Benzenamine, 4,4'-methylenebis[2-chloro-: Human health tier II assessment

04 July 2014

CAS Number: 101-14-4

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

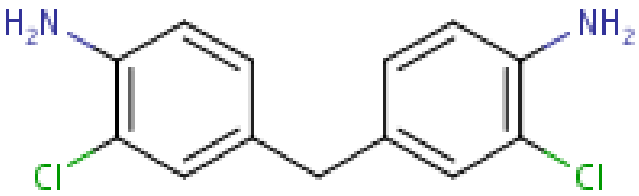
Disclaimer

NICNAS has made every effort to assure the quality of information available in this report. However, before relying on it for a specific purpose, users should obtain advice relevant to their particular circumstances. This report has been prepared by NICNAS using a range of sources, including information from databases maintained by third parties, which include data supplied by industry. NICNAS has not verified and cannot guarantee the correctness of all information obtained from those databases. Reproduction or further distribution of this information may be subject to copyright protection. Use of this information without obtaining the permission from the owner(s) of the respective information might violate the rights of the owner. NICNAS does not take any responsibility whatsoever for any copyright or other infringements that may be caused by using this information.

Acronyms & Abbreviations

Chemical Identity

Synonyms	4,4'-methylenebis(ortho-chloroaniline)

	4,4'-diamino-3,3'-dichlorodiphenylmethane MOCA MBOCA Curalin M
Structural Formula	
Molecular Formula	C13H12Cl2N2
Molecular Weight (g/mol)	267.16
Appearance and Odour (where available)	Colourless to yellow or light brown crystalline solid with a faint amine-like odour.
SMILES	c1(N)c(Cl)cc(Cc2cc(Cl)c(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).

The National Pollutant Inventory (NPI) holds data for all sources of emissions of the chemical in Australia.

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 reported commercial uses including as a curing agent, cross-linking agent and chain extender for polyurethane or polyurethane pre-polymers used in the production of urethane rubber products. Polyurethane products are a significant component of many common appliances, sporting goods, shock absorption pads, conveyor belts, mouldings for motor vehicle body parts and military equipment. The chemical is also used in coating applications where it reacts with other chemicals to set other glues, plastics and adhesives; and as a curing agent in roofing and wood sealing (IARC, 1993; NPI).

Restrictions

Australian

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

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' (SUSMP, 2013). Schedule 7 chemicals are labelled with 'Dangerous Poison'. Products for cosmetic and domestic use must not include poisons listed in Schedule 7.

Work health and safety regulations

The chemical is listed in Table 10.2 under Schedule 10 as a restricted carcinogen, which cannot be used at a concentration greater than 0.1 % without authorisation from the appropriate state or territory regulator (Safe Work Australia).

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; EurAzos, 2007; European Parliament and Council 2008).

Cosmetic

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

- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- Canada List of Prohibited and Restricted Cosmetic Ingredients (The Cosmetic Ingredient "Hotlist");
- EU Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the composition of cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain—Table 1.

Other

The chemical is 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):

- R45 Carc. Cat. 2 (carcinogenicity); and
- Xn; R22 (acute toxicity).

Exposure Standards

Australian

The chemical has an exposure standard of 0.22 mg/m^3 (0.02 ppm) time weighted average (TWA) with skin notation. This indicates that 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) as follows.

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

- 0.005 mg/m^3 in Japan, South Africa, and New Zealand;
- 0.01 mg/m^3 in Netherland, Germany and Austria;
- 0.01ppm in Portugal, Venezuela, Nicaragua, Colombia and Italy;
- 0.11 mg/m^3 (0.01 ppm) in different countries such as South Korea, Singapore, Hong Kong, Indonesia, Belgium, Iceland, Denmark; Malaysia, Spain, and the United Arab Emirates;
- 0.22 mg/m^3 (0.02 ppm) in different countries such as Canada, Mexico, Croatia, France (TLV), and the USA; and

- 0.22 mg/m^3 in Switzerland, Greece, Poland and Argentina (short-term exposure limit (STEL) of 2 ppm).

