Phenol, 5-[(2-hydroxyethyl)amino]-2-methyl-: Human health tier II assessment

11 April 2014

CAS Number: 55302-96-0

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.

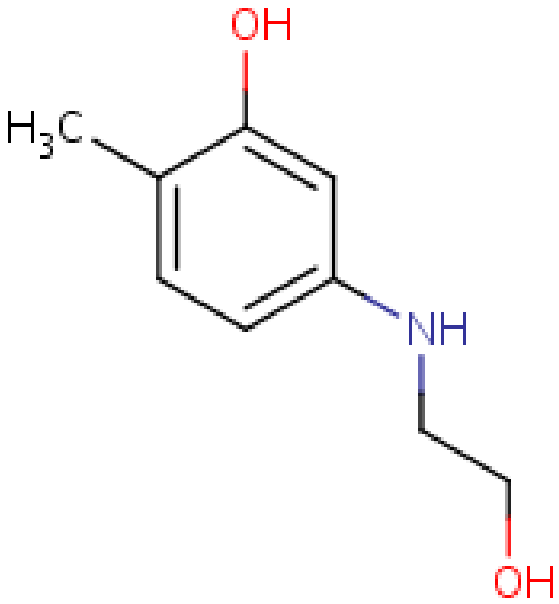
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-methyl-5-(N-beta-hydroxyethylamino)phenol 5-((2-hydroxyethyl)amino)-o-cresol 1-methyl-2-hydroxy-4-(beta-hydroxyethyl)aminobenzene 2-hydroxy-4-(beta-hydroxyethyl)aminotoluene 6-methyl-3-beta-hydroxyethylaminophenol
Structural Formula	
Molecular Formula	C9H13NO2
Molecular Weight (g/mol)	167.2
Appearance and Odour (where available)	Odourless powder
SMILES	c1(C)c(O)cc(NCCO)cc1

Import, Manufacture and Use

Australian

The chemical is on the 'List of chemicals used as hair dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

The chemical has reported cosmetic use in permanent hair dye preparations.

International

The following international uses have been identified through Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Household Products Database; and eChemPortal: OECD High Production Volume chemical program (OECD HPV) and the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemical has reported cosmetic use as:

- an oxidative coupler in permanent hair dye preparations, including to colour eyelashes.

The final concentration in oxidative hair dye formulations is indicated as 1.5 % after mixing with hydrogen peroxide (SCCP, 2006).

The chemical has reported site-limited use including:

- as an intermediate in the manufacturing of azo and sulfur dyes for dyeing furs and feathers (CIR, 1990).

Restrictions

Australian

No known restrictions have been identified.

This chemical is not listed in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) and it is not considered to be covered under the Schedule 6 entry for phenol in the SUSMP.

International

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

- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III – Part 2 List of substances provisionally allowed;
- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down;
- New Zealand Cosmetic Products Group Standard—Schedule 5 - Table 1: Components Cosmetic Products Must Not Contain Except Subject to the Restrictions and Conditions Laid Down.

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

In an in vitro study which used a typical oxidative hair dye formulation containing the chemical at 1.5 %, the percutaneous absorption of the chemical through human skin (obtained from four female donors) was found to be 2.58 µg/cm² (1.49-4.56 µg/cm²) (SCCP, 2006).

In another in vitro study with a dye base containing the chemical (stated as 0.1 mole of the chemical per 0.1 mole of p-phenylenediamine), the percutaneous absorption was found to be 0.044 % through the human skin and 0.025 % through the rat skin (CIR, 1990).

Acute Toxicity

Oral

The chemical has low acute oral toxicity.

The median lethal dose (LD50) in Sprague Dawley (SD) female rats was greater than 2000 mg/kg bw (OECD Test Guideline (TG) 420). Observed adverse effects included noisy breathing, piloerection and swollen abdomen in one animal. No deaths were recorded at 2000 mg/kg bw (SCCP, 2006).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is not irritating to the skin.

