1,4-Benzenediamine, N4,N4-diethyl-2-methyl-, monohydrochloride: Human health tier II assessment

13 February 2015

CAS Number: 2051-79-8

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.

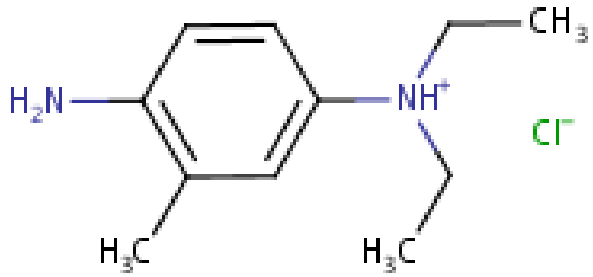
These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, 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

Acronyms & Abbreviations

Chemical Identity

Synonyms	4-amino-N,N-diethyl-m-toluidine hydrochloride 2-amino-5-diethylaminotoluene monohydrochloride 4-amino-3-methyl-N,N-diethylaniline hydrochloride toluene-2,5-diamine, N(sup 5),N(sup 5)-diethyl-, monohydrochloride 4-diethylamino-2-methylaniline monohydrochloride
Structural Formula	
Molecular Formula	C11H18N2.ClH
Molecular Weight (g/mol)	214.738
Appearance and Odour (where available)	White odourless crystalline solid
SMILES	c1(N)c(C)cc(N(CC)CC)cc1_Cl

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 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: Organisation for Economic Co-operation and Development High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use in hair dye preparations.

The chemical has reported domestic uses including in:

- paints, lacquers and varnishes; and
- cleaning/washing agents.

The chemical has reported commercial use including as:

- aerosol propellant; and
- absorbent or adsorbent.

The chemical has reported site-limited use as a photochemical agent.

The chemical has a non-industrial use in pharmaceuticals.

Restrictions

Australian

The chemical is not listed in the *Poisons Standard* (*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' (SUSMP, 2014).

Appendix C:

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

Appendix C chemicals are 'substances of such danger to health as to warrant prohibition of sale, supply and use' (SUSMP, 2014).

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; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

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):

- T; R25 (acute toxicity)

- Xi; R36 (irritation)
- Xi; R43 (sensitisation)

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

When data are not available for the chemical, available data for structurally similar chemicals (analogues), 2,5-toluenediamine (CAS No. 95-70-5) and 2,5-toluenediamine sulfate (2,5-TDS, CAS No. 615-50-9) were used where appropriate.

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in the HSIS (Safe Work Australia). The available data support this classification.

The oral median lethal dose (LD50) was reported as 200 mg/kg bw in rats (ChemIDPlus Advanced; RTECS).

Dermal

The available data are not sufficient to determine the chemical's degree of acute dermal toxicity.

The dermal LD50 is >1000 mg/kg bw in guinea pigs (ChemIDPlus Advanced; RTECS).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

No data are available.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in the HSIS (Safe Work Australia). No data are available on the chemical or a suitable analogue to support this classification. In the absence of any information, the existing classification is not recommended for amendment.

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in the HSIS (Safe Work Australia). Available human case study reports (see **Observation in Humans**) support this classification.

A structurally similar chemical, 2,5-toluenediamine (CAS No. 95-70-5), is also a known skin sensitiser (NICNAS).

Observation in humans

The following human case studies support the existing classification of the chemical as a skin sensitiser.

In a study conducted in 114 laboratory workers, the chemical was reported to be a contact allergen. Positive patch test results indicated that the chemical was able to penetrate all glove materials used (Liden, 1984).

A 39-year-old man exposed to the chemical in a photographic developing product reported itching and reddening of his wrists six weeks after exposure. The investigations on the condition proved the chemical was responsible for the dermatitis (Petzoldt & Vogt, 1970).

A 29-year-old man developed a pruritic reaction on the fingers, arms and forearms, five days after exposure to a photographic developer containing the chemical. There was a dissemination of the lesions in locations where there had been no contact with the developer, that disappeared in the absence of further contact with the chemical. Skin tests confirmed that this chemical was the source of these symptoms (Aboin et al., 2006).

Repeated Dose Toxicity

Oral

No data are available for the chemical. Based on the data available for a structurally similar chemical, 2,5-toluenediamine sulfate (2,5-TDS, CAS No. 615-50-9), this chemical is considered to cause serious damage to health from repeated oral exposure, warranting hazard classification.

The following information is available for 2,5-TDS (SCCS a, 2012; NICNAS):

- in a 90-day study (OECD TG 408), Sprague Dawley (SD) rats (n = 15/dose), received 2,5-TDS in deionised water at oral gavage doses of 0, 2.5, 5, 10 or 20 mg/kg bw/d, established a no observed adverse effect level (NOAEL) of 2.5 mg/kg bw/d (or 1.4 mg/kg bw/d for free base), based on increased aspartate aminotransferase (AST) levels from 5 mg/kg bw/d in females. Increased incidence of abnormal-shaped pituitary glands at the highest dose were reported (sex not specified). Further evaluation of the study's results later reported an NOAEL of 10 mg/kg bw/d, based on elevated AST levels and other pathological findings such as muscle degeneration in multiple organs (not indicated) at 20 mg/kg bw/d.
- another 90-day study in SD rats established an NOAEL of 10 mg/kg bw/d based on increased AST levels at 20 mg/kg bw/d correlated with microscopic changes in the skeletal muscle (thigh, diaphragm, tongue and periocular muscle of the eye). However, these changes were comparable to controls at the end of the 28-day recovery period.

