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

Cyclohexanamine, 4,4'-methylenebis-

Evaluation statement

25 September 2023

Draft

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AICIS evaluation statement

Subject of the evaluation

Cyclohexanamine, 4,4'-methylenebis-

Chemical in this evaluation

Name	CAS registry number
Cyclohexanamine, 4,4'-methylenebis-	1761-71-3

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 statement includes a human health risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

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

Based on international use information, the chemical is mainly used in the manufacture of epoxy resins and thermoplastics. The epoxy resins and thermoplastics containing the chemical have several commercial applications including paints, coatings, adhesives, and sealants. Although some of these commercial products may be used in domestic settings, based on available information this is not expected to be widespread. Chemicals manufactured from the chemical may also be used as food contact materials.

Human health

Summary of health hazards

The identified health hazards are mostly based on available data for the chemical. For some of the endpoints, read across data from a close chemical analogue, 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (CAS No. 6864-37-5) were used as supporting evidence. The chemical and the analogue are structurally similar cyclic aliphatic hydrocarbons with a common functional primary amine group. They have similar physio-chemical properties and are expected to produce similar toxicological effects.

Based on the available data, the chemical:

- is not considered to be a skin sensitiser.
- is not considered to have genotoxic or carcinogenic potential.

The chemical is corrosive, causing severe skin burns (dermal necrosis after ≥3 minutes of exposure) and serious eye damage in studies in rabbits.

The chemical caused significant systemic toxicity following chronic oral exposure in two short term studies (22-52 days) in rats. Vacuolar degeneration is the main indicator of organ toxicity. Abnormal vacuolisation was seen in many organs including the stomach, liver, eyes, brain, and skeletal muscle, with the skeletal muscle showing tissue degeneration. These effects are consistent with those seen in various sub-chronic repeat dose studies (up to 90 days) with the close chemical analogue, where vacuolisation followed by tissue degeneration was the main indicator of systemic toxicity. An adjusted lowest observed adverse effect level (LOAEL) for the chemical is estimated to be 20 mg/kg bw/day.

Occupational exposure to some chemicals used in epoxy resin manufacture (including CAS No. 1761-71-3) has been associated with scleroderma-like syndrome (a chronic condition affecting connective tissue in the body including skin).

The chemical may cause some reproductive toxicity following repeated oral exposure but the adverse effects seen are not sufficient to warrant classification. The main indicator of reproductive toxicity was reduced implantation sites. This was consistent with the effects seen with the close chemical analogue. Signs of developmental toxicity included reduced viability index and increased postnatal loss. However, the significance of these effects is uncertain. Read across data from the chemical analogue also show that there is no clear evidence of effects on development.

Based on available data, the chemical has

- moderate acute oral toxicity (LD50 380–1000 mg/kg bw)
- moderate dermal acute toxicity (LD50 1580 mg/kg bw in males)
- likely high acute inhalation toxicity based on read across from structural analogue.

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 (ingestion)	Acute Tox. 4	H302: Harmful if swallowed
Acute toxicity (dermal)	Acute Tox. 4	H312: Harmful in contact with skin
Acute toxicity (inhalation)	Acute Tox. 2	H330: Fatal if inhaled
Skin corrosion	Skin Corr. 1	H314: Causes severe skin burns and eye damage

Health hazards	Hazard category	Hazard statement
Serious damage to eyes/eye irritation	Eye Damage 1	H318: Causes serious eye damage
Specific target organ toxicity (repeated exposure)	STOT Rep. Exp. 2	H371: May cause damage to organs through prolonged or repeated exposure

Summary of health risk

Public

There are no identified risks to the public that require management.

Since Australian use data are not available for the chemical, use patterns in Australia are assumed to be similar to those overseas. Based on the available international use information, it is unlikely that the public will be exposed to the chemical directly. Although the public could come into contact with articles and/or coated surfaces, it is expected that the chemical will be bound within articles and coated surfaces. Based on available data, negligible exposure through identified use in food contact materials is expected.

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical systemic long term, systemic acute and local health effects, exposure to 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 corrosivity classification are expected to be sufficient to protect workers from any potential reproductive toxicity.