The undiluted chemical produced no skin irritation in New Zealand White rabbits (OECD TG 404) (SCCP, 2006). Details of the study are not available.

The chemical applied at 1.6 % and 5 % (in ethanol) on abraded and intact skin of six New Zealand White rabbits (occlusive patches for 24 hours), produced minimal skin irritation. The primary irritation index (PII) was 0.8 and 0.17, respectively (CIR, 1990).

Eye Irritation

The chemical is an eye irritant and warrants a hazard classification.

The undiluted chemical produced eye irritation in New Zealand White rabbits (OECD TG 405) (SCCP, 2006). Iris lesion scores were not available due to corneal opacity. The cumulative mean indices for corneal opacity, redness and chemosis were 2.33, 2.00 and 3.33, respectively. The effects were reversible within 72 hours with a marked decrease in chemosis (SCCP, 2006).

The chemical tested at 2 % concentration in an aqueous solution of carboxymethylcellulose (OECD TG 405) did not induce eye irritation in rabbits (SCCP, 2006). Similar results were obtained when a hair dye formulation containing the chemical (concentration of the chemical not stated) was applied to the eyes of six albino rabbits at 2 % in propylene glycol (CIR, 1990).

Sensitisation

Skin Sensitisation

The chemical is not a skin sensitiser.

The chemical was not found to induce dermal sensitisation when tested on CBA/J mice in a murine local lymph node assay (LLNA) conducted according to the OECD TG 429 (SCCP, 2006). Stimulation indices (SI) were 0.81, 1.31, 0.61, 0.53 and 0.44 at doses of 2.5, 5, 10, 25 and 50 %, respectively, while a SI of 8.39 was calculated for the positive control at 25 %.

In a guinea pig sensitisation study (test guidelines not indicated), the chemical at 5 % concentration in ethanol was applied to the skin of 12 Hartley guinea pigs for six hours; those were then allowed a 24-hour non-treatment period. This procedure was repeated nine times (induction phase). After a two-week non-treatment period, the chemical was applied to new sites on the skin for 24 hours (challenge phase). No positive results were recorded (CIR, 1990).

However, a hair dye fomulation containing the chemical (concentration not available) had a moderate potential for inducing an allergic response (sensitisation index of 0.6) in a Magnusson sensitisation test in 10 Hartley guinea pigs (CIR, 1990). This could be due to other ingredients in the hair dye formulation.

Observation in humans

Human studies are available with formulations containing the chemical at up to 17 % concentration showing minimal skin sensitisation reactions. Some reactions reported in these studies could be due to other ingredients in these formulations.

A cream formulation containing the chemical at 1.25 % was applied to the skin of 100 subjects, each with history of contact allergies, for 48 to 72 hours. A formulation containing 2 % p-toluenediamine was used as the positive control. Only 5 subjects showed positive reactions to the formulation with the chemical against 12 for the positive control. The study concluded the formulation containing the chemical was "a less potent sensitiser than the positive control" (CIR, 1990).

In another test, a formulation containing the chemical at 17 % was tested on 100 patients (dermal patches on the back for 48 hours). Only two subjects showed positive reactions: erythema, oedema and vesiculation. The study concluded that the formulation did not cause sensitisation on normal skin (CIR, 1990).

Repeated Dose Toxicity

Oral

The chemical is not considered to cause serious damage to health from repeated oral exposure.

In a 90-day study, SD rats were administered the chemical by gavage at doses of 0, 50, 220 or 1000 mg/kg bw/d (OECD TG 408). A no observed adverse effect level (NOAEL) of 220 mg/kg bw/d was reported based on the treatment-related effects at the highest dose: loud breathing, decreased muscular movement, coloured urine, hypersalivation, regurgitation and proteinuria in both males and females, and decreased body weight gain in females (SCCP, 2006).

