Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

# 2-Propenamide, *N,N*-dimethyl- (Dimethylacrylamide)

## Evaluation statement

**30 June 2022**

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# AICIS evaluation statement

## Subject of the evaluation

2-Propenamide, *N,N*-dimethyl- (Dimethylacrylamide)

## Chemical in this evaluation

| Name | CAS registry number |
|---|---|
| 2-Propenamide, *N,N*-dimethyl- | 2680-03-7 |

## Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to human health.

## 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 introduction, use and 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. The chemical is used internationally in a wide range of site limited applications, including in the manufacture of adhesive and sealant products, water treatment products and inks and toners. Domestic use in adhesives has also been identified, although this is not considered to be widespread.

While the chemical is listed in the International Nomenclature Cosmetic Ingredient (INCI) dictionary, with a reported function of use as a surface modifier, limited evidence of use in cosmetic products has been identified for the chemical. The chemical may be present as an impurity in polymers used in cosmetic products (concentrations up to 600 ppm).

### Human health

#### Summary of health hazards

Based on the available toxicological information for the chemical the critical health effects for risk characterisation include:

- systemic acute effects from oral and dermal exposure
- local effects (eye irritation).

Although very limited, there is some evidence to suggest the chemical can cause skin sensitisation following prolonged dermal exposure.

The chemical has moderate to high acute oral and dermal toxicity. The median lethal dose (LD50) for oral exposure was determined as 315.8 mg/kg bw. No guideline studies were available for acute dermal toxicity. However, mortalities were observed in skin irritation studies and a repeat dose toxicity study following exposure to 500 and 1000 mg/kg bw. For inhalation exposure, the median lethal concentration (LC50) was considered to be >776 ppm (highest achievable vapour concentration). Clinical signs following oral exposure include hunching posture, depression, and ataxia or ptosis.

The chemical is not considered to be a skin irritant. Although a repeat dose toxicity study found haematological changes associated with minimal irritation, a non-guideline study performed in rabbits did not find increased skin irritation following exposure to *N,N*-dimethylacrylamide for 24 hours.

The chemical has potential to cause serious eye damage. In an eye irritation study performed in rabbits, ocular exposure to the chemical caused increased corneal opacity, redness, chemosis and iritis. Reversibility of effects was not investigated. Ex vivo studies show that the chemical reduces tissue viability. An in vitro study on isolated bovine cornea found the chemical to be a severe irritant to the eye. An in vitro eye corrosion study using reconstructed human cornea like epithelium found that the chemical is predicted to meet the criteria for serious eye damage or irritation.

Based on the available data, the chemical is not expected to be sensitising to skin. Two guinea pig maximisation tests found little evidence of skin sensitisation potential of the chemical. Observations in humans have shown that continuous, prolonged dermal exposure to *N,N*-dimethylacrylamide from glucose sensor patches in diabetics can elicit allergic contact dermatitis. However, data are limited and equivocal.

Repeat dose toxicity information is limited. In repeated dose toxicity studies in rats, reductions in food consumption and bodyweights were observed. Based on a reproductive/developmental toxicity study, a no observed adverse effect level (NOAEL) of 5 mg/kg bw/day was determined for oral repeated exposure. Signs of systemic toxicity were observed at higher doses, such as poor general condition, closed eyelids, piloerection and reduced attention. The NOAEL for dermal repeated exposure was 10 mg/kg bw/day based on adverse effects such as minimal nephropathy and minimal dilatation of the renal pelvis. Based on limited data from in vivo studies, there is no evidence of neurotoxicity following exposure to the chemical.

The chemical is not considered to have genotoxic potential. Although positive results were reported in some in vitro mutagenicity assays, the chemical was reported to have negative results in an in vivo mammalian erythrocyte micronucleus test.

Based on the available data, exposure to the chemical is not expected to cause specific adverse effects on fertility/sexual function and development.

## 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) for hazard classes relevant for

work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

| 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 |
| Serious eye damage/eye irritation | Eye Damage 1 | H318: Causes serious eye damage |

### 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 adhesive products. However, this use is not expected to be widespread. In addition, exposure to DIY products is incidental and normal precautions to avoid prolonged contact are expected. The public may be exposed to the chemical at low concentrations as an impurity in cosmetics. Although the public could come into contact with articles 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. Therefore, there are no identified risks to the public that require management.

