day; 5 days/week). No signs of toxicity or neurotoxicity were observed at any test dose. The NOAEL was reported to be 700 mg/kg bw/day although no rationale was available (OECD 2002; REACH).

Inhalation

Based on the available data, the chemical may cause local effects at the site of contact following inhalation exposure. There were no clinical signs indicative if impaired respiratory function. Neurotoxic effects observed in oral and dermal toxicity studies were not observed.

In a 90 day repeated dose inhalation toxicity study according to OECD TG 413), Wistar rats (10/sex/dose) were administered the chemical by nose only inhalation at concentrations of 0, 10, 25 or 62.5 mg/m^3 (aerosol) for 6 hours/day, 5 days/week. There were no clinical signs of toxicity and no treatment related effects on neurobehaviour. Terminal body weights were decreased in male rats of the mid (-11.0%) and high dose (-12.7%) groups. Local lesions in the nasal cavity, such as degeneration, squamous metaplasia and respiratory metaplasia of olfactory mucosa were reported in female rats at ≥25 mg/m^3 (1 mid dose female rat and 2 high dose female rats. The degree of severity was described as slight to minimal. The no observed adverse effect concentration (NOAEC) was determined to be 10 mg/m^3 for local effects and 62.5 mg/m^3 for systemic effects (OECD 2002; REACH).

In a 14 day GLP inhalation study, Sprague Dawley (SD) male rats (5/dose) were exposed to the chemical by nose only inhalation at concentrations of 0, 12, 60 or 300 mg/m^3 (dust) for 6 hours/day, 7 days/week. No mortalities or clinical signs of toxicity (e.g. body weight, organ weight or grip strength) were observed. There were no treatment related histopathological findings in the sciatic and tibial nerves, testes, epididymis and nasoturbinal tissues (including the nasopharynx). Based on histopathological findings in the larynx (focal squamous metaplasia (minimal) and liver (hypertrophy of central lobular hepatocytes) of rats at ≥60 mg/m^3, the NOAEC was assumed to be 12 mg/m^3 although these organs were not evaluated at this dose (OECD 2002; REACH).

Genotoxicity

Based on the available data, the chemical is not expected to have genotoxic potential.

In vitro

In a bacterial reverse mutation test (OECD TG 471), the chemical was not mutagenic in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and *Escherichia coli* WP2 at concentrations up to 5000 µg/plate, with or without metabolic activation (OECD 2002; REACH).

In a mammalian chromosome aberration test (OECD TG 473) in Chinese hamster lung (CHL/IU) cells, the chemical was not clastogenic up to 900 µg/mL (10mM), with or without metabolic activation (OECD 2002; REACH).

In a mammalian cell gene mutation test (OECD TG 476) in Chinese hamster fibroblasts (V79), the chemical was not mutagenic at the *hprt* locus up to 860 µg/mL, with or without metabolic activation (REACH).

In vivo

In a mammalian erythrocyte micronucleus test (OECD TG 474) in NMRI mice (5/sex/dose), the chemical did not induce micronuclei in bone marrow cells of the mice at oral gavage doses up to 350 mg/kg bw. There were no signs of toxicity during the study (REACH).

In a dominant lethal assay in CD-1 mice, no effects were observed regarding early embryonic loss or post implantation loss after exposure (males) to the chemical for approximately 100 days in drinking water up to 49 mg/kg/day (OECD 2002).

Carcinogenicity

No reliable data are available to evaluate carcinogenicity for the chemical. Based on differences in genotoxic potential, the classified mutagen and carcinogen acrylamide cannot be considered as a suitable analogue for this endpoint.

Reproductive and development toxicity

Based on the available data, the chemical may have potential to cause developmental toxicity (decreased foetal weight and viability) at doses greater than 100 mg/kg bw/day following repeated exposure. Developmental effects were not consistently seen in all studies and were mostly observed secondary to maternal toxicity. No effects on fertility were observed in any study.

The results from a 2-generation reproductive toxicity study and a developmental neurotoxicity study provide evidence of neurotoxic effects in offspring due to transfer of the chemical in the milk, which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section).

In a GLP compliant combined reproduction/developmental toxicity screening study conducted in accordance with OECD TG 421, SD rats (13/sex/dose) were administered the chemical by oral gavage once daily at 0, 12.5, 50 or 200 mg/kg bw/day. Male rats were exposed for 42 days, and female rats from 14 days before mating to lactation day 3. Mortality was reported in one male and 4 females, and morbidity in one female at 200 mg/kg bw/day. Body weight gain was decreased at ≥50 mg/kg bw/day, and food consumption at 50 and 200 mg/kg bw/day in males and females, respectively. At the high dose, reported signs of toxicity in parental animals included dragging of hindlimbs, pneumonia, decreased maternal copulation rate, delayed parturition, and abnormal nursing. For pups, bodyweight and viability were decreased at 200 mg/kg bw/day. Fertility indices, oestrous cyclicity or reproductive organs were not affected by treatment. The NOAELs were 12.5 mg/kg bw/day for parental effects and 50 mg/kg bw/day for reproductive and developmental effects (OECD 2002).

