Ethanol, 2-(2,4-diamino-5-methylphenoxy)-, dihydrochloride: Human health tier II assessment

01 September 2015

CAS Number: 113715-27-8

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.

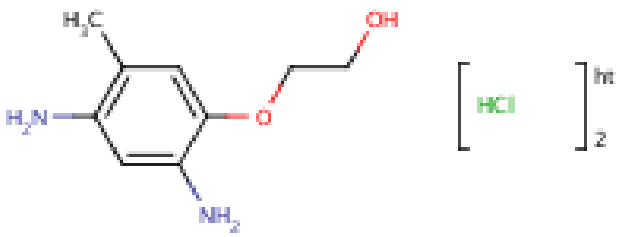
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2,4-diamino-5-methylphenoxyethanol HCl 2,4-diamino-5-(2-hydroxyethyloxy)-toluol-dihydrochloride 1-methyl-2,4-diamino-5-(2-hydroxyethyloxy)-benzene-dihydrochloride HB-Blau Colipa No A116
Structural Formula	
Molecular Formula	C9H14N2O2.2ClH
Molecular Weight (g/mol)	255.14
Appearance and Odour (where available)	White-pink coloured crystalline powder

SMILES	c1(OCCO)c(N)cc(N)c(C)c1

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 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 oxidative hair dye formulations.

The maximum concentration in hair dyes is indicated as 3.0 %. Since oxidative hair dyes are mixed with hydrogen peroxide before use, the use concentration on hair is 1.5 % (SCC, 2000; SCCNFP, 1999).

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Cosmetic 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; and
- 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

Following oral administration of 30 mg of radiolabelled chemical (99 % pure) to rats, 61 % of the administered dose was excreted in urine and 35 % in faeces, with 73 % of the administered dose being excreted within the first 24 hours (SCC, 2000).

Formulations containing the radiolabelled chemical at 3 % were applied to the clipped dorsal skin of Sprague Dawley (SD) rats (n = 3/sex) for 30 minutes, and rinsed off with shampoo and water. The majority of the applied chemical (98.9–99.2 %) was removed from the skin by rinsing. Only 0.32–1.09 % of the administered chemical remained at the application site. Between 0.054 % and 0.147 % of the administered dose was recovered in the faeces (31–44 %) and urine (54–68 %) within 72 hours of application. The amount of radiolabelled chemical distributed in the carcass or organs was near or below the detection limit (SCC, 2000).

Acute Toxicity

Oral

The chemical has moderate acute oral toxicity in animal tests, warranting hazard classification.

The median lethal dose (LD50) in rats was reported to be 875 mg/kg bw in females and 725 mg/kg bw in males. The LD50 in mice was reported to be 1100 mg/kg bw in females and 1040 mg/kg bw in males. Observed sublethal effects included increased activity following exposure (which decreased after 10 minutes), spasms and side position (SCC, 2000).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Only limited data are available. The chemical up to 3 % concentration is not expected to be irritating to the skin.

The chemical at 3 % in distilled water (1 mL) was applied to the clipped dorsal skin of five Pirbright guinea pigs. After four hours, the patch was removed and the treated skin was washed. Observations were made according to the Draize method. No skin irritation was observed at any time up to a week after exposure (SCCNFP, 1999).

Eye Irritation

Only limited data are available. The chemical up to 3 % concentration is not expected to be irritating to the eyes.

The chemical at 3 % in a solution (0.1 mL) was instilled into the right eye of five female Pirbright guinea pigs. The left eye remained untreated as a control. Observations were made according to the Draize scale at 0.5, 1, 2, 3, 4, 6, 7 and 24 hours after the treatment. No eye irritation was observed at any time (SCC, 2000).