The recommended exposure limit (REL) by the National Institute for Occupational Safety and Health (NIOSH) is 0.003 mg/m^3 [skin].

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a TLV of 0.01 ppm (0.11 mg/m³) TWA to 'minimise the significant risks of cyanosis, methaemoglobinaemia, adverse effects including cancer of the kidney, and bladder' (ACGIH, 2011). In addition, the ACGIH has assigned a skin notation for the chemical, 'in recognition of the consensus that skin absorption from direct contact is a major source of occupational absorption' and A2—Suspected human carcinogen notation.

In 2009, the United Kingdom Health and Safety Executive (UK HSE) recommended that workers' exposure to the chemical should be as low as reasonably practicable—below an airborne working exposure limit (WEL) of 0.005 mg/m^3.

In 2010, the European Scientific Committee on Occupational Exposure Limits (SCOEL) characterised the chemical 'as a genotoxic carcinogen to which a threshold cannot be assigned'. Hence, a health-based OEL was not recommended for the chemical. A 'skin' notation was considered warranted (SCOEL, 2010).

Health Hazard Information

Toxicokinetics

The chemical can enter the body through dermal, oral and inhalation routes, with skin considered to be a major route of uptake (SCOEL, 2010; NTP, 2011; IARC, 2012). The chemical accumulates in tissues and is excreted in the urine and faeces (predominantly as metabolites).

Radiolabelled ^{14}C-MOCA was administered to Sprague Dawley (SD) rats orally through gavage (11 µg) and dermally (50 µg/L). Following oral administration, 68 % percent of the chemical was eliminated by urinary and faecal excretion in the first 24 hours after exposure. By 72 hours, an additional 16.5 % was excreted in urine (predominantly as metabolites), while 13.7 % was retained in tissues. Following dermal administration, 2.5 % of the chemical was excreted in the urine and faeces in the first 72 hours after exposure. This suggests high bioaccumulation and slow release of the chemical following dermal administration (REACH).

The tissue distribution of the chemical after a single exposure in SD rats was highest in the liver, followed by the kidney, lung, spleen, urinary bladder, testes, brain, and lymphocytes (ATSDR, 1994). The distribution pattern is relatively uniform in laboratory animals. In a similar investigation, high concentrations of the radiolabelled chemical were identified in the liver, small intestine, and adipose tissue in Osborne-Mendel rats 1–3 hours after intraperitoneal injection (dose: 1.5 mg). By 24 hours, 40 % of the chemical was retained with the highest levels were found in the large intestine and adipose tissue (REACH).

The chemical can be metabolised through N-acetylation, N-hydroxylation, N-oxidation, and ring hydroxylation. These processes can be followed by conjugation with glucuronate or sulfate. It can also undergo oxidation due to its methylene bridge (not found in most other aromatic amines). The major site of metabolism for the chemical is in the liver (microsomal), but the process can also occur in mammary glands and the urinary bladder, which are significant targets for the induction of tumours by aromatic amines (McQueen & Williams, 1990). The identified metabolic products include N-hydoxy-MOCA, N-nitroso-MOCA, and 5-hydroxy-MOCA (Morton et al., 1988). Humans, rats and dogs can metabolise the chemical to N-hydoxy-MOCA by cytochrome P450 enzymes. The N-acetylation detoxification pathway observed with other aromatic amines is not considered to be significant for this chemical. Only low concentrations of N-acetyl-MOCA and N,N'-diacetyl-MOCA were found in workers and animals exposed to the chemical. This could be a result from the rapid deacetylation of these metabolites (IARC, 2010; IARC, 2012).

Furthermore, the N-hydroxylation of the chemical involves the microsomal P450 enzyme system, an important process leading to adduct formation (Morton et al., 1998). This was demonstrated in a rat study that showed an increase in hydroxylation following treatment of the chemical with phenobarbital. These observations were further confirmed from findings in studies using human liver microsomes and purified liver cytochrome P450 monooxygenases. Activation of the chemical was shown to be catalysed by phenobarbital-inducible enzymes (Butler et al., 1989).