In a GLP compliant 2-generation reproductive toxicity study (modified reproductive assessment by continuous breeding (RACB) protocol), Swiss CD-1 mice (18 or 19/sex/group) received 0, 24, 80 or 240 ppm of the chemical in drinking water for 27 weeks. The premating exposure period was 7 days. The corresponding doses for F0 (100 days exposure) were 0, 4.5, 15.4, and 49 mg/kg bw/day, and for F1 (74 day exposure) were 6.8, 23.8, and 71.3 mg/kg bw/day. In the F0 generation, there were no reported signs of parental toxicity including neurotoxicity or effects on reproductive performance. In the F1 generation, there were significant reductions in body weight and grip strength in all treated animals at weaning. The changes in body weight were less than 10% and not dose related. The grip strength effects were observed at 3 weeks and had reversed by week 5 indicating that lactation may have contributed to effects. There were no adverse effects on fertility or development. (OECD 2002; REACH).

In a GLP compliant prenatal developmental study similar to OECD TG 414, pregnant Swiss CD–1 mice (15-30 per dose) were administered the chemical by gavage at 0, 60, 120 or 180 mg/kg bw/day on gestational days (GD) 6–17. Dams were sacrificed on GD 17 and the foetuses examined. Maternal weight gain and gravid uterine weight were decreased at 180 mg/kg bw/day. Relative maternal liver weight was increased at ≥120 mg/kg bw/day although absolute liver weight was not affected. There were no reported clinical signs of neurotoxicity. The percentage of non-live implants per litter exhibited a dose-related increasing trend, with the high dose group significantly increased over the control group. A significant decrease in foetal body weight was observed at 120 mg/kg bw/day (-7%) and 180 mg/kg bw/day (-15%). No teratogenic effects were observed. The maternal and foetal NOAELs were considered to be 60 mg/kg bw/day in this study (OECD 2002).

In a GLP compliant developmental neurotoxicity study similar to OECD TG 426, pregnant Wistar rats (25 per dose) were administered the chemical by gavage at 0, 15, 50 or 150 mg/kg bw/day from GD 7 to post-natal day (PND) 20. One pup/sex/litter (if possible) were assigned to 4 groups to have a total of 20 pups selected per sex per group (REACH).

The following observations were conducted:

- Group A - Neurohistopathological and morphometric evaluation of brain and brain weights (PND 21-22)
- Group B - Behavioural ontogeny (righting reflex; beginning on PND 2); locomotor activity (PND 13, 17, 25±2, and 60±2); neurohistopathological evaluation of central

nervous system and peripheral nervous system, morphometric evaluation of brain and brain weights (PND 70-73)
- Group C - Sexual maturation: vaginal patency (from PND 25 onwards) and balanopreputial separation (from PND 35 onwards); acoustic startle (PND 25±2 and 60±2); Biel maze (PND 23-27); brain weights (PND 63-70)
- Group D - Detailed clinical (arena) observations (PND 25±2, 35±2, 45±2 and 60±2); grip strength (20±1, 35±2 and 60±2); Biel maze (PND 65-70); brain weights (PND 74-83)

In pregnant dams treated at 150 mg/kg bw/day, uncoordinated movements and abnormal gait of the hindlegs were observed from treatment week 5. This increased in incidence as treatment progressed and eventually occurring in most animals. Decreased body weight and body weight gain correlated with reduced food consumption was observed in dams at 150 mg/kg bw/day. There were no treatment related effects on body weight or clinical signs of toxicity in dams treated at 15 or 50 mg/kg bw/day. There were no effects on live birth index or pup viability at any dose.

At 150 mg/kg/day, mean pup body weights were lower throughout the pre-weaning and post-weaning period, although mean body weight gain was higher in the post weaning period. There were no effects on sexual maturation.

At 150 mg/kg/day, startle response measurements showed a statistically significantly lower mean average and maximum response amplitude for males and females on PND 25. This remained low at PND 60 but was not statistically significant indicating only partial recovery during the study period. At 50 mg/kg/day, mean maximum response amplitude of females appeared slightly lower for all measurement blocks on PND 25. This effect had reversed by PND 60.

At 150 mg/kg/day, a lower mean forelimb grip strength was recorded on PND 20 and 35 for both sexes (0.55x and 0.73x of control for males and females, respectively on PND 20 and 0.82x and 0.88x of control for males and females, respectively on PND 35). Males at 150 mg/kg/day additionally showed a lower mean hindlimb grip strength on PND 20 and 35 (0.76x and 0.90x of control, respectively). On PND 60, only mean hindlimb grip strength of males at 150 mg/kg/day appeared marginally lower (0.90x of control), while the effect on forelimb grip strength had recovered. Time to acquire righting reflex, hearing and pupillary reflex, rectal temperature, motor activity and learning and memory were considered not affected by treatment. There were no histopathological findings in the peripheral and central nervous system.

Overall there were no treatment related effects on development. Neurotoxic effects observed in pups are similar to those commonly observed for the chemical and not a specific neurodevelopmental effect. There were no effects on other neurodevelopmental parameters.

Neurotoxicity

Based on single dose and repeated dose toxicity studies in animals for the chemical, the chemical is determined to have neurotoxic potential, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section).

Neurotoxic effects have been observed in animals following single and repeated dose toxicity studies. Effects included degeneration of sciatic nerve fibres, neurocyte necrosis in cerebellum, decreased grip strength decreased muscle tone reduced rotarod performance, peripheral neuropathy and histopathological changes of the peripheral nervous system.

Reversible effects on grip strength were observed in a repeated dose dermal toxicity study. No effects have been observed following inhalation exposure (see **Acute toxicity and Repeated dose toxicity** for details).

The structurally related chemical acrylamide is a well-established neurotoxic chemical. Similar effects for grip strength and histopathological observations related to neurotoxicity are observed for both chemicals. However, effects for acrylamide are observed at much lower doses than methacrylamide in both acute and repeated dose toxicity (OECD 2002).

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