# Benzenamine, 4,4'-methylenebis-: Human health tier II assessment

**04 July 2014**

## CAS Number: 101-77-9



## Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

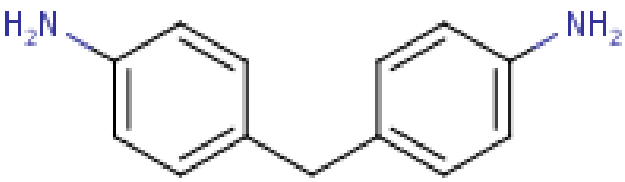
For more detail on this program please visit:www.nicnas.gov.au

**Disclaimer**



Acronyms & Abbreviations

## Chemical Identity

| | |
|---|---|
| Synonyms | 4,4-methylenedianiline<br>MDA<br>4,4-diaminodiphenylmethane<br>Bis(p-aminophenyl)methane<br>Aniline, 4,4'-methylenedi- |
| Structural Formula |  |
| Molecular Formula | C13H14N2 |
| Molecular Weight (g/mol) | 198.26 |
| Appearance and Odour (where available) | Colourless to pale yellow to tan flakes or lumps with a faint amine like odour. |
| SMILES | c1(N)ccc(Cc2ccc(N)cc2)cc1 |

# Import, Manufacture and Use

## Australian

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

The use of the chemical is restricted in Australia (see **Restrictions**: Australian).

## International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has the following commercial uses as:

- an epoxy hardening agent in adhesives, encapsulants, coatings, filament windings and binders;
- a curing agent for neoprene;
- an antioxidant and curative agent in rubber; and
- a corrosive inhibitor.

The chemical has the following site-limited uses:

- as an intermediate in the closed-system production of isocyanates (CAS No 101-68-8), polyisocyanates and polyurethane elastomers (IARC, 1986; NTP, 2011); and
- as an intermediate in producing azo dyes.

The presence of an azo dye, which may break down to the chemical, has been reported for one item of clothing in the past few years under the European Union (EU) rapid alert system (RAPEX, 2014).

# Restrictions

## Australian

This chemical is listed in the *Poisons Standard*—the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) (SUSMP, 2013) in Schedule 7.

Schedule 7 chemicals are described as 'Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply'. Schedule 7 chemicals are labelled with 'Dangerous Poison'. Products for cosmetic and domestic use must not include poisons listed in Schedule 7 (SUSMP, 2013).

### International

The chemical is restricted under Annex XVII to REACH Regulations. 'The chemical cannot be used in substances and preparations placed on the market for sale to the general public in individual concentrations ≥0.1 %' (European Parliament and Council 1999; European Parliament and Council 2006; European Parliament and Council 2008).

The chemical is listed on the following (Galleria Chemica):

***Cosmetic:***

- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- China List of Banned substances for use in Cosmetics; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

***Other:***

The chemical is listed on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2013). In the EU, companies could have legal obligations if the chemical that they produce, supply, or use is included on the candidate list whether on its own, in mixtures, or present in articles.

## Existing Work Health and Safety Controls

### Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Carc. Cat. 2; R45 (carcinogenicity);

Muta. Cat. 3; R68 (mutagenicity);

T; R39/23/24/25 (acute toxicity);

Xn; R48/20/21/22 (repeated dose toxicity); and

R43 (skin sensitisation).

### Exposure Standards

#### Australian

The chemical has an exposure standard of 0.81 mg/m³ (0.1 ppm) time weighted average (TWA). Notices: Sk (absorption through the skin may be a significant source of exposure) (Safe Work Australia).

*Guidance on the interpretation of workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

#### International

The following exposure standards are identified (Galleria Chemica).