Moreover, single intraperitoneal injections of the chemical (doses: 0.4–100 mg/kg bodyweight (bw)) to male SD rats induced dose-dependent increases in microsomal epoxide hydratase, ethoxycoumarin O-deethylase and glutathione S-transferase (Wu et al., 1989). This study also reported elevated levels of ethoxyresorufin-O-deethylase (EROD), a measure of aryl hydrocarbon receptor (AHR) agonism, following exposure to the chemical.

The chemical is metabolised to produce highly reactive products that are capable of reacting with tissue macromolecules including DNA and haemoglobin. Metabolic activation to DNA-reactive intermediates occurs by multiple pathways including N-oxidation in the liver, O-acetylation in the bladder, and peroxidative activation in the mammary gland and other organs. DNA adducts formed by chemical reactions have been identified in the liver and lungs of rats, in the urinary bladder of dogs, and urothelial cells in humans. Haemoglobin adducts have also been detected in humans and animals. It is suggested that these processes play a significant role in the toxicity of the chemical. The same major MOCA-DNA adduct is formed in the target tissues for carcinogenicity in animals (rat liver and lung; dog urinary bladder) as are found in urothelial cells from a man with known occupational exposure to MOCA (IARC, 1993; IARC, 2010; IARC, 2012).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). The reported median lethal dose (LD50) values for rats, in the range 750–2100 mg/kg bw, support this classification (ACGIH, 2011). Reported signs of toxicity include cyanosis, weight loss, deep breathing, lethargy, distended stomachs and bladders, histopathological changes in the liver and adrenal glands, congested kidneys and enlarged spleeens (ACGIH, 2011:REACH).

Dermal

The chemical shows low acute toxicity in an animal test using dermal exposure. The median lethal dose (LD50) in rats is >2000 mg/kg bw.

In an acute dermal toxicity study, which was conducted in accordance with OECD Test Guideline (TG) 402 standards, male and female (Crl:WI (Han)) rats were dermally exposed (occlusive) to the chemical at 2000 mg/kg bw for 24 hours. The only reported treatment-related effect was scabs on the neck at the end of the observation period. No abnormalities or deaths were reported in this study (REACH).

Inhalation

No data are available.

Observation in humans

Data concerning acute toxicity of the chemical are limited.

Haematuria was reported in a small group of workers exposed to the chemical (in addition to other chemicals). Effects were mild and reversible within a week from the cessation of chemical exposure (ACGIH, 2011).

Conjunctivitis in both eyes was diagnosed in a worker whose face was sprayed with a hot liquid form of the chemical. The worker also reported feeling ill in the stomach. Rapid excretion of the chemical was also observed during the first 24 hours after exposure (SCOEL, 2010; ACGIH, 2011).

Corrosion / Irritation

Skin Irritation

Limited data are available. The chemical is reported to slightly irritate the skin of guinea pigs (ACGIH, 2011).

Eye Irritation

Limited data are available. The chemical is reported to be slightly irritating to the eyes of rabbits (ACGIH, 2011).

Sensitisation

Skin Sensitisation

The chemical did not induce dermal sensitisation when tested in a CBA/J mouse (OECD TG 429-compliant) local lymph node assay (LLNA) (REACH). No evidence of skin sensitisation was reported in a guinea pig sensitisation study (ACGIH, 2011).

Repeated Dose Toxicity

Oral

Limited information is available for repeated dose oral toxicity for the chemical. However, a no observed adverse effect level (NOAEL) of 2 mg/kg bw/day was reported from a 42-day oral gavage study in rats.