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 should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate control under the relevant jurisdictions and 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 to manage risk arising from storing, handling, and using potential hazardous chemicals depend on the physical form and the manner in which chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to 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 safety data sheets (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

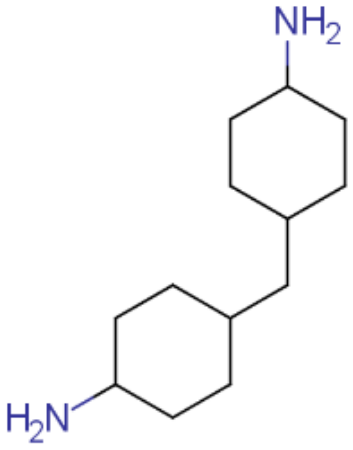
Considering the proposed means of managing risks, the Executive Director proposes to be satisfied that the identified human health risks can be managed within existing risk management frameworks. This is provided that:

- all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory
- 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	Cyclohexanamine, 4,4'-methylenebis-
CAS No.	1761-71-3
Synonyms	bis(4-aminocyclohexyl)methane 4,4'-methylenebis(cyclohexylamine) PACM (p-diamino-dicyclohexyl-methane)
Molecular formula	C13H26N2
Molecular weight (g/mol)	210.36
SMILES	NC1CCC(CC1)CC2CCC(N)CC2
Chemical description	Multi-constituent substance. The chemical has three geometric isomers – trans-trans, cis-cis or cis-trans.
Structural formula	

Relevant physical and chemical properties

The physical properties of the chemical are determined by the geometric isomer ratio.

Physical form	The chemical is a clear liquid when the trans-trans isomer content is approximately 20-25%. It is a yellowish solid

	melt (non-granular material) when the trans-trans isomer is greater than 50%.
Melting point	-17.7 to 15°C (liquid); 33.5 to 45°C (solid)
Boiling point	320 and 329.76°C
Vapour pressure	0.0549 Pa at 20°C (liquid); 0.00018 hPa at 25°C (solid)
Water solubility	12.3 g/L at 20°C
pKa	10.2 and 11.1 at 20°C
log K_{ow}	2.03 at 25°C (liquid)

Introduction and use

Australia

No specific information about the introduction, use and end use of the chemical in Australia has been identified.

International

Most of the identified uses for the chemical are in site limited applications, mainly in the manufacture of epoxy resins and thermoplastics (Chemwatch n.d.; Pubchem n.d.; REACH n.d.; SPIN n.d.; US EPA 2012).

Epoxy resins and thermoplastics manufactured from the chemical have commercial applications in construction materials, paints and varnishes, sealants, fillers and adhesives, and in food packaging. Some of these products may be used in a domestic setting (e.g., in home maintenance) (Pubchem n.d.). However, no consumer uses have been registered for the chemical in the European Union (EU) (REACH n.d.) or the United States of America (USA) (DeLima Associates). The OECD SIDS Initial Assessment Report (OECD 2011) states that there are no consumer uses of the chemical. The chemical is registered for use in the manufacture of food contact materials in the EU and the USA (see **International regulatory status** section).

The chemical is:

- listed on the Organisation for Economic Co-operation and Development (OECD) List of High Production Volume (HPV) Chemicals (OECD 2004)
- the US Environmental Protection Agency (EPA) HPV Program Chemical List (US EPA 2012)-
- registered under REACH with a global range of >1000 tonnes/year (REACH n.d).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

The chemical is not specifically listed in the *Poisons Standard – The Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP). However, the chemical falls under the scope of the following Schedule 5 group entry for 'Amines used as curing agents for epoxy resins' (TGA 2023).

Schedule 5 chemicals are substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label (TGA 2023).

Workers

The chemical is not listed on the HCIS (SWA n.d.).

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

International regulatory status

Exposure standards

The following exposure standards were identified (Chemwatch n.d.) – Maximum Permissible Concentration (MPC) of 2 mg/m^3 (Belarus and Russia).

European Union

The chemical is listed on the 'European Commission Regulation (EU) No. 10/2011 on plastic materials and articles intended to come into contact – Annex I'. The chemical is authorised for use as a food contact material with a specific migration limit of 0.05 mg/kg food (ECHA n.d.).

