1,3-Benzenediamine, 4-ethoxy-6-methyl-, dihydrochloride: Human health tier II assessment

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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.

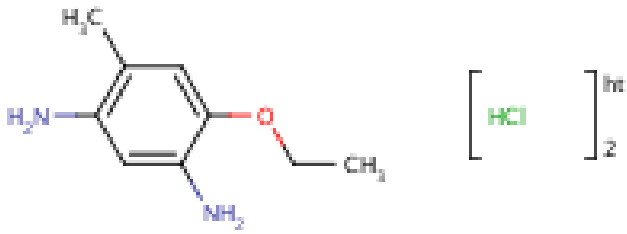
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2,4-diamino-5-ethoxytoluene dihydrochloride 2,4-diamino-5-methylphenetole hydrochloride 4-ethoxy-6-methyl-m-phenylenediamine Colipa No. A133 Ethoxyblau
Structural Formula	
Molecular Formula	C9H14N2O.2ClH
Molecular Weight (g/mol)	239.14
Appearance and Odour (where available)	Pink-violet coloured crystals.
SMILES	c1(OCC)c(N)cc(N)c(C)c1

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified. The chemical was not reported on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

International

The following international uses have been identified through the European Commission Cosmetic Ingredients and Substances (CosIng) database and the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary.

The chemical has reported cosmetic use in hair dyes.

The maximum use concentration of the chemical in hair dyes is 2.0 %. Since permanent hair dyes are mixed with hydrogen peroxide before use, the maximum in-use concentration of the chemical is 1.0 % (SCCNFP, 1999).

Restrictions

Australian

No known restrictions have been identified specifically for the chemical.

There is a group entry in Schedule 6 of the Poisons Standard (the *Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) for 'Phenylenediamines and alkylated phenylenediamines not elsewhere specified in these Schedules'. 'Phenylenediamines, including alkylated and arylated derivatives, in preparations for skin colouration and dyeing of eyelashes or eyebrows **except** when included in Schedule 6' are listed in Schedule 10 (Appendix C) of the SUSMP (2015). However, these group entries do not include alkoxy-substituted derivatives of phenylenediamines (SUSMP, 2015).

International

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

- EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

After oral administration in Sprague Dawley (SD) rats, 50 % of the radiolabelled chemical was excreted in the urine and 45 % in faeces (EC SCC, 2000).

In SD rats, the majority of a radiolabelled sample applied (using two hair dye formulations, both containing 2 % of the chemical and one also containing hydrogen peroxide) to the dorsal skin for 30 minutes was removed from the skin by rinsing (98.4–99.1 %). The mean percutaneous absorption was 0.46 % and 0.078 % in the absence and presence of hydrogen peroxide, respectively. Excretion after cutaneous application was 0.451 % and 0.076 % (without and with hydrogen peroxide, respectively), with 56–58 % being in the urine and 42–44 % in faeces (EC SCC, 2000).

Acute Toxicity

Oral

Based on the available data, the chemical has been reported to have moderate acute oral toxicity, although the data are not sufficient to validate this conclusion.

The chemical (as a 10 % aqueous solution) was administered by oral gavage doses to CF1 mice (n = 10/sex/group) at 350 or 800 mg/kg bw and 200 or 600 mg/kg bw for females and males, respectively. Wistar rats (n = 6/sex/group) were also administered a 10 % solution of the chemical at 500 or 1000 mg/kg bw and 500 or 1250 mg/kg bw for females and males, respectively. The chemical was reported to have moderate acute oral toxicity with an 'approximate' median lethal dose (LD50) between 200 and 2000 mg/kg bw. Animals showed reduced activity and 'abnormal position' during the 14-day observation period (EC SCC, 2000). No mortalities were reported in the study.

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Only limited data are available. The chemical at a 3 % concentration is not irritating to the skin.

A skin irritation study was conducted using a 3 % solution of the chemical in five, female Pirbright white guinea pigs. Closed patches containing the test solution (1 mL) were applied to clipped skin on the flank area for four hours. No skin irritation response was observed in any of the animals, up to four days after the patch was removed (EC SCC, 2000).

Eye Irritation

Only limited data are available. The chemical at a 3 % concentration is not irritating to the eyes.

Five, female Pirbright white guinea pigs were administered a 3 % solution of the chemical (0.1 mL, reported to be pH 2.1) into the conjunctival sac of the right eye. No effects were observed up to seven hours post-application (EC SCC, 2000).

Sensitisation

Skin Sensitisation

Based on the available information, the chemical is expected to be a skin sensitiser, warranting hazard classification.

Pirbright white guinea pigs (n = 10 females) were induced with a 0.1 % solution of the chemical in Ringer's solution via intradermal injection to the clipped shoulder region, followed by a topical application of a 40 % solution of the chemical. After two weeks, the animals were challenged with a 30 % solution of the chemical. Two of 10 test animals showed slight to moderate erythema (EC SCC, 2000). The SCCNFP (1999) report stated that this study used too low an intradermal induction concentration. The cosmetic product containing the chemical was reported to have a label warning for risk of sensitisation (SCCNFP, 1999).