In a combined repeated dose and reproductive/developmental toxicity study (OECD TG 422), the chemical was administered orally by gavage to SD rats once daily for 42 days in males or 42-55 days in females. The doses tested were 0, 0.4, 2, 10, and 50 mg/kg/day. Changes in organ weights, haematology and clinical chemistry profiles were observed in the highest dose group of both sexes and, to a lesser extent, in females exposed to 10 mg/kg bw/day. Histopathological abnormalities in the liver, spleen and kidneys were also observed. These include swelling of the centrilobular zone and fatty degeneration of liver cells (intermediate zone) in the rats dosed with 50 mg/kg of the chemical. Single cell necrosis was detected in a number of male rats. The chemical's effect in the kidneys manifested as an increased tendency for mild basophilic change in male renal tubules at the top two doses, although this was not considered significant compared with the controls. The chemical-induced moderate haemosiderin deposits were observed in animals in the top two doses and extramedullar haematopoiesis in the spleen was also reported in animals from the top dose group. These effects generally appeared to be reversible (REACH).

Similar to other aromatic amines, slight cyanosis and methaemoglobinaemia have been observed in repeated dose studies in rats and dogs (ACGIH; 2011).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available well-conducted in vitro and in vivo studies, the chemical is considered genotoxic. However, sufficient information is not available to determine the mutagenicity in germ cells. The available data support the need for classification (refer to **Recommendation** section).

The chemical and the N-hydroxylated metabolite were positive in bacterial mutation assays (Ames test) in *Salmonella typhimurium* strains TA98 and TA 100, with or without metabolic activation, respectively.

The following positive results were observed in several other in vitro assays using the chemical and/or the N-hydroxylated metabolite (IARC 2010; SCOEL 2010; IARC 2012):

- chromosomal aberration (CA) test in Chinese hamster lung cells (CHL/IU) (cultured lung-derived fibroblast) with metabolic activation;
- hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus mutation in human lymphoblastoid cells;
- mouse lymphoma TK assay;
- sister chromatid exchange (SCE) in Chinese hamster ovary cells; and
- unscheduled DNA synthesis assay in cultured mouse, rat or Syrian hamster hepatocytes.

In addition, the chemical induced aneuploidy in yeast and transformation/inhibition of intercellular communication in cultured mammalian cells.

Both in vivo and in vitro tests demonstrated positive results for SCE in rat lymphocytes and micronucleus induction in the bone marrow of mice (IARC, 1993; SCOEL, 2010). In *Drosophilia melanogaster*, the chemical produced sex-linked recessive mutations. However, data from the mammalian/rodent in vivo studies do not provide sufficient information to determine whether or not the chemical reached the germ cells (ACGIH, 2011).

The genotoxicity of the chemical in exposed workers has been demonstrated by the higher frequencies of micronucleus and SCE observed in the exfoliated bladder epithelial cells and in peripheral lymphocytes (IARC, 2010).

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 carcinogenicity of the chemical has been investigated in rats, mice and dogs. The results showed that the chemical caused different types of cancer between species and sexes. In rats (Wistar, Charles River CD-1) and mice (HaM/ICR), daily exposure to the chemical (feeding and subcutaneous injection) resulted in the development of multi-organ tumours. These include benign and malignant liver hepatocellular adenoma or carcinoma in both sexes of rats and in female mice. Increased incidences of adenoma and adenocarcinoma in the lung and malignant haemangiosarcoma (cancer of blood vessels) were also identified in rats. Exposure to the chemical also caused mammary gland cancer (adenocarcinoma) in rats of both sexes and Zymbal gland carcinoma in males. In these studies, the duration of the chemical exposure ranged between 16 months to a lifetime with doses between 0–1000 mg/kg. Furthermore, treatment-related cancer-related effects in the urinary bladder (transitional-cell carcinoma) and in the urethra (mixed transitional-cell carcinoma and adenocarcinoma) were reported in female beagle dogs following dietary administration in capsule form, 3–5 days a week for six weeks to nine years (NTP, 2011; IARC, 2012).