**Workers**

During product formulation and manufacture, dermal, ocular and inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, cleaning and maintenance of 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 may 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 effects and systemic health effects following acute exposure, the chemical could pose a risk to workers. Control measures to minimise dermal and ocular effects are needed to manage the risk to workers (see **Proposed means for managing risk** 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 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
- 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 the 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.

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

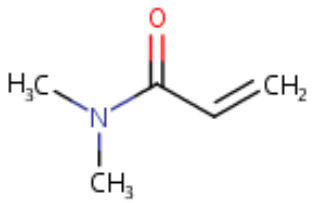
The conclusions of this evaluation are based on the information described in this statement.

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-Propenamide, *N,N*-dimethyl- |
| CAS No | 2680-03-7 |
| Synonyms | Dimethylacrylamide (INCI)<br>*N,N'*-dimethylacrylamide<br>*N,N*-dimethylprop-2-enamide<br>*N,N*-dimethylpropenamide<br>DMAA |
| Structural formula |  |
| Molecular formula | C5H9NO |
| Molecular weight (g/mol) | 99.13 |
| SMILES | CN(C)C(=O)C=C |
| Chemical description | - |

## Relevant physical and chemical properties

| | |
|---|---|
| Physical form | Colourless to pale yellow liquid |
| Melting point | 100 °C |
| Boiling point | 89–91 °C |
| Vapour pressure | 0.065 kPa at 20 °C |
| Water solubility | 1,000 g/L at 20 °C |
| log $K_{ow}$ | -0.3 at 23 °C and pH 6 |

# Introduction and use

## Australia

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

## International

The following international uses have been identified through the:

- European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers
- Galleria Chemica (Chemwatch)
- Substances in preparations in Nordic countries (SPIN) database
- European Commission Cosmetic Substances and Ingredients (CosIng) database
- United States (US) Personal Care Products Council International Nomenclature Cosmetic Ingredients (INCI) directory
- the US Chemical Data Reporting under the Toxic Substances Control Act 2012/2016
- Other data sources via eChemPortal including the US Environmental Protection Agency (EPA), Canada Domestic Substances List (DSL), and Aggregated Computational Toxicology Resource (ACToR).

Based on the available information the chemical has site limited use as an intermediate in the manufacture of:

- polymers
- bulk and fine chemicals
- adhesives and binding agents
- products such as pH regulators, flocculants, precipitants and neutralisation agents
- water treatment products
- inks and toners.

Some of these commercial uses may also be used in domestic applications. There were no identified products containing the chemicals in North American consumer product databases (DeLima Associates). Consumer uses in adhesives were reported under the US Chemical Data Reporting (CDR) under the Toxic Substances Control Act (US EPA 2016) and the 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. No consumer uses are registered under REACH.

The chemical is listed in the INCI Dictionary, with a reported function of use as a surface modifier (Personal Care Products Council). The chemical was also reported to be used in personal care products under the US Chemical Data Reporting (CDR) under the Toxic Substances Control Act (US EPA 2016) However this appears to be related to polymers manufactured from the chemical. The chemical was not identified as being used in cosmetic products in the United States of America or in the EWG Skin Deep database (DeLima Associates; EWG; Personal Care Products Council).

It is noted that polymers manufactured from the chemical have reported use in cosmetics, with various functions (Personal Care Products Council). Levels of acrylamide were reported

to be < 600 ppm in acrylamide polymers which is considered representative of levels likely for the chemical (CIR, 2005).

# 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 not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (SWA).

# International regulatory status

## Exposure standards

The following Protective Action Criteria (PAC) (formerly known as Temporary Emergency Exposure Limits (TEELs)) are available for the chemical (Chemwatch; US DOE 2018):

- PAC-1 = 0.15 mg/m3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, these effects are not disabling, are transient and reversible upon cessation of exposure.' (US DOE 2018).
- PAC-2 = 1.7 mg/m3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience irreversible or other serious, long-lasting, adverse health effects or an impaired ability to escape.' (US DOE 2018).
- PAC-3 = 50 mg/m3, concentration of the chemical 'above which it is predicted that the general population, including susceptible individuals, when exposed for more than one hour, could experience life-threatening adverse health effects or death.' (US DOE 2018)

As stated by the US DOE, these values are intended for use until Acute Exposure Guideline Levels (AEGLs) or Emergency Response Planning Guidelines (ERPGs) are adopted for chemicals.

# Health hazard information

## Toxicokinetics

Limited toxicokinetic data are available for the chemical.