Sensitisation

Skin Sensitisation

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

In a Magnusson and Kligman skin sensitisation study (OECD test guideline (TG) 406), Pirbright guinea pigs (n = 10 females) were induced by administering three pairs of intradermal injections—0.1 % chemical in Ringer solution, 0.1 % chemical in Freund's complete adjuvant (FCA), and 1:1 mix of FCA:Ringer solution. After one week, topical induction was carried out using a 40 % aqueous solution of the chemical in a patch for 48 hours. The animals were challenged two weeks after the last induction using a patch containing a 40 % aqueous solution of the chemical. Erythema was observed in four test animals. The chemical was reported to be a moderate skin sensitiser in guinea pigs (SCCNFP, 1999).

A Buehler test was performed (OECD TG 406) in Pirbright guinea pigs (n = 20) by topically administering a diluted formulation (25 % formulation in deionised water) containing the chemical at 1.5 %, once a week for three weeks. Two weeks after the last induction, the animals were challenged with a 1 % dilution of the same formulation (which contained 1.5 % the chemical) and the application area was depilated after 24 hours. Observations were made at 2, 24 and 48 hours following depilation. No sign of skin sensitisation was observed at this low concentration of the chemical (SCCNFP, 1999).

The potency for skin sensitisation was predicted for 229 hair dye substances, by using a quantitative structure–activity relationship (QSAR) model based on the local lymph node assay (LLNA). The chemical was predicted to be a strong skin sensitiser, with a predicted effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) value of 0.3 (Sosted, 2004).

The QSAR modelling using OASIS–TIMES (Optimized Approach based on Structural Indices Set–Tissue MEtabolism Simulator; version 2.27) predicted negative results for skin sensitisation for the parent chemical but three of its metabolites were predicted to be strong skin sensitisers. However, the parent chemical was out of the applicability domain of the model used for these predictions, indicating greater uncertainty about the reliability of the results.

The QSAR modelling for skin sensitisation using the OECD QSAR Toolbox (version 3.2) indicated that there were no protein binding alerts for the parent chemical or its metabolites.

Repeated Dose Toxicity

Oral

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

In a subchronic study, Wistar rats (n=15/sex/dose) were administered the chemical (99 % purity) via oral gavage doses of 0, 15, 30 or 60 mg/kg bw/d, five days per week for 3 months. There were no mortalities. A no observed adverse effect level (NOAEL) of 30 mg/kg bw/day was determined based on increased spleen weight (significant in females) and histopathological changes in the spleen (decreased haematopoiesis) observed at 60 mg/kg bw/day. The minor biochemical changes (decreased creatinine and urea, increased glucose levels) observed in all treated rats were not considered toxicologically important (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 was not genotoxic in several in vitro genotoxicity assays (Ames tests with *Salmonella typhimurium* strains TA97, TA98 and TA100, with or without metabolic activation up to 6000 µg/plate and a gene mutation assay using mouse lymphoma cells L5178Y, with or without metabolic activation up to 1250 µg/mL) (SCC, 2000).

In an in vivo micronucleus test, the chemical induced no micronucleated polychromatic erythrocytes in hepatocytes of mice that received the chemical at 600 mg/kg bw. An unscheduled DNA synthesis assay also gave negative results when rats were administered the chemical in drinking water at up to 600 mg/kg bw (SCC, 2000).

The QSAR modelling using OASIS–TIMES predicted that the parent chemical would be negative for mutagenicity in various assays (Ames test, chromosomal aberrations, in vivo liver clastogenicity and in vivo micronucleus), but several metabolites were predicted to be mutagenic. However, the parent chemical was out of the applicability domain of the model used for these predictions, indicating uncertainty about the reliability of these results.

The QSAR modelling for genotoxicity using the OECD QSAR Toolbox indicated that there were DNA binding alerts, as well as genotoxicity alerts, for the parent chemical and its metabolites. The aromatic amine structure of the chemical and metabolism of the chemical to form nitrenium ions were the main predicted mechanisms for genotoxicity.

Carcinogenicity

No carcinogenicity data are available for the chemical. The available information is insufficient to determine the carcinogenicity effects of the chemical.