Limited epidemiological studies are available to evaluate an association between exposure to the chemical and bladder cancer risk (NTP, 2011; IARC 2012). The data from epidemiological studies in humans reported a number of cases of urinary bladder tumours, papillary urothelial neoplasm (grade 1) and non-invasive papillary transitional cell carcinoma (grades 1 and 2) among the workers in the polyurethane plants. These affected workers had direct contact with the chemical at different times and for different exposure durations (Ward et al., 1988; Chen et al., 2005; Dost et al., 2009). These studies considered exposure history and workers' lifestyle and suggested that the chemical exposure is likely to be the primary cause of the neoplastic changes (SCOEL, 2010).

The chemical is listed in the National Toxicology Program (NTP) *Report on carcinogens* (twelfth edition) as 'reasonably anticipated to be a human carcinogen' (NTP, 2011). The International Agency for Research on Cancer (IARC) has reviewed and subsequently concluded that it is 'carcinogenic to humans' (Group 1). Although data from human studies provided inadequate evidence for carcinogenicity, in making the overall evaluation, the Working Group considered that the genotoxicity of 4,4'-methylenebis(2-chlorobenzenamine) is well documented and its toxicological profile is similar to that of ortho-toluidine, thus indicating a common mode of action. The chemical 4,4'-methylenebis(2-chlorobenzenamine) has been shown to interact with DNA to form adducts in urothelial cells, and with haemoglobin to form adducts in the blood of workers exposed to this compound. Induction of sister chromatid exchange and micronuclei in urothelial cells and lymphocytes of exposed workers has also been shown (IARC, 2012).

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical does have specific reproductive or developmental toxicity (REACH). In a combined repeated dose toxicity study and reproduction/developmental toxicity study (OECD TG 422) (see **Repeated dose toxicity: Oral** for study details), there was no evidence of reproductive and developmental toxicity. The NOAEL for reproductive and developmental effects is 50 mg/kg bw/day (top dose tested).

Risk Characterisation

Critical Health Effects

The chemical is both genotoxic and carcinogenic in animals. Although there is limited direct evidence for carcinogenicity in humans, based on the mechanistic considerations and the observation of DNA adducts, sister chromatid exchange and micronuclei in urothelial cells and lymphocytes of exposed workers (refer to **Toxicokinetics** and **Carcinogenicity** sections), the chemical is reasonably anticipated to be carcinogenic in humans.

The chemical may cause sytemic acute effects (acute toxicity by oral exposure).

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. The chemical is currently listed on 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.

Although the public might come into contact with articles manufactured using the chemical, releases of the chemical from the polymeric articles during their use phase are expected to be very low. Therefore the risk to the public is not considered to be unreasonable.

Occupational Risk Characterisation

Occupational exposure to the chemical can occur during its production and use in the polyurethane industry, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. 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.

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. The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation** section).

Based on the available data, the current specific exposure standard may not be adequate to mitigate the risk of adverse effects. However, the use of the chemical is restricted in Australia (see **Restrictions**: **Australian**) and *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).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

This chemical is a restricted carcinogen in Australia under the Work Health Safety Regulations 2011. Suppliers of this chemical and persons conducting a business or undertaking (PCBU) using this chemical, have specific obligations to protect the safety of workers using/handling/storing the chemical (Work Health and Safety Regulations 2011). The information about the status of the chemical as a restricted carcinogen under the Work Health Safety Regulations 2011 will be included in the Australian Inventory of Chemical Substances (AICS) according to section 13(1)(b) of the *Industrial Chemicals (Notification and Assessment) Act 1989*.

In addition, it is recommended that Safe Work Australia consider whether the interaction of the current controls adequately minimises the risk to workers.

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 the classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
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, 2011.

