Phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]- and its dihydrochloride: Human health tier II assessment

24 April 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]-	110952-46-0
Phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]-, dihydrochloride	135043-63-9

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

Grouping Rationale

The chemical, phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]-, dihydrochloride (CAS No. 135043-63-9) is a salt resulting from phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]- (CAS No. 110952-46-0; referred to as the parent base in this report) reacting with two molecules of hydrochloric acid. The parent base and its salt have been grouped together for assessment due to their similar toxicological properties and uses.

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; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemicals have reported cosmetic uses as substances in hair dye products.

Restrictions

Australian

No known restrictions have been identified.

International

The chemicals are listed on the following:

- The 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;
- The European Union (EU) Regulation (EC) No 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 Worker Health and Safety Controls

Hazard Classification

The chemicals are 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

The hazards of both the parent base (phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]-, CAS No. 110952-46-0) and its salt (phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]-, dihydrochloride, CAS No. 135043-63-9) were assessed using the toxicological data available on the salt (EC SCC, 2000). Where data are unavailable for the parent base, the data available for the salt are considered relevant for the hazard assessment due to the structural similarity of the two chemicals. However, the dihydrochloride salt could have different properties from the parent base with respect to local effects.

Toxicokinetics

The chemicals have slow dermal absorption and the absorbed fraction is extensively excreted within 24 hours.

The salt was applied to the skin of Sprague Dawley (SD) rats in two different hair dye formulations (containing 3 % of the salt or 1.5 % of the salt when mixed with 9 % hydrogen peroxide) or as a solution in water (containing 1.5 % of the salt). The formulation or solution was left on the skin for 30 minutes and then rinsed with a 3 % solution of a proprietary shampoo, followed by water at approximately 37 °C. After rinsing, 90.9–95.1 % of the salt was removed from the skin. The mean percutaneous

absorption was 0.032–0.42 % of the salt. The salt was mainly excreted within the first 24 hours following application (89–97 %) and the excretion was via the urine (90–94 %) and faeces (6–10 %) (EC SCC, 2000).

Acute Toxicity

Oral

The chemicals are considered to have moderate acute toxicity based on results from animal tests following oral exposure to the salt, warranting hazard classification. The median lethal dose (LD50) for the salt is 400–1600 mg/kg bw in rats and mice (strains not specified). Observed sub-lethal effects included reduced activity, orange discolouration of the urine and death (EC SCC, 2000).

Dermal

The chemicals have low acute toxicity based on results from an animal test following dermal exposure to the salt. The LD50 in rats (strain not specified) for the salt is >2000 mg/kg bw. Observed sub-lethal effects included chromodacryorrhoea (shedding red-coloured tears) and white foci on the left kidney.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Limited data are available. The salt is not considered to be a skin irritant.

In a study with five female Pirbright white guinea pigs, a 3 % solution of the salt was applied occlusively to the clipped back of the animals for four hours. The salt was washed off following application. No signs of irritation were observed and the Draize score was zero (EC SCC, 2000).

In a study with three female New Zealand White rabbits, the undiluted salt was applied occlusively to the clipped back of the animals for four hours. The salt was washed off following application. Slight oedema was observed in one animal 24 hours after application and the Draize score was 0.1 (EC SCC, 2000).

Eye Irritation

Limited data are available. The salt is not considered to be an eye irritant.

In a study with five female Pirbright white guinea pigs, a 1.5 % solution of the salt was instilled into the conjunctival sac of the right eye of each animal. No signs of irritation were observed and the Draize score was zero (EC SCC, 2000).

In a study with three female New Zealand White rabbits, the undiluted salt was instilled into the conjunctival sac of the right eye of each animal. One animal had minimal redness of the conjunctivae 24 hours after application and the Draize score was 0.2 (EC SCC, 2000).

Sensitisation

Skin Sensitisation

The chemicals are considered to be skin sensitisers, warranting hazard classification.

In a Magnusson Kligman study with 20 Pirbright white guinea pigs, three series of intradermal injections (two injections of 10 % solution of the salt, two injections of 10 % of the salt in Freund's complete adjuvant (FCA) and two injections of FCA) were given to the animals during the induction phase. On day seven following the induction phase, a topical induction patch using the undiluted salt was applied. Both challenges with a topical application of the undiluted salt and a re-challenge with a topical application of the salt at 3 % concentration produced slight to moderate erythema in 15/20 animals, indicating a sensitising potential (EC SCC, 2000).

In a separate Magnusson Kligman study with 20 female Dunkin Hartley guinea pigs, three series of intradermal injections (two injections of 0.63 % solution of the salt, two injections of 1.25 % of the salt in FCA and two injections of FCA) were given to the animals during the induction phase. On day seven following the induction phase, a topical induction patch using 50 % of the salt was applied. A challenge with a topical application of the salt at 12.5 % concentration did not produce positive reactions in the animal. The study was considered inadequately performed as the induction concentrations were too low (EC SCC, 2000).

