1,3-Benzenediamine, 2-methyl-: Human health tier II assessment

22 November 2013

CAS Number: 823-40-5

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.

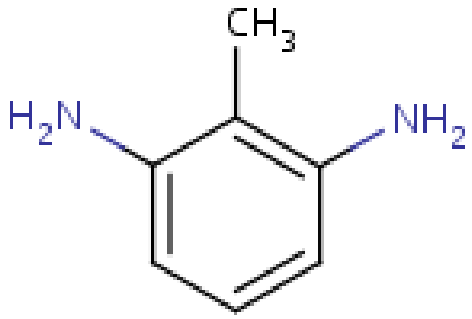
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	toluene-2,6-diamine 2,6-TDA 2-methyl-m-phenylenediamine 1,3-diamino-2-methylbenzene 2,6-diamino-1-methylbenzene
Structural Formula	
Molecular Formula	C7H10N2
Molecular Weight (g/mol)	122.17
Appearance and Odour (where available)	Clear colourless solid
SMILES	c1(N)c(C)c(N)ccc1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the European Union Final Risk Assessment Report (EU RAR); the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; eChemPortal; National Cancer Institute (NCI) and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported site-limited use:

- as an intermediate in manufacturing toluene diisocyanate (TDI) and in the production of various dyes (e.g. for furs, textiles).

The chemical is a primary component of toluenediamine (TDA, CAS No. 25376-45-8) commercial mixture. In the EU, the registered manufacturers advise against using TDA in commercial (professional) or consumer applications (REACH).

Restrictions

Australian

This chemical is not listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). However there is a group entry in Schedule 6 and Appendix C of the SUSMP that includes this chemical:

- Schedule 6:

'TOLUENEDIAMINE not elsewhere specified in these Schedules:

(a) in hair dye preparations except when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye. written in letters not less than 1.5 mm in height; or

(b) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement: WARNING - This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use. written in letters not less than 1.5 mm in height.'

Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.

- Appendix C:

'TOLUENEDIAMINES in preparations for skin colouration and dyeing of eyelashes or eyebrows except when included in Schedule 6.'

Appendix C chemicals are substances dangerous enough to warrant prohibition of sale, supply and use.

International

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

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

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):

- Xn; R21/22 (acute toxicity)
- Xi; R43 (sensitisation)
- Muta. Cat. 3; R68 (mutagenicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are identified.

Health Hazard Information

The chemical is a component of toluenediamine (TDA) commercial mixture. TDA (CAS No. 25376-45-8) comprises 80 % 2,4-TDA (CAS No. 95-80-7) and 20 % 2,6-TDA (CAS No. 823-40-5). In the absence of data on the chemical, hazard information/data available on TDA and/or 2,4-TDA were used in this assessment. However, 2,4-TDA is considered an acceptable analogue for local effects only.

Toxicokinetics

In animals, the chemical is well absorbed through the gastrointestinal tract when administered orally. It is almost completely metabolised into four main compounds (3-hydroxy-2,6-diaminotoluene; 4-hydroxy-2-acetylamino-6-aminotoluene; 2-acetylamino-6-aminotoluene, and 2,6-di(acetylamino)-toluene) following hydroxylation and N-acetylation, and rapidly excreted in the urine (85 % recovered in the urine of rats within 24 hours) (Cunningham et al., 1989; Marklund et al., 2001).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in HSIS (Safe Work Australia). No data are available on the chemical. Based on the data available for a salt of the chemical (2,6-TDA dihydrochloride), this classification is warranted.

In a non-guideline study, Fischer 344 rats and B6C3F1 mice were administered 2,6-toluenediamine dihydrochloride (CAS No. 15481-70-6) as a single oral dose from 100 mg/kg bw to 10000 mg/kg bw (two animals/dose). Mortality occurred from administering 1000 mg/kg bw in rats, and from administering 100 mg/kg bw in mice (1/2 and 2/2 deaths were recorded for 100 mg/kg bw and 300 mg/kg bw, respectively) (NCI, 1980). Reported signs of toxicity include haemorrhage of the upper portion of the stomach and intestinal tract of the rats, starting at 1000 mg/kg bw (NCI, 1980). A median lethal dose (LD50) is not reported but is estimated to be between 100 and 300 mg/kg bw in mice.

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in HSIS (Safe Work Australia). No data are available for the chemical. Based on the data available for toluenediamine (TDA, CAS No. 25376-45-8), this classification is supported.

An LD50 of 463 mg/kg bw in female rabbits was reported for toluenediamine (TDA, CAS No. 25376-45-8) (OECD Test Guideline (TG) 402). When tested at dermal doses of 50 to 1000 mg/kg bw, the signs of toxicity included poor general appearance, respiratory distress, convulsions, paralysed hind legs, discolouration of skin, discolouration of kidneys, haemorrhages, changes in the liver, ulcers in the gastrointestinal tract and enlarged adrenals (EU RAR, 2008; REACH, 2013).