The chemical 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 oral and dermal exposure. As the log $K_{ow}$ value of *N,N*-dimethylacrylamide is below 3, the chemical is unlikely to bioaccumulate with intermittent workplace exposure patterns. Continuous exposures; however, may result in accumulation. In the dermal repeated dose toxicity study (see **Repeat Dose Toxicity: Dermal**), reported renal toxicity suggests some level of distribution of the chemical and/or its metabolites to the kidneys (REACH).

The low molecular weight and water solubility of the chemical are likely to favour urinary excretion.

The chemical *N,N*-dimethylacrylamide was shown to be metabolised in vitro by mouse hepatic microsomal enzymes in a NADPH-generating system as well as by hepatic glutathione S-transferases. Following incubation with hepatic microsomes *N,N*-dimethylacrylamide was metabolised to *N*-methylacrylamide (REACH).

## Acute toxicity

### Oral

Based on the available data, the chemical has moderate acute oral toxicity. Hazard classification is warranted.

In a non-GLP compliant acute oral toxicity study similar to OECD TG 401, Sprague Dawley (SD) rats of both sexes (5 animals/sex/dose) were treated with a single dose of the chemical at 46.4, 100.0, 215.0 or 464.0 mg/kg bw. The LD50 was recorded as 315.8 mg/kg bw. Reported sublethal signs of toxicity included slight depressed activity at 4 hours following administration in the animals that received the chemical at 46.4, 100.0 or 215.0 mg/kg bw. In the animals that received the highest dose, slightly depressed activity was observed in all animals immediately after administration. Hunching, depressed activity and ataxia or ptosis was observed at one hour, followed by mortalities at 24 hours in all animals that received the highest dose. No mortality occurred in the other dose groups. No observable gross pathology was noted at death or termination (REACH).

In a non-guideline study with male SD rats, the LD50 was determined to be 0.365 mL/kg bw (specific gravity=0.96). Few experimental details are available. Hyperirritability was reported prior to death, along with cutaneous vasodilatation of ears, tail and feet. Pathological findings following necropsy included hyperaemia of the lungs, blood around the mouth and nose and petechial haemorrhages (NTRL 1970).

An LD50 value of 460 mg/kg bw in mice was reported (no study details available) (CCOHS).

### Dermal

Based on the limited available data, the chemical has moderate to high acute dermal toxicity. Hazard classification is warranted.

In a 90 day dermal toxicity study comparable to OECD TG 411 (see **Repeat Dose Toxicity: Dermal**), SD rats of both sexes (10/sex/dose) were administered *N,N*-dimethylacrylamide by dermal application at 10, 200 and 500 mg/kg bw/day; 6h/day (dermal); 7 days/week. At the highest dose, mortality occurred in 2/20 female rats within the first week of dosing. On the basis of this study the dermal LD50 can be assumed to be >500 mg/kg bw (REACH).

An LD50 value of 540 µL/kg bw in rabbits was reported (no study details available) (CCOHS).

In a skin irritation/corrosion study similar to OECD TG 404, 6/6 rabbits (strain not specified) exposed to 1 mL of the chemical for 24 hours deceased within 72 hours of treatment (REACH). Limited study details are available.

In a non-guideline irritation study in male albino rabbits, 0.5 mL of the chemical at a concentration of greater than 98.5% was applied to the skin of 6 animals for a 24 hour period. Within 24 hours after treatment 3 of the 6 rabbits were deceased (NTRL 1970).

### Inhalation

Based on the available data, the chemical is not acutely toxic at the highest achievable vapour concentration.

In an acute inhalation toxicity study, SD rats (5/sex) were exposed to the chemical at 776 ppm (highest achievable vapour concentration at 35 ºC) via nose only inhalation for one hour. No mortality occurred. Reported signs of toxicity included fur coated with faeces/urine at one hour after exposure. No other signs of toxicity were observed for the remainder of the study. The only pathological sign reported to be observed at necropsy was red lungs in 3 out of 5 females. Based on this study, the LC50 was considered to be >776 ppm (3.1 mg/L) (REACH).

## Corrosion/Irritation

### Skin irritation

Based on the available data, the chemical is not considered to be a skin irritant.

In a non-GLP compliant skin irritation study similar to OECD TG 404, 6 rabbits (strain and sex not specified) were treated with the chemical for 24 hours under occlusive conditions. Observations were recorded at 24 and 72 hours after patch removal. The following mean scores were reported for observations at 24 and 72 hours: 0 for erythema and 0 for oedema respectively (maximum score of 4). Based on this study, the chemical was not considered to be a skin irritant (REACH).