United States of America

The chemical is listed on the United States Food and Drug Administration (US FDA) Inventory of food contact substances – Threshold of Regulation (TOR) Exemptions (US FDA n.d.). The US FDA sets the following use limitations:

- Methylene-bis-cyclohexamine and sucrose amine polyether polyol as components of polyurethane coatings at maximum use levels of 1.15% and 3.75% by weight, respectively. The polyurethane coatings would be limited to repeat-use applications involving dry food at room temperature (120°F or below).

Human exposure

Public

Direct public exposure to the chemical is not expected. Public exposure is most likely to be minimal, resulting from the use of products containing the chemical in a converted or bound state. Similar to the structurally related chemical, 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (CAS No. 6864-37-5) public exposure is considered unlikely due to:

- the difficulty of diffusion in a cross-linked system
- the low vapour pressure of the chemical.

Results of migration investigations for 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (CAS No. 6864-37-5) indicated no evidence of migration from different food contact materials (AICIS 2022).

Health hazard information

Toxicokinetics

No toxicokinetic studies are available. Based on its physio-chemical properties (low molecular weight, moderate water solubility and partition co-efficient (log Kow 2.03) and corrosive nature, the chemical is expected to be well absorbed through oral, inhalation and dermal routes (OECD 2011; REACH n.d.). Adverse effects seen in acute and chronic toxicity studies indicate systemic distribution following absorption. Being a primary amine, the chemical is expected to be metabolised predominantly through oxidation, conjugation and other enzymatic reactions leading to detoxification and excretion in urine or faeces (OECD 2011; REACH n.d.). As a result, the chemical is expected to have a low bioaccumulation potential (REACH n.d.).

Acute toxicity

Oral

Based on the available data, the chemical has moderate acute oral toxicity. Reported median lethal dose (LD50) values were in the range 380-1000 mg/kg bw warranting hazard classification.

An oral median lethal dose (LD50) of 380 mg/kg bw was determined in Sprague Dawley (SD) rats in a GLP-compliant study. The study was conducted similarly to the US EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS) test guideline (TG) 81-1 (similar to OECD TG 401) with acceptable deviations (OECD 2011; REACH n.d.). The animals were administered the chemical by oral gavage at doses ranging from 100 to 1000 mg/kg bw (no controls were used). Most animal deaths in both sexes occurred on day 1. Reported clinical signs included ruffled appearance in all dose groups, and in the higher dose groups piloerection, genital staining, convulsions, stained body, dark nasal staining, muzzle staining and/or lethargy. Treatment related macroscopic findings were seen only in the non-surviving animals and these included signs of irritated stomach, dark liquid in the stomach and lower gastrointestinal tract, pale lungs and kidneys, pale liver, and haemorrhagic lungs.

An oral LD50 of 625 mg/kg bw was determined in SD rats in another acute oral toxicity study conducted similarly to OECD TG 401 with acceptable deviations (REACH n.d.). The oral gavage doses tested in the study were 398, 501, 631 and 794 mg/kg bw. Reported clinical signs included weakness, shortness of breath, tremors, salivation, severe diarrhoea, and collapse. Macroscopic findings included inflammation of the gastric mucosa and liver, renal and pulmonary hyperaemia (increased blood flow).

Other non-guideline studies included LD50 values ranging from 670 to 1000 mg/kg bw in rats and 500 mg/kg bw in mice (REACH n.d.).

Dermal

Based on the available data, the chemical has moderate acute dermal toxicity. Acute toxicity seen in males at 1580 mg/kg bw warrants hazard classification.

A dermal LD50 of 2110 mg/kg bw with confidence limits from 1380 to 3220 mg/kg bw was determined in New Zealand White (NZW) rabbits in an acute dermal toxicity study conducted according to US EPA OPPTS 81-2 (similar to OECD TG 402). At 1580 mg/kg bw 3 out 5 male animals died but no mortality was observed in the female rabbits. Reported clinical signs seen only in males included loss of body weight and signs of necrosis (OECD 2011).

In another acute dermal toxicity study conducted according to US EPA OPPTS 81-2 (similar to OECD 402), no mortality was observed in NZW rabbits (5 per sex) tested with a single dose of 1000 mg/kg bw (OECD 2011).

The structurally related chemical, 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (CAS No. 6864-37-5) is toxic in contact with skin (LD50 of 200–400 mg/kg bw) (AICIS 2023).