Inhalation

No data are available for the chemical. Based on the data available for toluenediamine (TDA, CAS No. 25376-45-8), the chemical is expected to have low acute inhalation toxicity.

In a non-guideline study, rats and mice were exposed to 5.57 mg/L of TDA vapour–dust mix with a high amount of particles for four hours. During the observation period of 14 days following the exposure, no mortalities were recorded. Reported signs of toxicity include poor general appearance and laboured respiration (EU RAR, 2008).

Corrosion / Irritation

Skin Irritation

No data are available on the chemical. Based on the available data on 2,4-TDA (CAS No. 97-80-5) and TDA (CAS No. 25376-45-8), the chemical is not considered a skin irritant.

In a skin irritation study (OECD Test Guideline (TG) 404), 2,4-TDA (500 mg) produced no skin irritation in three New Zealand White rabbits. The mean erythema (redness) and oedema (excessive amount of fluid in tissues) scores were zero (EU RAR, 2008).

Limited information is available on TDA. It produced either negative or a slightly positive responses (below the classification threshold) for skin irritation (EU RAR, 2008; REACH).

Eye Irritation

No data are available on the chemical. Based on the available data on 2,4-TDA (CAS No. 97-80-5), the chemical is not considered to be an eye irritant.

In an eye irritation study (OECD TG 405), 2,4-TDA produced no significant eye irritation (EU RAR, 2008). A single dose of 100 mg was instilled into the eyes of three rabbits and the effects were recorded for a period of 72 hours. The only effect reported was a slight conjunctival redness (maximum score = 1), therefore 2,4-TDA is not classifiable as an eye irritant.

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). Based on the data available for 2,4-TDA and TDA, this classification is supported.

A Magnusson Kligman study (OECD TG 406) was conducted in guinea pigs with 2,4-TDA (0.5 % used for intradermal induction and 50 % for topical induction). Animals showed positive skin reactions during the first and second challenges (10/10 to a 25 % concentration in the first challenge and 5/10 to a 5 % concentration in the second challenge) (EU RAR, 2008).

In a local lymph node assay (LLNA) (OECD TG 429) with TDA, an EC3 (effective concentration needed to produce a three-fold increase in lymphocyte proliferation) of 19 % was reported, indicating it is a weak skin sensitiser (Vanoirbeek et al., 2009). While the results for TDA could be considered to be due only to its 2,4-TDA content, it is likely that the close chemical relationship between 2,4-TDA and 2,6-TDA would result in similar protein reactivity, giving rise to similar sensitisation potential.

Repeated Dose Toxicity

Oral

No data are available on the chemical. Based on the data available for a salt of the chemical (2,6-TDA dihydrochloride; CAS No.15481-70-6), the chemical is not considered to cause serious damage to health from repeated oral exposure.

In a 90-day study (similar to OECD TG 408), 2,6-TDA dihydrochloride was orally administered at doses of 100, 300, 1000, 3000 or 10000 ppm in rats and at 10, 30, 100, 300 or 1000 ppm in mice (NCI, 1980). In addition to reduced weight gain in rats at all doses, toxic effects were characterised by slight to moderate thyroid enlargement, bilateral adenomatous hyperplasia (benign cell overgrowth) of the thyroid, darkening of nasal turbinates, numerous lymph nodes and organs (spleen, liver, kidneys and adrenals), bone marrow hyperplasia and nephrosis (degenerative lesions of renal tubules) at 10000 ppm. At this dose, 2/10 males and 7/10 females died during the study. Darkening of the nasal turbinates and bilateral adenomatous hyperplasia of the thyroid also occurred in rats at 3000 ppm. No significant abnormalities were recorded at the lower doses (NCI, 1980). A lowest observed adverse effect level (LOAEL) of 3000 ppm (225 mg/kg bw/day) was suggested (Marklund et al., 2001). No deaths were reported in mice. The signs of toxicity for mice included reduced weight gain (at 300 ppm in males and at 1000 ppm in females); squamous papilloma (benign tumour derived from the epithelium) of the forestomach and renal hyperpigmentation at 1000 ppm (NCI, 1980). A no observed effect level (NOEL) of 100 ppm (15 mg/kg bw/day) was reported for mice (Marklund et al., 2001).

A two-year repeated dose toxicity study (similar to OECD TG 451) was conducted using 2,6-TDA dihydrochloride in rats at 250 or 500 ppm and in mice at 50 or 100 ppm. The only sign of toxicity was reduced body weight gain (17 % and 27 % reduction in female rats at 250 and 500 ppm, respectively and <10 % reduction in male rats and mice at all doses) (NCI, 1980).

Dermal

No data are available.

Inhalation

No data are available.

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.