The sensitisation potency of the chemical was predicted in a study on 229 hair dye substances using a Quantitative Structure Activity Relationship (QSAR) model based on the local lymph node assay (LLNA). The study predicted the chemical to be a moderate to strong sensitiser, with an estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) value of 5.1 (Sosted, 2004).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause severe effects following repeated oral exposure.

Wistar rats (n = 15/sex/dose and n = 22/sex for control groups) were administered the chemical at 5, 10 or 20 mg/kg bw/day via oral gavage, five days per week for 90 days. No treatment-related deaths occurred during the study and no histopathological changes were noted. The only treatment-related effect observed was dark discolouration of the thyroids in all animals that received the highest dose. The no observed adverse effect level (NOAEL) was reported to be 20 mg/kg bw/day (EC SCC, 2000).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

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

The chemical gave negative results for genotoxicity in the following in vitro assays (EC SCC, 2000):

- an Ames test in *Salmonella typhimurium* strains TA97, TA98 and TA100, with or without metabolic activation at up to 6000 µg/plate;
- a mouse lymphoma fluctuation assay in LY5178Y cells, with or without metabolic activation; and
- a sister chromatid exchange assay in Chinese hamster ovary cells, with or without metabolic activation at up to 2390 µg/mL; the cytotoxic concentration was reported to be >717 µg/mL and >239 µg/mL in the presence and absence of metabolic activation, respectively.

The chemical gave negative results in an in vivo micronucleus test when NMRI mice were administered the chemical at 1000 mg/kg bw in drinking water. There were clear indications of the test material reaching the bone marrow of mice and a cytotoxic effect was observed 24 hours after application, but not after 72 hours (EC SCC, 2000).

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the chemical. Based on the available genotoxicity data, this chemical is not considered to be carcinogenic.

Experimental genotoxicity data indicated that the chemical is not genotoxic (see **Genotoxicity**). The QSAR modelling using OASIS–TIMES (Optimized Approach based on Structural Indices Set–TIssue MEtabolism Simulator) predicted positive results for in vitro genotoxicity and mixed results for in vivo genotoxicity. However, the chemical was out of the applicability domain of the models used for these predictions, indicating greater uncertainty about the reliability of the results.

Primary aromatic amines undergo metabolism to 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 DNA, provided that they are sufficiently stabilised so as not to undergo further reactions.

The stability of the nitrenium ions is correlated with mutagenicity, for example in the Ames test, with metabolic activation (Benigni & Bossa, 2011). For the chemical, the Ames test results were negative (see **Genotoxicity**), which indicates a lower carcinogenic potential.

Expert rules, based on the chemical structure and reaction mechanism for carcinogenicity, can be used to determine the carcinogenic potential of a chemical. However, for this chemical, there are no existing expert rules to identify with greater certainty whether it is carcinogenic or not. Therefore, the available genotoxicity studies are used in the overall weight of evidence analysis to ascertain the chemical's carcinogenicity.

Reproductive and Developmental Toxicity

Only limited data are available and are not sufficient to derive a conclusion on reproductive or developmental toxicity of the chemical.

The chemical was administered to pregnant Wistar rats by oral gavage, at doses of 0, 5, 15 and 30 mg/kg bw/d on gestation day (GD) 5–15. The rats were euthanised on GD 20. No maternal mortality, toxicity or foetal abnormalities were observed (EC SCC, 2000).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the potential for skin sensitisation.

Data are lacking for acute or repeated dose dermal and inhalation toxicity. Limited data are available for eye and skin irritation, indicating low concentrations of the chemical are not irritating to the eyes and skin. The data available on reproductive and developmental toxicity were also limited.

Public Risk Characterisation

No uses have been identified in Australia, although the international uses indicate the chemical has been used in hair dyes. Many countries, including those in the European Union, have prohibited the use of this chemical in cosmetics. Currently, there are no restrictions in Australia on using this chemical in cosmetics.

If this chemical is included in cosmetic products containing N-nitrosating agents, carcinogenic nitrosamine compounds could be formed (SCCS, 2012).

In the absence of any regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk if used in cosmetics.

Occupational Risk Characterisation

Given the critical health effects and lack of data on some health end points, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemical 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.

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 cosmetics 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

Given the risk characterisation, it is recommended that the chemical should be included in the Poisons Standard (the *Standard for the Uniform Scheduling of Medicines and Poisons* — SUSMP) for cosmetic and hair dye use.

Consideration should be given to the following, the:

- chemical could have moderate skin sensitisation potential;
- lack of data on reproductive and developmental toxicity;
- use of this chemical in cosmetics is prohibited overseas; and
- risk could be controlled by including warning statements on the label of hair dye formulations containing the chemical at any concentration.

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]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[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 the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal 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:

- 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 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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The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) 2015. The Poisons Standard No: 6. Accessed at http://www.comlaw.gov.au/Details/F2015L00128/Download

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