An occupational exposure limit (OEL), time weighted average (TWA), threshold limit value (TLV), permitted exposure limit (PEL) or short-term value (STV) of:

- 0.08 mg/m³ (0.01 ppm) in countries such as New Zealand (Workplace Exposure Standards), South Africa, United Kingdom, Poland (Maximum Allowable Concentration) and Ireland;
- 0.1 mg/m³ in Switzerland, Austria, and Germany;
- 0.2 mg/m³ (0.1 ppm) in Czech Republic;
- 0.4 mg/m³ in Japan;
- 0.8 mg/m³ (0.1 ppm) in Norway, Denmark, Indonesia, Greece, South Korea, Iceland and Croatia;
- 0.81 mg/m³ (0.1 ppm) in countries such as Canada, the USA, the United Arab Emirates (UAE) and Singapore;
- 0.82 mg/m³ (0.1ppm) in Spain and Belgium; and
- 0.1 ppm in Peru, Nicaragua, Colombia and Italy.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a TLV of 0.81 mg/$m^3$ (0.1 ppm). This value is 'intended to minimize the potential for adverse effects on the liver that were reported to include jaundice, hepatitis, cirrhosis, and tumorigenicity' (ACGIH, 2011).

# Health Hazard Information

## Toxicokinetics

The toxicokinetics of the chemical have been investigated in laboratory animals and in humans. These studies demonstrated that 4,4-methylenedianiline (MDA) can be readily absorbed following dermal, oral and inhalation (in the form of dusts and aerosols) exposure. Dermal absorption could be higher in humans and rats and appears to be increased by skin occlusion (El-hawari et al., 1986; ATSDR, 1998; BAuA, 2010). In animal studies, immediately washing the skin with soap and water did not remove significant proportions of the chemical. This could lead to delayed dermal absorption.

Although data are limited, with the exception of the liver, there appears to be no preferential accumulation of the chemical in tissues. Elimination routes are mainly through the urine, with small fractions in the faeces (El-hawari et al., 1986; ATSDR, 1998; BAuA, 2010).

The available data regarding the metabolism of the chemical are limited. N-Acetyl MDA (main metabolite in humans and rats) and N,N'-diacetyl MDA have been detected in human and animal urine. This is a result of N-acetylation of the chemical catalysed by N-acetyltransferase 1 (NAT1) and 2 (NAT2) in the liver. Based on similarity to other aromatic amines, it is assumed that the chemical can be metabolised by cytochrome P450 through N-oxidation. This process leads to the formation of N-hydroxy MDA, which reacts to form nitroso-MDA or a range of Phase II metabolites. The condensation of nitroso-MDA with the non-metabolised or N-hydroxy form of the chemical produces azo-MDA and azoxy-MDA. Results from an in vitro study with rabbit liver microsomes demonstrated formation of three metabolites: the azo-MDA, azoxy-MDA, and nitroso-MDA. The chemical has been shown to form adducts with haemoglobin in studies in rats (ATSDR, 1998; BAuA, 2010).

The chemical contains two amino groups. Unlike monoaromatic amines (in which N-acetylation competes with N-oxidation) N-acetylation could enhance oxidation of the second amine group, thereby increasing risk of toxic effects in people who are rapid acetylators (Zhang et al., 2006).

Moreover, single intraperitoneal injections of the chemical to male Sprague Dawley (SD) rats induced dose-dependent increases in microsomal epoxide hydratase and ethoxycoumarin O-deethylase (Wu et al., 1989). In this study, elevated levels of ethoxyresorufin-O-deethylase (EROD), a measure of aryl hydrocarbon receptor (AHR) agonism, were also observed in the treated animals. The chemically-induced increase in glutathione-S-transferase activity in vascular smooth muscle cells was also reported (SCOEL, 2012).

## Acute Toxicity

### Oral

The chemical is classified as hazardous with the risk phrase ‘Toxic: danger of very serious irreversible effects if swallowed’ (T; R39/25) in HSIS (Safe Work Australia). The damage to the liver, bile and eyes in animals following single exposure supports this classification.