Many in vitro studies showed positive results with the chemical:

- a bacterial gene mutation test (similar to OECD TG 471) in *Salmonella typhymurium* strains showed positive results only with metabolic activation with doses from 500 µg/plate to 5000 µg/plate (REACH); another Ames test using *S. typhymurium* strain TA98 and one other strain overexpressing O-acetyltransferase (OAT), showed positive results only with metabolic activation (Toyoda et al., 2009);
- a chromosome aberration test (similar to OECD TG 473) using Chinese hamster ovary (CHO) cells gave positive results without metabolic activation, hence a clastogenic response was recorded at 14, 16 and 18 mM (REACH);
- a chromosome recombination assay (similar to OECD TG 481) using *Saccharomyces cerevisiae* (yeast) gave positive results without metabolic activation at doses from 20 to 24 mg/mL. No recombination was observed with metabolic activation (Brennan and Schiestl, 1997).

Most in vivo studies with the chemical produced negative or weak positive results:

- in a micronucleus test (similar to OECD TG 474) the chemical administered orally to rats for 28 days (doses not indicated) produced weak mutagenicity only with metabolic activation (HSDB);
- in an unscheduled DNA synthesis (UDS) test (similar to OECD TG 486) (conducted concurrently with the study above), the chemical was found to be weakly mutagenic only with metabolic activation (HSDB);
- in a 13-week study on F344 gpt Delta transgenic rats (similar to OECD TG 488), no increase in mutation frequency was recorded after administering 500 ppm of the chemical in the diet. No micronuclei were found in the liver cells (Toyoda et al., 2009);
- in another study (OECD TG 488), transgenic mice received the chemical orally at 1000 ppm for 30 or 90 days. The mutation frequency was not significantly increased (Cunningham et al., 1996);
- in a study comparing the induction of DNA adducts (covalent bonds between DNA and chemical) in rats using 2,4-TDA (CAS No. 95-80-7) and the chemical, no significant induction of DNA adducts was recorded for the chemical after intraperitoneal administration of 250 mg/kg bw in F344 rats (Taningher et al., 1995; Marklund et al., 2001).

Most of the in vitro studies gave positive results. However, only negative or weak mutagenic responses at high doses were reported for in vivo studies. Based on the available evidence and considering that both TDA (CAS No. 25376-45-8) and 2,4-TDA (CAS No. 95-80-7) are Category 3 mutagens, the chemical is considered to have similar genotoxic properties.

Carcinogenicity

Based on the information available, the chemical is not expected to be carcinogenic.

No data are available on the chemical. A two-year feeding study (OECD TG 451) was conducted in rats and mice using a salt form of the chemical (2,6-TDA dihydrochloride; CAS No.15481-70-6) at 250 or 500 ppm. 2,6-TDA dihydrochloride did not induce significant carcinogenic effects in either species. The observed tumors (adenomas and carcinomas) in the liver, pancreas, thyroid and mammary glands were not statistically significant (NCI, 1980).

The chemical's lack of carcinogenic potential was explained by comparing it with 2,4-TDA (a known carcinogen) (Cheung et al., 1996). While 2,4-TDA was reported to induce its own activation through binding to the cytosolic aromatic hydrocarbon receptor (AhR) involved in gene transcription mechanisms to induce CYP1A1, 2,6-TDA did not induce CYP1A1 required for activation.

Moreover, the available genotoxicity data on the chemical showed lack of interaction with DNA. The chemical does not bind to DNA to form adducts, in contrast to the isomer 2,4-TDA (Marklund et al., 2001).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (mutagenicity);
- local effects (skin sensitisation); and
- systemic acute effects (acute toxicity from oral and dermal exposure).

Public Risk Characterisation

Given that the main use of the chemical is as an intermediate to manufacture other chemicals, it is unlikely that the public will be exposed to the chemical. It is expected that the chemical will not be present in final consumer products, although it is likely to have properties that would make it useful for applications such as hair dyes.

Many countries such as Canada, New Zealand and in the European Union have restricted the use of this chemical in cosmetics.

In Australia, a chemical group (toluenediamines) which includes this chemical is listed on Schedule 6 and Appendix C of the SUSMP, with restriction/prohibition for its use in specific cosmetics products. The Schedule 6 entry in the SUSMP allows toluenediamines to be included in hair dye preparations and in eyelash and eyebrow tinting products with specific requirements. Considering the hazard properties of this chemical, it will cause unreasonable risks to consumers if it is used in hair dyes and eyelash and eyebrow tinting products.

Occupational Risk Characterisation

Given the critical health effects (mutagenicity, skin sensitisation and acute toxicity), the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemical are implemented. Based on the available data, the hazard classification in HSIS is considered appropriate.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in hair dye and eyebrow/eyelash tinting products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

At present, the chemical falls within the scope of the listing of 'toluenediamines' in Schedule 6 of the SUSMP for use in hair dye preparations under specified conditions. Considering the serious health effects possible from exposure to this chemical (potential for mutagenicity) it is recommended that the chemical be excluded from this group entry in Schedule 6 of the SUSMP. A separate Appendix C entry is recommended for this chemical to prohibit its use in hair dye preparations and in eyelash and eyebrow tinting products.

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	Harmful if swallowed (Xn; R22)* Harmful in contact with skin (Xn; R21)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)

[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 dermal 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 may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- 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 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

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

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