Inhalation

Based on read across data from structural analogue, the chemical is expected to have high acute inhalation toxicity warranting hazard classification.

Based on available data for 2,2’-dimethyl-4,4’-methylenebis(cyclohexylamine) (CAS No. 6864-37-5) (median lethal concentration (LC50) (inhalation, aerosol) of 0.42 mg/L) (AICIS 2023) the chemical is likely to have acute inhalation toxicity.

Corrosion/Irritation

Skin irritation

Based on the available data, the chemical is considered to be corrosive to skin. Corrosive effects were observed following a 3 minute exposure, however these were observed at the 24 hour and not at the 1hour observation period. The study did not investigate effects following 1 hour exposure. Overall hazard classification is warranted but data are not sufficient for sub-categorisation.

The chemical was found to be corrosive in a GLP-compliant skin irritation study conducted similarly to OECD TG 404 in NZW rabbits (REACH n.d.). The animals were treated with the undiluted chemical under semi-occlusive conditions for 3 minutes (n=3) and 2.75 hours (n=3). Observations were recorded at 1, 24, 48 and 72 hours in the 3 minute exposure group, and at 1 hour in the 2.75 hour exposure group. The severity of adverse effects seen warranted the early termination of 4 hour exposure period (to 2.75 hours) and the early termination of the

study. The following adverse effects were seen in the 3 minute exposure group at the treated sites:

- At the 1 hour observation period – very slight to well defined erythema and bleeding (haemorrhage of dermal capillaries) was seen in all animals and persisted at the 24hour observation period in 2 of the animals. Very slight oedema was seen in all animals and developed to moderate to severe oedema at the other observations.
- At the 24 hour observation period – green/brown coloured areas of possible dermal necrosis indicative of dermal corrosion were seen in one animal, which persisted at the 48 hour observation period. A hardened dark brown/black coloured scab, surrounded by well-defined erythema and with light brown discolouration of the epidermis was seen in the other two animals.
- An accurate evaluation of erythema and oedema was not possible at the 48 and 72hour observation periods due to the severity of the dermal reactions.

In the 2.75 hour exposure group, severe dermal necrosis, bleeding, and loss of skin elasticity were seen at the treated sites in all animals. These reactions extended beyond the treatment site in 2 animals.

A few other non-guideline studies reported evidence of corrosive effects in rabbits and slight irritation in guinea pigs when exposed to the chemical. (REACH n.d.).

Eye irritation

Corrosive chemicals are also considered to cause irreversible effects in the eyes.

The chemical produced severe irreversible eye damage in NZW rabbit in an eye irritation study (using Haskell Laboratories protocol) (OECD 2011; REACH n.d.).

A preliminary study tested the irritation potential of the chemical as a solid (10mg) and as a 10 % solution in propylene glycol (1 animal each). Results indicated that 10 mg of the test item, caused severe and extensive damage to the cornea, iris, and conjunctivae in unwashed eyes.

In the main study, 0.1 mL and 0.01 mL of the chemical as a liquid (due to isomeric composition) were instilled into one eye of each animal (n=2-3/dose/wash procedure), leaving the other eye untreated. The treated eye was subjected to 1 of the 4 wash procedures with tap water (no wash; wash for 1 min, 20 seconds after dosing; wash for 1 min, 2 minutes after dosing; and wash for 15 min as soon as possible after dosing). Observations were made after 1, 4, 24, 48 and 72 hours, and weekly up to 60 days. Results showed that the chemical (0.1 mL) produced severe and extensive damage to the cornea, iris, and conjunctivae in the unwashed eyes. The animals were sacrificed two days after treatment. The chemical dosed at 0.01 mL ($1/10^{th}$ of the standard dose) produced severe irritation in most animals with permanent ocular damage and/or corneal vascularisation seen in 2 of 3 animals where the eye was not washed.

Severe irreversible eye damage was also reported in NZW rabbit in another eye irritation study (non-GLP) in which the chemical undiluted (0.1 mL) was applied to the eye for an exposure period of 2 seconds prior to rinsing (REACH n.d.).

Sensitisation

Skin sensitisation

Limited data are available. Although there was some evidence of positive reactions in non-guideline studies, the significance of these findings cannot be evaluated. Based on the available in vitro, in silico data and data from structurally related chemicals the chemical is not considered to be a skin sensitiser.