Single exposure to 50–250 mg/kg bw MDA caused liver cell (hepatocellular) and bile duct necrosis, biliary epithelial injury, and cholestasis in rats. Changes to liver weights and enzymes were observed at lower exposures. Cats and dogs also displayed liver damage and appeared to more sensitive to the effects of the chemical than rats (ASTDR, 1998; OECD, 2002). Measurable changes in the liver and kidney were detected in cats following exposure to a 10 mg/kg dose. In addition, blindness due to retinal atrophy was noted in animals treated with 25–100 mg/kg of the chemical (ACGIH, 2011; SCOEL, 2012: REACH).

The lowest reported median lethal dose (LD50) reported in rats was 335 mg/kg bw (ASTDR, 1998).

### Dermal

The chemical is classified as hazardous with the risk phrase ‘Toxic: danger of very serious irreversible effects if in contact with skin’ (T; R39/24) in HSIS (Safe Work Australia). Limited data are available to evaluate this classification, although the classification is considered appropriate based on:

- liver damage observed in animals following dermal exposure over a short period of time;
- adverse hepatic effects observed in humans following dermal exposure (refer **Acute toxicity: observation in humans**);
- effects observed following acute oral toxicity; and
- the notation that absorption through the skin could be a significant source of exposure.

Wistar II albino rats exposed dermally to 500–5000 mg/kg MDA in dimethyl sulfoxide (DMSO) for 14 days resulted in dose-dependent mortalities within two days. In another study, deaths occurred within the first week of treatment at 1000 mg/kg dose in SD rats under semi-occlusive conditions. Other chemically-induced clinical signs (reversible) include apathy, increased shedding of bloody tears, and yellow coloured urine at doses of 500–2500 mg/kg. Jaundice was observed at day four of exposure in rats dosed with 2500 mg/kg MDA (REACH). Chemically-induced mortality was noted following the application of 168 mg/kg MDA (in acetone or methanol) to the clipped skin of male and female mice five days a week for two weeks (ASTDR, 1998).

Bile duct proliferation and necrosis in the liver were observed in rabbits that were dermally exposed to MDA for 10 consecutive days (ASTDR, 1998). Seven subcutaneous implantations of 125 mg/kg MDA in rats caused chronic hepatic cirrhosis within five months (ACGIH, 2011).

### Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic: danger of very serious irreversible effects through inhalation’ (T; R39/23) in HSIS (Safe Work Australia). While the available data do not support this classification, the toxicokinetics indicate that the chemical is easily absorbed by the body. Therefore, oral and dermal toxicokinetics support the classification. In addition, hepatitis was observed in some workers who might have been exposed through inhalation (see **Acute toxicity: observation in humans**).

The results from the acute 'whole body' inhalation study in SD rats showed reversible pathological changes in the liver observed after 24–48 hours of exposure to the chemical. In this study, rats were treated with 0.46 mg/L MDA for six hours. In addition, a 'nose/head only' dust inhalation exposure to 0.837 mg/L of MDA for four hours resulted in reversible exophthalmos (protruding eyes), tremors, curved body position, and ruffled fur in Tif RAIf (SPF) rats. In male and female cats, changes including salivation,

vomiting, discolouration of the sclera and conjuctivae were noted after exposing the animals to dust containing 0.1 mg/L MDA for six hours. No mortalities were observed in these studies (OECD, 2002; REACH).

### Observation in humans

Adverse hepatic effects have been reported in humans following oral and dermal and/or inhalation exposure to the chemical over a range of time periods. Reported symptoms included pain, jaundice, cellular infiltration, inflammation of the bile duct, cholestasis and excess levels of bilirubin in the blood (hyperbilirubinaemia), and increased levels of liver enzymes. Reported cases include:

- workers dermally exposed to the chemical as a curing agent/hardening agent;
- workers dermally exposed to the chemical through kneading mixtures containing the chemical;
- spray workers who applied an epoxy resin mixed with the chemical;
- a worker who was exposed to the chemical following an equipment malfunction (exposure was both by inhalation and skin contact);
- 84 people who consumed bread made from flour contaminated with the chemical; and
- individuals who accidentally drank mixtures containing the chemical.

Generally, the effects were reversible within days or up to several months.