In a Buehler test with 20 Pirbright white guinea pigs, the undiluted salt was applied occlusively to the shaved shoulder of the animals once a week for six hours, for three consecutive weeks, during the induction phase. Slight erythema was observed in 6/20 animals after the second and third induction. A challenge with a topical application of the salt as a 50 % aqueous solution and 3 % dilution in deionised water on the left and right flank, respectively, did not produce positive reactions in the animals (EC SCC, 2000).

In a separate Buehler test with 20 Pirbright white guinea pigs, a 25 % dilution of a hair dye formulation containing 2.5 % of the salt was applied occlusively to the shaved shoulder of the animals once a week for six hours, for three consecutive weeks, during the induction phase. A challenge with a topical application of the formulation as a 10 % aqueous solution with and without an oxidant were given to the animals on the left and right flank, respectively. The test was considered inadequately performed as irritation could not be assessed due to oxidative discolouration (EC SCC, 2000).

Repeated Dose Toxicity

Oral

Limited data are available. The available data suggest that the chemicals have low repeated dose toxicity based on results from animal tests following oral exposure.

In a repeated dose toxicity study, Fischer 344 (F344) rats (five animals/sex/group) were administered 0, 100, 316 or 1000 mg/kg bw/day of the salt daily for 28 days by oral gavage. In the 1000 mg/kg bw/day group, urine discolouration, decreased motor activity, disturbed locomotion, piloerection and hunched posture were observed in the first two weeks of treatment. A significant decrease in spleen weight was observed in the females of the 1000 mg/kg bw/day group. Significant increases in red blood cell count and serum cholesterol were observed in the females and males of the 1000 mg/kg bw/day group, respectively. The no observed adverse effect level (NOAEL) was 316 mg/kg bw/day (EC SCC, 2000).

In a separate repeated dose toxicity study, Wistar rats (15 animals/sex/group) were administered 0, 10, 20 or 40 mg/kg bw/day of the salt daily for 90 days by oral gavage. No signs of toxicity were reported in this study (EC SCC, 2000).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available data from in vitro and in vivo studies, the chemicals are not considered to be genotoxic.

In vitro studies

A bacterial point mutation assay was conducted using three *Salmonella typhimurium* strains (TA97, TA98 and TA100) at concentrations of 1–10000 µg/plate of the salt, in the absence and presence of a rat liver metabolic activation system. Negative results were obtained from the study (EC SCC, 2000).

A bacterial point mutation assay was conducted using five *S. typhimurium* strains (TA98, TA100, TA1535, TA1537 and TA1538) at concentrations of 8–5000 µg/plate of the salt, in the absence and presence of a rat liver metabolic activation system. Negative results were obtained from the study (EC SCC, 2000).

A chromosomal aberration test was conducted using Chinese hamster ovary (CHO) cells. The salt was tested up to maximum concentrations of 185 and 6.86 µg/mL in the absence and presence of a rat liver metabolic activation system, respectively. In the absence of the metabolic activation system, the salt induced a significant increase in cells with chromosomal aberrations at 185 µg/mL, indicating clastogenic potential in this study (EC SCC, 2000).

In vivo studies

In a micronucleus assay in bone marrow cells conducted using NMRI mice (six animals/sex/group), the salt was administered at concentrations of 0, 140, 470 or 1400 mg/kg bw by oral gavage. Bone marrow cells were collected 24, 48 and 72 hours after administration of the salt and the polychromatic erythrocytes (PCEs) for five males and females in each group were examined. No increases in micronucleated PCEs were found in this study (EC SCC, 2000).

In a sister chromatid exchange (SCE) assay in bone marrow cells conducted using NMRI mice (five animals/sex/group), the salt was administered at concentrations of 10–2000 µM by oral gavage. No increases in SCEs were found in this study (EC SCC, 2000).

In an unscheduled DNA synthesis (UDS) assay conducted using Wistar rats (six animals/sex/group), the salt was administered at concentrations of 0, 100, 300 or 1000 mg/kg bw by oral gavage. The salt did not induce UDS in this study (EC SCC, 2000).

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the parent base and the salt. Based on the available genotoxicity data and mechanistic information, the chemicals are not considered to be carcinogenic.

Experimental in vitro genotoxicity data (refer to **Genotoxicity** section) showed that the chemical is not considered to be genotoxic. Quantitative Structure Activity Relationship (QSAR) modelling using OASIS–TIMES (Optimized Approach based on Structural Indices Set–TIssue MEtabolism Simulator) resulted in positive results for in vitro and in vivo genotoxicity, although it should be noted that the chemical was out of the applicability domain of the models. If a prediction is out of the applicability domain of the model, it indicates that there is greater uncertainty about the reliability of the models since the performance statistics from the training set might not be applicable to the chemical. Thus, QSAR model predictions for this chemical will not be included in the weight of evidence analysis of the carcinogenic potential of the chemical.

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 the induction of point mutations, particularly in the Ames test, with metabolic activation (Benigni & Bossa, 2011). For the chemical, the Ames test results were negative (refer to **Genotoxicity** section), which indicates a lower likelihood of any carcinogenic potential.