In vivo

The chemical was found to be a weak sensitiser in guinea pigs in a Buehler test conducted similarly to OECD TG 406 with acceptable deviations (REACH n.d.). The study deviated from the TG in using a high lipid diluent to maximise skin absorption, and in the number of applications performed during the induction phase. Guinea pigs (n=10) were induced with the chemical (induction dose unknown) in solution with 1:1 v/v acetone/dioxane and 13% guinea pig fat, dermally applied to abraded skin 9 times over 3 weeks. Following a 2 week rest period, the animals were challenged with 2% chemical in the same diluent used during the induction phase and was dermally applied to intact and abraded skin (n=5/skin type). Positive reactions were seen in 7 out of 10 animals. Although no data were available to determine the observation points following challenge, the study results noted that 1 of the 7 animals showed consistently positive reactions, while the reactions in the other 6 were transitory. There were no negative or positive control group animals in this study.

In another non-guideline study, the chemical produced some reactions in guinea pigs (REACH n.d.). Hartley guinea pigs (n=10) were treated with a single application of a paste containing 25% chemical in hydrophilic ointment. The animals (n=5/group) were then treated over a 3week period with either 9 dermal applications of the same, or 4 intradermal injections of 5% chemical in methanol/ethylene glycol solution. Following a 2 week rest period, the animals were challenged with intradermal or dermal application of 2% or 10% chemical to both intact and abraded skin (n=5/challenge type/dose). Maximum number responses (5/5 animals) ranging from mild to severe were seen in animals challenged intradermally with the chemical at 10%. Responses with the other dose/challenge combinations varied from slight to moderate in up to 3 animals out of 5. Severe inflammatory response was seen in one animal which was induced intradermally and challenged with dermal application of either 2% or 10%. There were no negative or positive control group animals in this study.

In vitro

The chemical did not show keratinocyte activating potential in an in vitro sensitisation ARE-Nrf2 Luciferase Test Method conducted similarly to OECD TG 442D (REACH n.d.). The chemical did not induce a significant luciferase activity as fold induction remained < 1.5. This indicates that the chemical result is negative for the second key event in the adverse outcome pathway for skin sensitisation.

In silico

The chemical has no structural alerts for skin sensitisation using the OECD Quantitative Structure-Activity Relationship (QSAR) Application Toolbox (OECD 2023) and the expert rule-based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (Lhasa Limited n.d.). The chemical was predicted to be a non-sensitiser using OASIS-TIMES (optimized approach based on structural indices set–tissue metabolism simulator) (OASIS LMC n.d). The prediction was out of domain but with 87% correct fragments.

Based on read across approach of C10-C13 primary amines (primary amines containing 10 to 13 carbon atoms), OECD concluded a lack of skin sensitisation potential for the chemical (OECD 2011). The close structural analogue, CAS No. 6864-37-5 is not a skin sensitiser based on negative results reported in guinea pigs (AICIS 2023).

Observation in humans

There was no evidence of positive sensitisation results at the concentrations tested in the following human patch test studies (OECD 2011):

- 87 metal workers with suspected contact dermatitis from epoxy resin (24 or 48 hour patch test with 0.25% of the chemical in petrolatum).
- 5 Swedish workers who had developed skin lesions after working with an isocyanate lacquer (48 hour patch test with 0.1% of the chemical in petrolatum).
- 5 occupationally exposed workers who had previously tested positive in a patch test to an amine hardener catalyst (patch test with 0.5% of the chemical in petrolatum).

Repeat dose toxicity

Oral

Based on the available data, the chemical is expected to cause significant systemic toxicity following chronic oral exposure. Vacuolar degeneration is the main indicator of organ toxicity. Abnormal vacuolisation was seen in many organs including the stomach, liver, eyes, brain, and skeletal muscle, with the skeletal muscle showing tissue degeneration, in two short term studies (22-52 days). These effects are consistent with those seen in various sub-chronic repeat dose studies (up to 90 days) with a close chemical analogue, CAS No. 6864-37-5, where vacuolisation followed by tissue degeneration was the main indicator of systemic toxicity (AICIS 2023).