Myocardial toxicity and retinal damage were also noted in one individual who accidentally drank a mixture containing the chemical (ASTDR, 1998; OECD, 2002, ACGIH, 2011; SCOEL, 2012).

## Corrosion / Irritation

### Skin Irritation

The chemical caused slight skin irritation in animal studies. The effects were not sufficient to warrant a hazard classification.

Mild skin erythema and oedema were observed in New Zealand White (NZW) rabbits exposed to 500 mg of MDA for 24 hours under an occlusive condition. No other effects were reported (OECD, 2002;  REACH).

### Eye Irritation

The chemical was reported to slightly irritate the eyes when tested in NZW rabbits using similar standards outlined in the OECD Test Guideline (TG) 405. The average scores for cornea/conjunctivae (redness) conjunctivae (chemosis) were given as 0.56/1.22/0.56 respectively. The effects were reversible within 72 hours (REACH).

In rabbits, lacrimation, abnormal contraction of the eyelid (blepharospasm) and conjunctival oedema were observed after applying a drop of MDA into rabbit eyes (SCOEL, 2012).

The effects are not sufficient to warrant a hazard classification.

## Sensitisation

### Skin Sensitisation

The chemical is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in HSIS (Safe Work Australia). Although the results from animal studies are not consistent with classification, observations in humans support the classification (see **Sensitisation: Observation in humans**).

In a guinea pig maximisation test (OECD TG 406), intradermal and epicutaneous induction of 5% of MDA, followed by a challenge of 2 % under an occlusive condition induced a positive skin sensitisation reaction. This was observed in 20 % of the animals tested (REACH). In another study, necrotising dermatitis was seen in rabbits dermally-exposed to 10 doses of 700 mg/kg MDA. By contrast, no skin sensitisation or irritation were seen in mice (ATSDR, 1998).

### Observation in humans

There is evidence that the chemical causes sensitisation in humans. The chemical also showed cross-reactivity to compounds with substitution in the para position (ATSDR, 1998).

Following a human repeated insult patch test (epicutaneous), a sensitisation reaction was reported for the chemical in 5/50 individuals at concentrations of 1, 2.5 and 5 %  in Dowanol 50B (as the vehicle) under occlusion (REACH).

Furthermore, the available data from case reports support the skin sensitisation potential of MDA. In Spain, three patients were diagnosed with allergic contact dermatitis from wearing shoes containing the chemical (Grimalt et al., 2009). In Finland, a small percentage of the patient population who were patch-tested showed a positive reaction to MDA (Liipo & Lammintausa, 2008). Additionally, one case of photosensitivity to the chemical was reported in a male subject who suffered from erythematous, pruritic dermatitis on his arm and forearm for four consecutive summers (ATSDR, 1998).

Cases of allergic reaction in exposed workers (occupational exposure) involved in producing polyurethane, rubber, and epoxy resins have also been documented (SCOEL, 2012).

## Repeated Dose Toxicity

### Oral

The chemical is classified as hazardous with the risk phrase 'Harmful: danger of serious damage to health by prolonged exposure if swallowed' (Xn; R48/22) in HSIS (Safe Work Australia). The available data support this classification.

Several well-conducted studies have demonstrated that chronic oral exposure to the chemical is toxic, most notably, to the liver, thyroid, and kidney of laboratory animals. Rats (SD, Fischer 344, Wistar, RAlf), mice (B6C3F1), cats and dogs exposed to a wide range of doses (0.83–800 mg/kg) of the chemical from 2–103 weeks resulted in the treatment-related (ATSDR, 1998; OECD, 2002; ACGIH, 2011; SCOEL, 2012) effects including:

- reduced survival rates in mice (associated with cancer effects—see **Carcinogenicity** section);
- a significant increase in weight of organs such as the adrenal and uterus;
- alterations of the thyroid including follicular cysts and follicular hyperplasia;
- pathological changes in the pituitary gland (basophile hypertrophy);
- liver damage including cirrhosis, necrosis, haemosiderosis, enlargement of cells; portal fibrosis, and inflammatory infiltration; and
- nephropathy and kidney mineralisation.