Agency for Toxic Substances and Disease Registry (ATSDR), 1994. Toxicological profile of 4,4'-methylenebis(2-chloroaniline)MBOCA (CAS 101-14-4). Accessed May 2014 at http://www.atsdr.cdc.gov/toxprofiles/tp45.pdf

Butler MA, Guengerich FP, Kadlubar FF 1989. Metabolic oxidation of the carcinogens 4-aminobiphenyl and 4,4'-methylene-bis(2-chloroaniline) by human hepatic microsomes and by purified rat hepatic cytochrome P-450 monooxygenases. Cancer Research 49(1) pp. 25-31

Cheever K, Richards D, Weigel W, Begley K, DeBord D, Swearengin T, Savage R Jr 1990. 4,4'-Methylenebis(2-chloroaniline) (MOCA): Comparison of macromolecular adduct formation after oral or dermal administration in the rat. Fundamental and Applied Toxicology 14 pp.273-283

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

Chen H, Liou SH, Loh CH, Uang SN, Yu YC, Shih TS 2005. Bladder cancer screening and monitoring of 4,4'-methylenebis(2-chloroaniline) exposure among workers in Taiwan. Adult Urology 66 pp. 305-310

Clayson, D (1981). Aromatic Amines: An Assessment of the Biological and Environmental Effects, pp 180. Washington, D.C: National Academies Press.

Dost A, Straughan J, Sorahan T 2009. Cancer incidence and exposure to 4,4'-methylene-bis-ortho-chloroaniline (MbOCA). Occupational Medicine 59 pp. 402-405

European Chemical Agency (ECHA) 2013. Support document for identification of 2,2'-dichloro-4,4'-methylenedianiline 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/90/search/+/del/75/col/INCLUSIONDATECL/type/desc/pre/2/view

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 May 2014 at https://jr.chemwatch.net/galleria/

International Agency for Research on Cancer (IARC) 1993. IARC monographs on the evaluation of carcinogenic risks to humans. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. Volume 57. Accessed on May 2014 at http://monographs.iarc.fr/ENG/Monographs/vol57/index.php

International Agency for Research on Cancer (IARC) 2010. IARC monographs on the evaluation of carcinogenic risks to humans. Some aromatic amines, organic dyes, and related exposures. Volume 99. Accessed on May 2014 at http://monographs.iarc.fr/ENG/Monographs/vol99/mono99.pdf

International Agency for Research on Cancer (IARC) 2012. IARC monographs on the evaluation of carcinogenic risks to humans. Chemical agents and related occupations. Volume 100 F. Accessed April 2014 at http://monographs.iarc.fr/ENG/Monographs/vol100F/mono100F.pdf

McQueen C and Williams G 1990. Review of the genotoxicity and carcinogenicity of 4,4'-methylene-dianiline and 4,4'-methylene-bis-2-chloroaniline. Mutation Research 239 pp. 133-142

Morton K, Lee MS, Siedlik P, Chapman R 1988. Metabolism of 4,4'-methylene-bis-2-chloroaniline (MOCA) by rats in vivo and formation of N-hydroxy MOCA by rat and human liver microsomes. Carcinogenesis 9(5) pp. 731-739

National Pollutant Inventory (NPI). Accessed April 2014 at http://www.npi.gov.au/index.html

NTP 2011.NTP Report on the Carcinogens, Twelfth Edition. 4,4'-Methylenebis(2-chloroaniline) (CAS No. 101-14-4). Accessed May 2014 at http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/methylenebis(chloroaniline).pdf

REACH Dossier. 4,4'-Methylenebis(2-chloroaniline) (CAS No. 101-14-4). Accessed May 2014 at Accessed April 2014 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

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

Safe Work Australia (SWA). National Model Regulations for the Control of Scheduled Carcinogenic Substances. Accessed May 2014 at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/239/NationalModelRegulationControlOfScheduledCarcinogenicSubstances_NOHSC1011-1995_PDF.pdf

Scientific Committee on Occupational Exposure Limits (SCOEL). Recommendation on occupational exposure limits for 4,4’-Methylene-bis-(2-chloroaniline) (MOCA) (June 2010). Accessed May 2014 at http://ec.europa.eu/social/BlobServlet?docId=6929&langId=en

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

Ward E, Halperin W, Thun M, Grossman HB, Fink B, Koss L, Osorio AM, Schulte P 1988. Bladder tumors in two young males occupationally exposed to MBOCA. American Journal of Industrial Medicine 14(3) pp. 267-272

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

Last update 04 July 2014

Share this page