### Eye irritation

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

The chemical is reported to cause moderate to severe eye irritation. Hazard classification is warranted (see **Recommendations** section).

In an eye irritation study similar to OECD TG 405, the chemical was instilled into one eye each of 6 rabbits. The eyes were observed at 24, 48 and 72 hours. The following mean scores were reported: corneal opacity 1/4, iritis 0.17/2, conjunctival redness 1.2/3, chemosis 2.4/4. Apart from the iritis, the observed effects were not reversible in all animals within 3 days. Iritis was observed in 1/6 animals and was fully reversible within 3 days. The full reversibility of effects over 21 days was not investigated (REACH).

In a GLP compliant ex vivo eye corrosivity/irritation study conducted according to OECD TG 437, the chemical was applied to 3 bovine corneas, per experiment. The mean in

vitro irritancy score (IVIS) was 59.1 (IVIS >55 is regarded as serious eye damage and IVIS ≤3 is UN GHS No Category). Based on the criteria of the assay, the chemical was considered to be corrosive or a severe irritant to the eye (REACH).

In a GLP compliant in vitro eye corrosion study conducted according to OECD TG 492, the chemical was topically applied to reconstructed human cornea like epithelium (RhCE) using the EpiOcular™EIT test method for the liquids protocol. Tissue viability was measured following exposure and a post-treatment incubation period. Tissue viability was determined to be 5%. Based on the decision criteria for this test (tissue viability >60% for EpiOcular™ EIT and SkinEthic™ HCE EIT liquids protocol), the chemical is predicted to meet the criteria for serious eye damage or eye irritation (REACH).

## Sensitisation

### Skin sensitisation

Based on the available data from guinea pig maximisation tests (GPMT), 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 non-GLP compliant in vivo skin sensitisation study similar to OECD TG 406 (GPMT), 10 female Hartley guinea pigs were treated with the chemical intradermally (5% w/w concentration, day 0) at induction phase. This was followed one week later by topical induction at 25%. The animals were then topically challenged with the chemical at 25% w/w for 24 hours. Very faint erythema was observed in the skin treated with 25% w/w concentration in 5 of the challenged animals 24 hours after the challenge. The very faint erythema was reported to have persisted at 48 hours in 2 of the 10 challenged animals (REACH).

In a non-GLP compliant in vivo skin sensitisation study similar to OECD TG 406 (GPMT), 10 female Hartley guinea pigs were treated with the chemical intradermally (5% w/w concentration, day 0) at induction phase. This was followed by topical induction at 100%. The animals were then topically challenged with the chemical at 100% w/w for 24 hours. No animals were reported to have positive reactions after challenge at either the first (24 hours after challenge) or second (48 hours after challenge) time reading (REACH).

### Observation in humans

A case study was undertaken in 7 diabetic subjects who had developed skin reactions to a particular brand of glucose sensor (temporary sensor adhered to the skin which continuously monitors glucose levels). The subjects were all found to be allergic to *N,N*-dimethylacrylamide, which was present in the adhesive in the sensor patch (Mowitz et al. 2018). A larger follow up study confirmed that *N,N*-dimethylacrylamide can contribute to the development of allergic contact dermatitis in a subset of users of glucose sensor devices (Ulriksdotter et al. 2020). These findings suggest that prolonged, continuous exposure to the chemical may elicit a sensitisation response in people with diabetes. These studies did not include control subjects; therefore, the findings are equivocal.

## Repeat dose toxicity

### Oral

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure. In the absence of more comprehensive information, hazard classification is not warranted.

In a GLP compliant study conducted in accordance with OECD TG 421, Wistar rats of both sexes (10/sex/dose) were administered *N,N*-dimethylacrylamide by oral gavage at 0, 5, 15 or 45 (first week) or 30 (from day 7) mg/kg bw/day, daily. Males were exposed for 29 days, females for 50 days. No treatment related mortality occurred during this study. Animals in the highest dose group were reported to show poor general condition, closed eyelids, piloerection and reduced attention. These effects were considered to be treatment related and the dose was reduced after one week. Significant body weight gain was also observed in males and females in the highest dose group, and in males in the 15 mg/kg bw/day group. Based on these effects, the NOAEL was considered to be 5 mg/kg bw/day (actual dose received). This effect level was based on treatment related signs of systemic toxicity at the higher doses tested (15 mg/kg bw/day (reduced body weight)) and 45/30 mg/kg bw/day (reduced body weight and clinical signs) (REACH).