Liver and thyroid effects have been reported in intermediate duration studies (16–22 weeks) with low observed adverse effect level (LOAEL) values of 25–100 mg/kg bw/day. In longer-term studies (103 weeks), effects were observed at 9 mg/kg bw/day in rats and 25 mg/kg bw/day in mice (lowest dose tested). The chemically-induced effects in the thyroid were observed at similar level, although slight stimulation of the follicular epithelium was noted in rats with three months' exposure to 7.5 mg/kg bw/day MDA (ATSDR, 1998; OECD, 2002).

### Dermal

The chemical is classified as hazardous with the risk phrase 'Harmful: danger of serious damage to health by prolonged exposure in contact with skin ' (Xn; R48/21) in HSIS (Safe Work Australia). Limited data are available to evaluate this classification. However, the classification is considered appropriate based on:

- liver damage observed in animals following dermal exposure over a short period of time;
- mortalities observed in repeated dose studies;
- adverse hepatic effects observed in humans following dermal exposure (refer **Acute toxicity: observation in humans)**;
- effects observed following repeated dose oral toxicity; and
- the notation that absorption through the skin may be a significant source of exposure.

In an OECD TG 411-compliant study, subchronic dermal exposure of rats (Alpk:APrSD) resulted in onset of skin lesions at doses 30–90 mg/kg/day. In this study, animals were exposed to MDA six hours/day, five days a week for 70 days. No other significant treatment-related changes were observed (REACH).

In a long-term dermal exposure study in mice, treatment with ≥5.3 mg/kg/day of MDA, three times a week for 104 weeks, caused a dose-related decrease in survival (ATSDR, 1998). Chemically-related mortality and liver damage have been observed in rabbits and rats following dermal or subcutaneous exposure over short periods of time (refer **Acute toxicity: dermal**).

### Inhalation

The chemical is classified as hazardous with the risk phrase 'Harmful: danger of serious damage to health by prolonged exposure through inhalation' (Xn; R48/20) in HSIS (Safe Work Australia). Limited data are available to evaluate this classification. However, the toxicity observed in oral repeated dose studies, together with the known systemic bioavailability of the chemical through all exposure routes, support this classification. In addition, adverse hepatic effects were observed in humans following potential inhalation exposure(refer **Acute toxicity: Observation in humans**);

There is limited information on the toxic effects of the chemical following repeated inhalation exposure. However, retinal degeneration (damage to photoreceptor and pigmented epithelial cells) was reported to be a prominent histopathological feature in guinea pigs from the 'nose-only' inhalation exposure to 0.44 mg/L of MDA. In this test, the animals were exposed for four hours daily, five days a week for two weeks. In addition to retinal damage, the guinea pigs also exhibited pulmonary granulomas and slight granulomatous pneumonitis. Moreover, intraperitoneal administration of MDA from 400 mg/kg produced clouding of the cornea in rats (SCOEL, 2012).

### Observation in humans

Adverse hepatic effects have been reported in humans following oral and dermal and/or inhalation exposure to the chemical (refer **Acute toxicity: Observation in humans section**).

## Genotoxicity

The chemical is classified as hazardous (Category 3 mutagenic substance) with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) in HSIS (Safe Work Australia). The available data support this classification.

The genotoxic potential of the chemical has been studied in several in vitro and in vivo sytems. Positive results were obtained in the following in vitro tests:

- reverse bacterial mutation assays in *Salmonella typhimurium* strains TA100, TA98, 1538, and TA1535 with metabolic activation only;

- forward mutation in L5178Y mouse lymphoma cells without metabolic activation;
- chromosomal aberrations in Chinese hamster ovary (CHO) and Chinese hamster lung (CHL) cells with metabolic activation (OECD, 2002; Matsuoka et al., 2008);
- dose-related induction of micronucleus and DNA strand breaks in Chinese hamster V79 cells (ATSDR, 1998; BAuA, 2010; SCOEL, 2012);
- unscheduled DNA synthesis in rat hepatocytes without metabolic activation; and
- DNA damage in *Saccharomyces cerevisiae*.