The release of AST is reported to be closely related to myotoxicity. Therefore, the increased AST level in plasma in treated rats indicates 2,5-TDS as an inducer of myodegenerative changes (SCCS a, 2012).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

No data are available for the chemical. Structurally similar chemicals, 2,5-toluenediamine (CAS No. 95-70-5) and 2,5-toluenendiamine sulfate (2,5-TDS; CAS No. 615-50-9) are not considered to be genotoxic (NICNAS). Therefore, this chemical is also not expected to be genotoxic.

Some in vitro genotoxicity tests indicated positive or weakly positive results for 2,5-toluenediamine, but in vivo tests showed no genotoxicity (SCCS a, 2012; NICNAS).

There are several in vitro and in vivo studies available for 2,5-TDS. It induced gene mutations in bacteria but not in mammalian cells in vitro. Negative results were observed in two in vivo mouse bone marrow micronucleus tests (with oral and intraperitoneal (i.p). administration) in an in vivo unscheduled DNA synthesis (UDS) test and in two dominant lethal assays. The chemical 2,5-TDS is considered to have no in vivo genotoxic potential (SCCS a, 2012; NICNAS).

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the chemical. Based on the available genotoxicity data for the two analogue chemicals, information available from Quantitative Structure Activity Relationship (QSAR) modelling and potential metabolic reactions of primary aromatic amines to produce reactive pro-carcinogenic nitrenium ions, this chemical is not considered to be carcinogenic.

Experimental genotoxicity data from animal studies (see **Genotoxicity**) indicated that the structurally similar chemicals 2,5-toluenediamine and 2,5-TDS are not genotoxic. QSAR modelling for the chemical using OASIS–TIMES gave positive predictions for in vivo genotoxicity. However, the chemical structure was out of the applicability domain of the QSAR models, indicating greater uncertainty about the reliability of the positive predictions. Therefore, QSAR model prediction for the chemical was considered not to outweigh the negative in vivo genotoxicity test results for the analogues, when using weight of evidence for carcinogenic potential of the chemical.

Primary aromatic amines undergo metabolism to produce reactive electrophiles as an initial step in the carcinogenic mechanism of action. This usually involves N-hydroxylation of the aromatic amines to an N-hydroxylamine and eventual formation of the pro-carcinogenic nitrenium ions. The highly reactive nitrenium ions covalently bind to cellular DNA, provided that they are sufficiently stabilised and not subject to further reactions. The stability of the nitrenium ions is correlated with mutagenicity (e.g. as in the Ames test with metabolic activation) (Benigni & Bossa, 2011). However, the presence of two or more electron-donating groups, particularly in the *ortho*- and/or *para*-positions of the chemical structure, reduces the metabolic N-hydroxylation and inhibits nitrenium ion formation (Vance & Levin, 1984; Shimizu & Yano, 1986; Serafimova et al., 2011). Therefore, the chemical is not considered to be a genotoxic carcinogen.

Reproductive and Developmental Toxicity

No data are available for the chemical. Based on the data available for 2,5-TDS (CAS No. 615-50-9), the chemical is not expected to have reproductive or developmental toxicity.

In a two-generation reproductive toxicity study (OECD TG 416) SD rats were administered 2,5-TDS at oral doses of 0, 5, 15 or 45 mg/kg bw/d (n = 24/sex/dose). No treatment-related effects were observed for reproductive parameters such as the duration of gestation, gestation index and number of live/dead pups per litter in either the P or F1 generation. The NOAEL for reproductive toxicity was 45 mg/kg bw/d (SCCS a, 2012).

In a teratogenicity study (OECD TG 414), SD rats (n = 23 mated females/dose) were orally administered 2,5-TDS at 0, 10, 50 or 80 mg/kg bw/d on gestation days (GD) 6–15. Reduced body weight gain was noted at 50 and 80 mg/kg bw/d, but was significant only at the highest dose. An increased post-implantation loss was recorded at 80 mg/kg bw/d. No significant effects on pup development were recorded. NOAELs of 50 mg/kg bw/d for maternal toxicity and embryotoxicity and 80 mg/kg bw/d for teratogenicity were established (SCCS a, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- local effects (skin sensitisation and eye irritation); and
- systemic acute effects from oral exposure.

The chemical can also cause harmful effects following repeated oral exposure.

Public Risk Characterisation

No Australian uses are identified. Considering the use of this chemical in hair dyes and domestic products (paints, varnishes and cleaning agents) overseas, the main route of public exposure is expected to be through the skin.

Many countries, including New Zealand and the European Union, have prohibited the use of this chemical in cosmetics. In Australia, a chemical group (toluenediamine), including this chemical, is listed on Schedule 6 and Appendix C of the *Poisons Schedule*, with restriction and prohibition on its use in specific cosmetic products. The Schedule 6 entry in the *Poisons Schedule* allows toluenediamines to be included in hair dye preparations and in eyelash and eyebrow tinting products with specific labelling requirements. Using the chemical in any domestic products will require the specific signal heading 'Poison' on the product label, strong warnings and safety directions.

If this chemical is included in cosmetic products containing N-nitrosating agents, there is the possibility of forming carcinogenic N-nitrosamine compounds (SCCS, 2012).

Considering the identified health risks, the existing control measures imposed through the *Poisons Schedule* are considered adequate to protect the public if this chemical is used in hair dye preparations or any domestic products.

Occupational Risk Characterisation

Given the critical health effects (skin sensitisation, eye irritation, acute and repeated dose toxicity), the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and oral exposure to the chemical are implemented.

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

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.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2014).

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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)*	Toxic if swallowed - Cat. 3 (H301)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)
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 if swallowed (Xn; R48/22)	May cause damage to organs through prolonged or repeated exposure through the oral route - Cat. 2 (H373)

[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 consumers

Products containing the chemical should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and ocular 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 could 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;

- 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 help meet 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.

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Last update 13 February 2015

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