### Dermal

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated dermal exposure. In the absence of more comprehensive information, hazard classification is not warranted.

In a GLP compliant 90 day study conducted in accordance with OECD TG 411, SD rats of both sexes (10/sex/dose) were administered *N,N*-dimethylacrylamide by dermal application at 10, 200 or 500 mg/kg bw/day; 6h/day (dermal); 7 days/week. As the highest dose resulted in overt systemic toxicity including 2 deaths, after 6 days of treatment the middle and highest dose levels were reduced to 75 and 250 mg/kg bw/day, respectively. The NOAEL was determined to be 10 mg/kg bw/day for the chemical, based on adverse effects such as minimal nephropathy observed in males at all doses and minimal dilatation of the renal pelvis in high dose and mid dose males. Treatment related alterations in haematology, clinical chemistry and urology parameters were seen. There was no evidence of neurotoxicity related to treatment with the chemical (REACH).

## Genotoxicity

Based on the available data, the chemical is not considered to be genotoxic.

Although positive results were reported in some in vitro assays, in vivo data for the chemical were negative.

### In vitro

Mixed results were reported in the following in vitro genotoxicity studies (REACH):

- Negative results were reported in a bacterial reverse mutation assay (OECD TG 471) in Salmonella typhimurium TA1535, TA1537, TA98 and TA100 and Escherichia coli WP2uvrA both 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 Chinese hamster ovary (CHO) cells both with (at 5020 µg/plate only) and without (at concentrations of 1520 and 2270 µg/plate) metabolic activation.
- Positive results were reported in a mammalian gene mutation assay (OECD TG 476) in the thymidine kinase (TK) locus in mouse lymphoma cells L5178Y mouse lymphoma both with and without metabolic activation at concentrations up to 2000 µg/plate.
- Negative results were reported in a mammalian gene mutation assay (OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (Hprt) locus in CHO cells both with and without metabolic activation at concentrations up to 1000 µg/plate.

### In vivo

In a mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, NMRI mice (6/sex/dose) were treated with a single dose of *N,N*-dimethylacrylamide by gavage at up to 400 mg/kg bw/day. The reported incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, and the chemical was not considered clastogenic (REACH).

## Carcinogenicity

No data are available. Based on differences in genotoxic potential, the classified mutagen and carcinogen acrylamide cannot be considered as a suitable analogue.

## Reproductive and developmental toxicity

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

In a guideline combined reproduction/developmental toxicity screening test conducted in accordance with OECD TG 421, Wistar rats of both sexes (10/sex/dose) were administered the chemical as a solution in drinking water at 5, 15 and 45 mg/kg bw/day. Animals were treated for 14 days in the premating period, throughout gestation and lactation, through to one day before sacrifice, with a total treatment period of 29 days in males and 50 days in females. All animals administered 45 mg/kg bw/day lost weight during the first study week; therefore, the highest dose was reduced from 45 to 30 mg/kg bw/day from study day 7 onwards. The reproductive NOAEL was 30 mg/kg bw/day as this was the highest prolonged treatment dose. No treatment related changes were seen in the testes, epididymides or ovaries. Male and female mating and fertility indices were also unaffected by treatment. Apart from secondary effects on pup weight due to the reduced body weight of the females, no treatment related adverse effects were observed on foetal development or pup viability (REACH).

## Neurotoxicity

Based on the limited data, the chemical is not expected to be neurotoxic.

In a non-guideline study, 5 male ddY mice were administered *N,N*-dimethylacrylamide by gavage twice weekly, at 1.7 mmol/kg for 10 weeks, both with and without metabolic activation. No neurotoxic effects were seen, as determined by rotarod analysis (Hashimoto et al. 1981).

In a non-guideline study, an unspecified number of male Wistar rats was administered 15 mM *N,N*-dimethylacrylamide ad libitum in drinking water for 15, 30 or 45 days. Despite the loss of body weight indicative of systemic toxicity, no clinical signs of neuropathy of the sciatic nerve were observed (Sakamoto and Hashimoto 1985).

Findings from a repeat dose toxicity study in SD rats (see **Repeat Dose Toxicity: Dermal**) included absence of peripheral neuropathy and no histopathological evidence of neurotoxicity in animals treated with *N,N*-dimethylacrylamide.

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