In addition, the chemical exposure also produced positive results in the following in vivo tests:

- DNA damage in rat liver cells (74 mg/kg);
- micronucleus induction (weakly positive) in the bone marrow and peripheral blood cells; and
- sister chromatid exchange (SCE) in Swiss mice (9 or 18 mg/kg) and in the Balb/c mice bone marrow cells (35 mg/kg).

Studies of the chemical's genotoxic potential in *Drosophila melanogaster* sex-linked recessive lethal mutation assays yielded conflicting results.

The observed genotoxic properties were ascribed to the reactive electrophile metabolites resulting from the N-hydroxylation of the chemical (ATSDR, 1998).

## Carcinogenicity

The chemical is classified as hazardous (Category 2 carcinogenic substance) with the risk phrase ‘May cause cancer (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

The carcinogenic potential of MDA has been extensively investigated in rats and mice. Exposure of these animals to the chemical and its dihydrochloride salt (not listed on the Australian Inventory of Chemical Substances) by various routes resulted in a number of tumours of the thyroid, adrenal glands and liver. Exposure of Fischer 344 (F344) and Wistar rats to MDA (including its dihydrochloride salt) at 20–300 mg/kg through gastric intubation, drinking water or subcutaneous injection for 30 days to two years resulted in a significant increase in development of tumours.

In a well-conducted National Toxicological Program (NTP) sponsored carcinogenicity study, exposure of F344 rats to its dihydrochloride salt in drinking water for two years caused a significant increase in the incidence of thyroid tumours (follicular-cell adenomas and carcinomas) and neoplastic nodules in the liver (NTP, 1983). The doses tested in this study were 9 and 16 mg/kg/day in males and 10 and 19 mg/kg/day in females. Malignant and benign liver tumours (hepatomas) were reported following subcutaneous administration of 1.4 g/kg bw MDA to Wistar rats for two years (SCOEL, 2012). Severe liver damage, including hyperplastic nodules and haemangiomas, were produced from oral intubation with 20 mg/kg of MDA in rats for 16 weeks (ACGIH, 2011).

In B6C3F1 mice, oral administration of MDA to males (25 and 57 mg/kg/day) and females (19 and 43 mg/kg/day) for 103 weeks caused increased incidences of follicular-cell adenomas of the thyroid, a dose-related incidence of thyroid gland follicular-cell hyperplasia, and hepatocellular adenomas (NTP, 1983; IARC, 1986; SCOEL, 2012). Furthermore, the male mice in this study exhibited benign adrenal-gland tumours, and females malignant lymphoma.

The mechanism for the carcinogenicity of MDA is still unclear. However, the biologically reactive metabolite, N-hydroxy-MDA resulting from the enzymatic oxidation of MDA, has been implicated in its toxicity.

Overall, the International Agency for Research on Cancer (IARC) has reviewed and subsequently concluded that it is ‘possibly carcinogenic to humans’ (Group 2B). The NTP also classified the chemical and its dihydrochloride salt as 'reasonably anticipated to be human carcinogens' (IARC, 1986).

## Reproductive and Developmental Toxicity

Reliable evidence for the reproductive and developmental toxicity of MDA is limited. The majority of the available studies were conducted before test guidelines and good laboratory practices (GLP) were implemented.

In these studies, exposure of SD rats to MDA (unspecified doses), once daily for 5–14 days caused increased weight of the uterus and a folliculoid endometrial response (ATSDR, 1998). Hepatic lesions in both foetuses and mothers were identified after treating pregnant Wistar rats with 50–300 mg/kg/day of MDA from gestation days (GD) 7–21. At the 300 mg/kg dose, defects in the neural tube were noted, although no lesions were seen in the liver of the affected foetuses (REACH). Teratogenic effects were also reported in a study in Leghorn hen eggs. In this study, 0.05 mL of a 10 % solution of MDA in ethanol was injected into the yolk of fertilised eggs prior to incubation. This caused reduced hatching and induced malformations in over 90 % of the surviving chicks (IARC, 1986). By contrast, mice exposed to the chemical did not produced any measurable reproductive or developmental changes (REACH).