The QSAR modelling for carcinogenicity using the OECD QSAR Toolbox (version 3.2) indicated that there are structural alerts for genotoxic carcinogenicity based on the aromatic amine structure of the chemical and its metabolites. However, in the absence of metabolite information from the toxicokinetic data, the significance of these metabolites is not known. The two in vivo genotoxicity studies in rodents gave negative results (see **Genotoxicity**).

Reproductive and Developmental Toxicity

No data are available on reproductive toxicity. Based on the limited data available, the chemical is not considered to cause developmental toxicity.

Pregnant Wistar rats (n=20/dose) were administered the chemical at oral gavage doses of 0, 30, 60 or 180 mg/kg bw/day, on gestation days 6–15 and sacrificed on day 20. Early resorptions were slightly increased at the highest dose (details not available). No treatment related effects were observed in foetuses at any dose level (SCC, 2000).

Risk Characterisation

Critical Health Effects

The critical health effects identified for risk characterisation include local effects (skin sensitisation) and systemic acute effects from oral exposure.

Data are not available on acute or repeated dose dermal and inhalation toxicity or carcinogenicity. Only limited data are available on skin and eye irritation (3 % concentration is not irritating to the eyes and skin), and reproductive toxicity.

Public Risk Characterisation

The international uses of this chemical in oxidative hair dyes indicate a maximum concentration of 3 % (or 1.5 % with hydrogen peroxide) (SCCNFP, 1999). Many countries including New Zealand and the European Union have prohibited the use of this chemical in cosmetics. The chemical was not reported to be used in hair dyes in Australia (NICNAS, 2007).

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

Currently, there are no restrictions on using this chemical in Australia. If the chemical is used in hair dyes, the main route of public exposure is expected to be through the skin, and the potential for skin sensitisation may pose an unreasonable risk.

Occupational Risk Characterisation

Given the identified critical health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal 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.

The data available support hazard classification of the chemical (see **Recommendation section**).

NICNAS Recommendation

The chemical was not reported to be used in hair dyes in Australia previously (NICNAS, 2007). The chemical is a skin sensitiser, and hazard data for some important health end points are lacking or inconclusive.

If the chemical is used in hair dyes in Australia, further regulatory controls such as scheduling may be required to manage the potential risk from skin sensitisation.

The chemical is recommended for Tier III assessment to determine whether it is used in hair dyes or for any other uses in Australia.

Regulatory Control

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]

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Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
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 industry

Control measures

Control measures to minimise the risk from oral and 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 may 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

European Commission Scientific Committee on Cosmetology (SCC) 2000. Reports of the Scientific Committee on Cosmetology (Ninth Series). Accessed July 2014 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/scc_o_9.pdf

Gago-Dominguez M, Castelao JE, Yuan J-M, Yu MC, Ross RK 2001. Use of permanent hair dyes and bladder-cancer risk. Int. J. Cancer 91, pp. 575–579.

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

International Agency for Research on Cancer (IARC) 2010. Occupational exposures of hairdressers and barbers and personal use of hair colourant. IARC Monographs Volume 99. Accessed July 2014 at http://monographs.iarc.fr/ENG/Monographs/vol99/mono99-17.pdf

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2007. List of Chemicals used as Dyes in Permanent and Semi-Permanent Hair Dyes in Australia.

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

Scientific Committee on Consumer Safety (SCCS) 2012. Opinion on Nitrosamines and Secondary Aminesin Cosmetic Products. Adopted at its 14th plenary meeting of 27 March 2012. Accessed January 2014 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_090.pdf

Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP) 1999. Opinion concerning 2,4-Diamino-5-methylphenoxyethanol HCL (Colipa n° A116). Accessed July 2014 at http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/sccnfp_opinions_97_04/sccp_out66_en.htm

Sosted H, Basketter DA, Estrada E, Johansen JD, Patlewicz GY 2004. Ranking of hair dye substances according to predicted sensitization potency: quantitative structure-activity relationships. Contact Dermatitis 51, pp. 241-254.

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