In a combined repeat dose toxicity and reproductive toxicity/developmental toxicity screening test (OECD TG 422, GLP-compliant), a No Observed Adverse Effect Level (NOAEL) of 15 mg/kg bw/day was determined for systemic toxicity in rats (OECD 2011; REACH n.d.). Wistar Han rats (n=10/sex/dose) were administered the chemical via oral gavage at 0, 15, 50 and 100 mg/kg bw/day, once daily for 7 days per week. Males were dosed from 3 weeks prior to mating, during mating, and up to termination (36 days). Females were dosed from 3 weeks prior to mating, during mating, post-coitum, and at least 4 days of lactation (48-52 days). Animals in the highest group were dosed at 150 mg/kg bw/day initially for the first 11 days but the dose was lowered to 100 mg/kg bw/day due to treatment related toxicity. Animal deaths were seen in the highest dose group (1 female at day 5 and 1 female at day 21). Toxicologically relevant adverse effects were seen from 50 mg/kg bw in both sexes. These effects included:

- Clinical signs: Hunched posture, yellow faeces, piloerection, lean appearance, lethargy, drooping eyes, excessive production of coloured tears and clicking rattling sounds in lungs (rales).
- Biochemistry parameters: Increased aspartate aminotransferase (ASAT) and reduced creatinine levels, along with increased relative weights of kidney and liver, corresponding to histopathological signs seen in these organs.
- Histopathology: Treatment related effects were seen in various organs including stomach (vacuolisation of stomach muscles), liver (centrilobular vacuolisation), skeletal muscle (vacuolar myofiber degeneration and myofiber degeneration), and the

eyes (vacuolisation in the iris). Vacuolisation of choroid plexus in the brain was seen at 100 mg/kg bw/day.

Based on these effects, the study concluded a parental NOAEL of 15 mg/kg bw/day. Applying an adjustment factor of 2.5 (based on the duration of exposure for males), an equivalent NOAEL of 6 mg/kg bw/day is derived for a 90-day exposure. The equivalent 90 day lowest observed adverse effect level (LOAEL) is 20 mg/kg bw/day.

In a non-guideline study two separate experiments were conducted. In the first, male Fischer rats (n=10/dose) were administered the chemical via oral gavage at 0, 25, 37.5, 50, 75 mg/kg bw/day 20-22 times in 4 weeks. In the second experiment male Fischer rats (n=5/dose) were administered the chemical via oral gavage, 8 times in 10 days (group A) or 17 times in 24 days (group B). Dose levels in the experimental groups were 50, 75 and 100 mg/kg bw/day for group A and 50 and 75 mg/kg bw/day for group B, respectively (no controls were used). In the second experiment electron microscopy was used to examine tissue. Vacuolar degeneration was seen in the liver, choroid plexus in the brain, eye, and skeletal muscle. Electron microscopy revealed myofibril disruption, dilatation of the sarcoplasmic reticulum or mitochondria and the presence of inclusion bodies of a lamellar structure. The doses at which these changes were seen were not reported but in the absence of any changes seen at 37.5 mg/kg bw/day, this dose was reported to be the NOAEL for the study (REACH n.d.).

Dermal

No data are available. Based on data from repeat dose oral toxicity studies and the high rate of dermal absorption, the chemical is expected to cause some systemic toxicity following chronic dermal exposure.

Inhalation

No data are available. Based on data from repeat dose oral toxicity studies and the high rate of absorption following inhalation, the chemical is expected to cause some systemic toxicity following chronic inhalation exposure. Mild liver toxicity and disturbed haemoglobin metabolism were the main signs of systemic toxicity observed in a 90 day inhalation study with the structurally related chemical, 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (CAS No. 6864-37-5) (AICIS 2023).

Observation in humans

Case reports from a Japanese epoxy resin polymerisation plant showed that occupational exposure to some of the chemicals in the plant (including CAS No. 1761-71-3) was associated with scleroderma-like syndrome (a chronic condition affecting connective tissue in the body including skin) (REACH n.d.).

Genotoxicity

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

In vitro

The chemical was not genotoxic in any of the available in vitro studies (OECD 2011; REACH n.d.), as detailed below:

- Bacterial reverse mutation assay (Ames test) (OECD 471): The chemical was reported to not induce mutations in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 or TA100 at concentrations up to 5000 µg/plate, with or without metabolic activation in various Ames tests.
- Mammalian cell gene mutation study (OECD TG 476): The chemical was reported to not induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells at concentrations up to 100 µg/mL with or without activation and 0.1 to 2 µg/mL with activation.
- Mammalian chromosomal aberration study (OECD TG 473): The chemical was reported to not induce chromosomal aberrations in Chinese hamster lung fibroblast (V79) cells at concentrations up to 1000 µg/mL with or without metabolic activation.