# Risk Characterisation

## Critical Health Effects

The chemical is both genotoxic and carcinogenic in animals. The critical health effects for risk characterisation also include systemic acute and chronic toxicity from all routes of exposure (refer to **Acute** and **Repeated dose toxicity** sections). The chemical has produced skin sensitisation in humans.

## Public Risk Characterisation

The chemical is currently listed in Schedule 7 of the SUSMP and therefore cannot be directly included in domestic products. These current controls are considered adequate to minimise the risk to public health posed by products containing the chemical.

The public could potentially be exposed to the chemical through its release from dyes and pigments manufactured using the chemical. The risk to the public from this route of exposure will be considered in subsequent IMAP assessments of the relevant chemicals.

## Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These can 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. Workers can be exposed to the chemical in the form of a liquid emulsion, solid pellets with dust, or solid pellets without dust. Dermal exposure due to contact with contaminated surfaces is considered the most significant route of exposure, although oral and inhalation exposure might occur. The chemical has been reported to penetrate through the skin of workers despite wearing nitrile gloves (NTP, 2011).

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

*Guidance on the Interpretation of workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

Based on the available data, the hazard classification in HSIS is considered appropriate.

# NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

However, the public could be exposed to the chemical due to its presence as an impurity in, or release due to breakdown of, other chemicals (see **Public risk characterisation**). The risk to the public from these routes of exposure will be considered in subsequent IMAP assessments of the relevant chemicals.

## Regulatory Control

### Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed (T; R39/23/24/25)* | Causes damage to organs - Specific target organ tox, single exp Cat. 1 (H370) |
| Sensitisation | May cause sensitisation by skin contact (Xi; R43)* | May cause an allergic skin reaction - Cat. 1 (H317) |
| Repeat Dose Toxicity | Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed (Xn; R48/20/21/22)* | May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373) |
| Genotoxicity | Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)* | Suspected of causing genetic defects - Cat. 2 (H341) |
| Carcinogenicity | Carc. Cat 2 - May cause cancer (T; R45)* | May cause cancer - Cat. 1B (H350) |

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

## Advice for industry

***Control measures***

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which can minimise the risk 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;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

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. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

***Obligations under workplace health and safety legislation***

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

# References

ACGIH (American Conference of Governmental Industrial Hygienists). Documentation of the Threshold Limit Values for Chemical Substances, ACGIH Signature Publications, 7th Edition. 4,4'-methylenedianiline 2011.

Agency for Toxic Substances& Disease Registry (ATSDR) 1998. Toxicological Profile for methylenedianiline (CAS 101-77-9). Accessed June 2014 at http://www.atsdr.cdc.gov/toxprofiles/tp122.pdf

Bundesanstalt fur Arbeitsschutz und Arbeitsmedizin (BAuA) 2010. Exposure-risk relationship for 4,4'-methylenedianiline. Accessed June 2014 at http://www.baua.de/en/Topics-from-A-to-Z/Hazardous-Substances/TRGS/pdf/910/910-4-4-methylenedianiline.pdf?__blob=publicationFile&v=1

ChemIDPlus Advanced. Accessed June 2014 at http://chem.sis.nlm.nih.gov/chemidplus/

El-hawari, Stoltz M, Czarnecki D, Alm Patricia 1986. Dermal absorption of 14C-labeled 4,4'-methylenedianiline (4,4'-MDA) in rats, guinea pigs, and monkeys. Environmental Protection Agency (EPA) Final Report. Accessed June 2014 at http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91013B7F.TXT

EurAzos (2007): EurAzos Final Report, Chemical Legislation European Enforcement Network.http://www.cleen-europe.eu/

European Chemical Agency (ECHA) 2013. Support document for identification of 4,4'-diaminodiphenylmethane (MDA) as a candidate list for substance of very high concern because of its carcinogenicity. Accessed June 2014 at http://echa.europa.eu/candidate-list-table/-/substance/175/search/101-77-9/term

European Parliament and Council 1999. Directive 1999/45/EC, Official Journal of the European Union, Publications Office of the European Union, Luxembourg. Accessed May 2014 at http://www.biosafety.be/PDF/1999_45.pdf.