In another 90-day study, SD rats were administered (gavage) a hair dye mixture containing the chemical (concentration not stated) with propylene glycol at 150 mg/kg bw/d. No deaths and no treatment-related effects were reported (CIR, 1990).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the negative results reported for in vivo studies, the chemical is not expected to be genotoxic.

The in vitro studies have shown some evidence of genotoxicity; but all in vivo studies indicated negative results, except for one positive finding at high dose possibly due to general toxicity (CIR, 1990).

Many in vitro studies conducted before 1990 have concluded that the chemical was not mutagenic (e.g. bacterial gene mutation assay (Ames) on *Salmonella typhimurium* strains, chromosome aberration test, forward mutation assay, mitotic gene conversion and unscheduled DNA synthesis tests) (CIR, 1990).

However, the recent in vitro studies indicated mixed results (SCCP, 2006):

- non-mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 at doses from 312.5 to 5000 µg/plate with and without metabolic activation (OECD TG 471);
- mutagenic in a micronucleus test (non-guideline) which used human lymphocytes without metabolic activation (at 547.2 µg/mL and for 20 hours treatment);
- mutagenic in a thymidine kinase (TK) gene mutation assay (OECD TG 476) with L5178Y mouse lymphoma cells after three hours of exposure at 0.313-10 mM without metabolic activation;
- non-mutagenic in a hypoxanthine-guanine phosphoribosyltransferase (HRPT) gene mutation assay (OECD TG 476) with L5178Y mouse lymphoma cells at doses 150 to 1670 µg/mL (10 mM maximum) with or without metabolic activation.

Most in vivo studies indicated negative results:

- non-mutagenic in a bone marrow micronucleus test (OECD TG 474) in rats exposed by gavage to a single dose of the chemical at 500 to 2000 mg/kg bw (SCCP, 2006);
- non-mutagenic in a bone marrow micronucleus test in CD1 mice exposed to the chemical at 1250 to 5000 mg/kg bw (CIR, 1990);

- non-mutagenic in another micronucleus test in Swiss mice exposed intraperitoneally (i.p.) to the chemical at 12.5 to 50 mg/kg bw (CIR, 1990);
- non-mutagenic in a micronucleus test in Swiss OF1 mice, administered with the chemical intraperitoneally at 800 mg/kg; however, the mice receiving the chemical at 1200 mg/kg i.p. had a significant increase in the frequency of micronuclei in the bone marrow cells, and this was assumed to be related to general toxicity (CIR, 1990);
- non-mutagenic in a sex-linked recessive lethal test on *Drosophila melanogaster* at 25 mM (CIR, 1990).

Carcinogenicity

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

In a two-year study (following the US National Cancer Institute (NCI) guidelines), the chemical was found non-carcinogenic when added to the drinking water of CGJ:BDF1 mice and F344/Ducrj rats at 1 or 2 % and 0.5 or 1 % respectively. Mean intakes of the chemical were estimated to be 1330 and 2620 mg/kg bw/d for male mice, 1530 and 3100 mg/kg bw/d for female mice, 246 and 485 mg/kg bw/d for male rats and 349 and 752 mg/kg bw/d for female rats, for low and high doses, respectively. Mortality among treated male mice was higher than the controls. In female mice, pituitary adenoma (benign tumours) frequency was higher in the controls (19 %) than treated groups (both 5 %), whereas leukaemia/lymphoma frequency was 33 % in controls, 40 % in the low dose and 16 % in the high dose groups. Mortality among female rats was higher in the controls than treated groups. In male rats, skin fibroma (begnin tumours) frequency was 6 % in the controls, 0 % and 17 % in the low and high dose groups respectively whereas leukaemia/lymphoma frequency was 22 % in the controls, 7 % and 2 % in the low and high dose groups respectively. No other significant tumour related effects were recorded. Based on the results, the SCCP concluded that the chemical was not carcinogenic under the conditions of the test (SCCP, 2006).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not expected to cause reproductive or developmental toxicity.