In vivo

The chemical was not genotoxic in 2 out of 3 available in vivo studies (OECD 2011; REACH n.d.), as detailed below:

- In two separate mammalian erythrocyte micronucleus studies (one conducted similarly to EU Method B. 12 and other to OECD TG 474), NMRI (Naval Medical Research Institute) mice (n=20-22/sex/dose) were given a single intraperitoneal injection of the chemical (dose of 50 mg/kg bw) in dimethyl sulfoxide (DMSO). The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups in either study, indicating a lack of clastogenicity (chromosome damage).
- The OECD SIDS Initial Assessment Report (OECD 2011) states that the chemical tested positive in a third micronucleus assay with methodological limitations. No study details were reported.

In silico

There were no structural alerts for in vitro mutagenicity (Ames test) using DEREK Nexus (Lhasa Limited n.d.). There were no alerts for Ames mutagenicity, chromosomal aberrations and in vivo mutagenicity (micronucleus) profilers in the OECD QSAR Toolbox (OECD 2023) The chemical was predicted to be in vitro Ames negative in OASIS TIMES (OASIS LMC n.d.). The prediction was within the applicability domain of the model.

Carcinogenicity

No data are available. Based on the absence of genotoxicity in vitro and in vivo, and lack of any signs of hyperplastic or pre-neoplastic lesions in repeat dose toxicity studies, the chemical is not expected to be carcinogenic.

Reproductive and development toxicity

Based on the available data, the chemical may cause some reproductive toxicity following repeated oral exposure but adverse effects seen are not sufficient to warrant classification. The main indicator of reproductive toxicity was reduced implantation sites. This was consistent with the effects on fertility seen with the close chemical analogue, 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (CAS No. 6864-37-5). Signs of developmental toxicity included reduced number of live offspring and increased postnatal loss. However, the significance of these effects is uncertain. Read across data from the chemical analogue, 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (CAS No. 6864-37-5) show that there is no clear evidence of effects on development.

In a combined repeat dose toxicity and reproductive toxicity/developmental toxicity screening test (OECD TG 422) (see **Repeat dose toxicity – Oral** section), the chemical was administered to Wistar rats via oral gavage at 0, 15, 50 and 100 mg/kg bw/day. No abnormalities were seen in the reproductive organs of infertile animals. Limited information on results were available. No treatment related effects were seen on spermatogenesis. Oestrous cycle changes were not examined. Reduced number of implantation sites were seen in the two highest dose group females. There was a statistically significant reduction in the number of live offspring in the highest dose group females. There was an increased postnatal loss noted at 50 mg/kg bw/day (7.2% of living pups) and a corresponding reduction in the viability index to 92.8%. The change was not statistically significant. Post-natal loss at 100 mg/kg bw/day (1.4%) was similar to controls. There were no effects on pup body weight and external macroscopy did not reveal treatment related findings. The study findings concluded a reproductive and developmental NOAEL of 15 mg/kg bw/day (OECD 2011; REACH n.d.).

In a 28 day study conducted similarly to OECD TG 407 with acceptable deviations (see **Repeat dose toxicity – Oral** section), male Fisher rats (n=5-10/dose) were administered the chemical via oral gavage at 0, 25, 37.5, 50, 75 and 100 mg/kg bw. Histopathological examination of the testes showed no treatment related effects (REACH n.d.).

Reproductive toxicity was seen with the structurally related chemical analogue, 2,2'-dimethyl-4,4'-methylenebis(cyclohexylamine) (CAS No. 6864-37-5) (AICIS 2023). In an extended one generation reproductive toxicity study with the chemical analogue reduced implantation sites along with reduced litter sizes was the main indicator of effects on fertility. Effects were sufficient to warrant classification. These effects were not observed in a combined repeat dose toxicity and reproductive toxicity/developmental toxicity screening test. There was no clear evidence of effects on development based on the findings of several studies with the chemical analogue.

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