European Parliament and Council 2006. Annex XII: Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles. Regulation (EC) No 1907/2006, Accessed May 2014 at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1907:20130701:EN:PDF#page=234

European Parliament and Council 2008. Annex 1 to Directive 67/548/EEC, Regulation (EC) No 1272/2008, Official Journal of the European Union, Publications Office of the European Union, Luxembourg. Accessed May 2014 at http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2014:163:FULL&from=EN.

Galleria Chemica. Accessed June 2014 at https://jr.chemwatch.net/galleria/

Grimalt R, Vilaplana J, Romaguera C 2009. Three cases of allergic contact dermatitis to 4,4'-diaminodiphenylmethane. Contact Dermatitis 60 pp. 346-347

International Agency for Research on Cancer (IARC) 1986. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 39. Some chemicals used in plastics and elastomers. Accessed June 2014 at http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono39.pdf

Liippo J& Lammintausta K 2008. Contact sensitization to 4,49-diaminodiphenylmethane and to isocyanates among general dermatology patients. Contact Dermatitis 59 pp. 109–114

Matsuoka A, Haishima Y, Hasegawa C, Matsuda Y, Tsuchiya T 2008. Organic-solvent extraction of model biomaterials for use in the in vitro chromosome aberration test. Journal of Biomedical Materials Research Part A 86(1) pp. 13-22

National Toxicology Program (NTP) 1983. Technical report on the carcinogenesis studies of 4,4'-methylenedianiline dihydrochloride (CAS No. 1355-44-8) in F344/N rats and B6C3F mice (drinking water studies). Accessed June 2014 at http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr248.pdf

NTP 2011.NTP Report on the Carcinogens, Twelfth Edition. 4,4'-methylenedianiline and its dihydrochloride (CAS Nos. 101-77-9 and 13552-44-8)). Accessed June 2014 http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/methylenedianiline.pdf#search=101-77-9

Organisation for Economic Co-operation and Development (OECD) 2002. Screening Information Data Set on 4,4'-Methylenedianiline (CAS 101-77-9). The United Nations Environment Programme (UNEP) Publications. Draft of 01.12.99. Accessed June 2014 at http://www.chem.unep.ch/irptc/sids/OECDSIDS/101779.pdf

RAPEX The rapid alert system for non-food dangerous products (RAPEX). European Commission, Directorate-General Health& Consumers. Accessed June 2014 at http://ec.europa.eu/consumers/safety/rapex/alerts/main/index.cfm?event=main.search

REACH Dossier. 4,4'-methylenedianiline (CAS No. 101-77-9). Accessed June 2014 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed June 2014 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Scientific Committee on Occupational Exposure Limits (SCOEL) 2012. Recommendation on occupational exposure limits for 4,4'-4,4'-diaminodiphenylmethane (MDA). Accessed June 2014 at ec.europa.eu/social/BlobServlet?docId=7724&langId=en

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2013. Accessed June 2014 at http://www.comlaw.gov.au/Details/F2013L01607/Download

Wu K, Leslie CL, Stacey NH 1989. Effects of mutagenic and non-mutagenic aniline derivatives on rat liver drug-metabolizing enzymes. Xenobiotica 19(11) pp. 1275-1283

Zhang X, Lambert J, Doll M, Walraven J, Arteel G, Hein D 2006. 4,4’-methylenedianiline-induced hepatotoxicity is modified by N-acetyltransferase 2 (NAT2) acetylator polymorphism in the rat. Journal of Pharmacology and Experimental Therapeutics 316(1) pp. 289-294

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