In a prenatal developmental toxicity study (OECD TG 414), the chemical was administered by gavage to SD mated female rats at 0, 100, 300 or 1000 mg/kg bw/d from days 6 to 19 of gestation. No deaths or clinical signs of toxicity were recorded. No treatment-related effects were observed in the litters. No sign of developmental toxicity (frequency of variations and malformations) was observed. A NOAEL of 1000 mg/kg bw/d was reported for both maternal toxicity and embryotoxicity (SCCP, 2006).

In another prenatal developmental toxicity study, the chemical was administered orally at doses of 0, 50, 300 or 1800 mg/kg bw/d to pregnant Charles River rats from days 6 to 15 of gestation. No deaths or clinical signs of toxicity were recorded. At 300 and 1800 mg/kg bw/d, post-implantation loss was slightly higher than the controls, and mean litter weight and mean foetal weight were lower than the controls at 1800 mg/kg bw/d. However, the NOAEL was reported as 1800 mg/kg bw/d due to lack of maternal toxicity and embryotoxicity. No sign of developmental toxicity (incidence of visceral and skeletal abnormalities) was observed (CIR, 1990; SCCP, 2006).

Risk Characterisation

Critical Health Effects

The chemical is an eye irritant. Apart from that, there are no other health concerns identified relevant for risk characterisation.

Data on acute or repeat dose dermal and inhalation toxicity are lacking. Toxicokinetic studies have shown low dermal absorption of the chemical through human skin (in vitro studies) at low concentrations anticipated in hair dye formulations. Therefore, dermal toxicity is not expected from exposure to the chemical at low concentrations in hair dyes.

The chemical is an odourless powder and therefore inhalation exposure is possible for workers at dye formulation plants.

Public Risk Characterisation

Although the public may be exposed to the chemical through the use in hair dyes/eyelash colouring products, given the low hazard of the chemical and anticipated low concentrations in these products, the chemical is not considered to pose an unreasonable risk to public health.

New Zealand and the European Union have restricted the use of this chemical in cosmetics. The chemical, once mixed under oxidative conditions, should not exceed 1.5 % in hair dyes or eyelash products.

Currently, there are no restrictions on using this chemical in hair dyes and eyelash colouring products in Australia. If the chemical is included in cosmetic products containing N-nitrosating agents, carcinogenic compounds could be formed (SCCP, 2012).

Occupational Risk Characterisation

During manufacturing of dyes, exposure of workers to the chemical may occur, particularly where manual or open processes are used. The level and route of exposure will vary depending on the work practices employed.

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

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

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]
Irritation / Corrosivity	Irritating to eyes (Xi; R36)	Causes serious eye irritation - Cat. 2A (H319)

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

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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

ChemIDPlus Advanced. Accessed March 2014 at http://chem.sis.nlm.nih.gov/chemidplus/

Cosmetic Ingredient Review (CIR) 1990. Final Report on the Safety Assessment of 2-Methyl-5-Hydroxyethylaminophenol. Journal of The American College of toxicology Vol. 9, No. 2, 1990.

Cosmetic Ingredients and Substances Database (CosIng). Accessed at http://ec.europa.eu/consumers/cosmetics/cosing/

European Chemicals Agency (ECHA), Classification and Labelling Inventory. Accessed at http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database

Galleria Chemica. Accessed at http://jr.chemwatch.net/galleria/

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

Personal Care Product Council (INCI Dictionary). Accessed at http://www.ctfa gov.org/jsp/gov/GovHomePage.jsp

Scientific Committee on Consumer Products (SCCP) 2006. Opinion on 2-methyl-5-hydroxyethylaminophenol COLIPA No. A31. Adopted by the SCCP during the 7th plenary meeting of 28 March 2006. Accessed at http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_040.pdf

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 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_090.pdf

US Household Products Database. Accessed March 2014 at http://householdproducts.nlm.nih.gov/advancedsearch.htm

Last update 11 April 2014

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