Reproductive and Developmental Toxicity

Limited data are available. Based on the available data, the chemicals are not expected to have reproductive and developmental toxicity potential.

In a reproductive and developmental toxicity study, pregnant SPF-Albino Wistar rats (20 animals/group) were administered 0, 10, 20 or 40 mg/kg bw/day of the salt daily by oral gavage on gestational days (GD) 5–15. All rats were euthanised on GD 20. A significant decrease in food consumption was observed in the animals treated with 40 mg/kg bw/day of the salt during the late gestational phase. At termination of the study, the animals treated with 40 mg/kg bw/day of the salt showed slightly increased uterine weights. No other signs of toxicity were observed. A reproductive and developmental no observed effect level (NOEL) of 40 mg/kg bw/day was established in this study (EC SCC, 2000).

Risk Characterisation

Critical Health Effects

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

Public Risk Characterisation

The chemicals are not on the ‘List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia’ (NICNAS, 2007).

The ASEAN, EU and New Zealand have prohibited the use of these chemicals in cosmetic products. Currently, there are no restrictions in Australia on using these chemicals in cosmetics or hair dye preparations. If the chemicals are used in hair dyes, in the absence of any regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk. The chemicals are not genotoxic and the likelihood of carcinogenic potential is low.

Given that the chemicals are not used for hair dyeing in Australia, it is unlikely that the public will be exposed to the chemicals.

Occupational Risk Characterisation

During product formulation, exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic acute and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals 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 the appropriate controls.

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

NICNAS Recommendation

Assessment of the chemicals is considered to be sufficient provided that the recommended classification is adopted, and labelling 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

While there is no identified use of the chemicals in Australia based on a review of voluntary surveys, should the chemical be used for hair dyeing in the future, it could potentially cause unreasonable risks to consumers and public risk management measures would need to be considered.

Work Health and Safety

The chemicals are 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	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 exposure to the chemicals 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 chemicals are 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 chemicals, 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

References

Benigni R and Bossa C 2011. Mechanisms of Chemical Carcinogenicity and Mutagenicity: A Review with Implications for Predictive Toxicology. Chem. Rev. 2011, 111, 2507-2536.

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Galleria Chemica. Accessed April 2015 at **http://jr.chemwatch.net/galeria/**

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

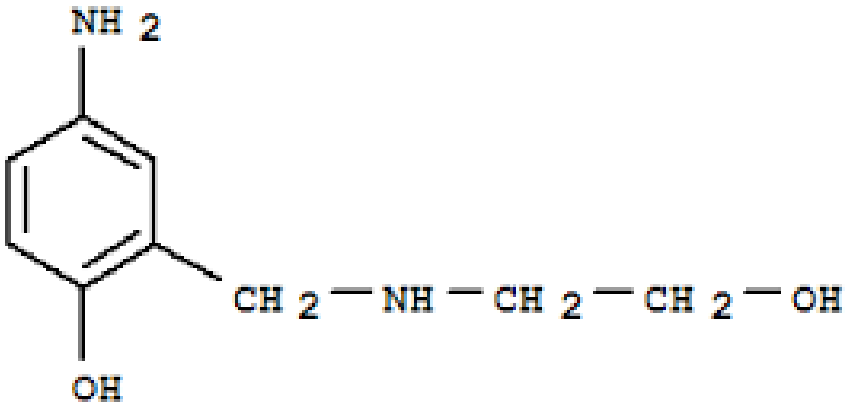
United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary. Accessed April 2015 at **http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp**

US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR). Accessed April 2015 at **http://actor.epa.gov/actor/faces/ACToRHome.jsp**

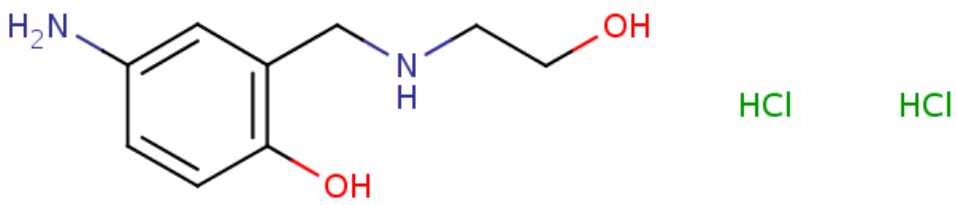
Last Update 24 April 2015

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]-** hydroxyethylaminomethyl-p-aminophenol
CAS Number	110952-46-0
Structural Formula	

	
Molecular Formula	C9H14N2O2
Molecular Weight	182.011

Chemical Name in the Inventory and Synonyms	**Phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]-, dihydrochloride** phenol, 4-amino-2-[[(2-hydroxyethyl)amino]methyl]-, hydrochloride (1:2) hydroxyethylaminomethyl-p-aminophenol HCl
CAS Number	135043-63-9
Structural Formula	

	
Molecular Formula	C9H14N2O2.2ClH
Molecular Weight	255.1434

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