Phenol, 4-[(2-hydroxyethyl)amino]-3-nitro-: Human health tier II assessment

21 April 2016

CAS Number: 65235-31-6

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.

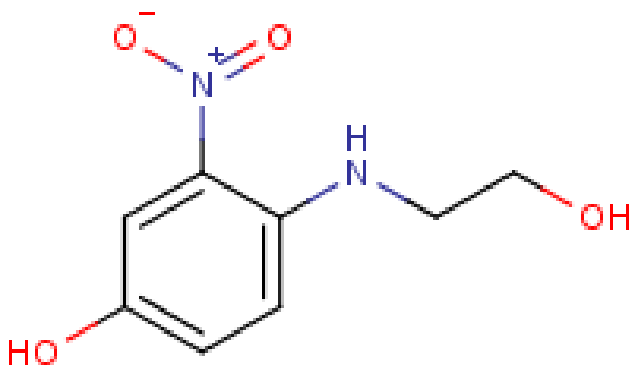
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1-hydroxy-3-nitro-4-(ß-hydroxyethyl)-aminobenzene 3-nitro-4-n-(beta-hydroxyethyl)aminophenol 3-nitro-p-hydroxyethylaminophenol 4-((2-hydroxyethyl)amino)-3-nitrophenol
Structural Formula	
Molecular Formula	C8H10N2O4
Molecular Weight (g/mol)	198.18
Appearance and Odour (where available)	Greenish-brown powder
SMILES	c1(NCCO)c(N(=O)=O)cc(O)cc1

Import, Manufacture and Use

Australian

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

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

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 chemical has reported cosmetic use as a hair dye substance in oxidative and non-oxidative hair dye products.

Restrictions

Australian

No known restrictions have been identified.

International

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

- The Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down: ‘(a) the maximum authorised concentration in the finished cosmetic product as a hair dye substance in non-oxidative hair dye products is 1.85 %; (b) after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 3.0 %; (c) do not use with nitrosating systems; (d) maximum nitrosamine content: 50 µg/kg; and (e) keep in nitrate-free containers’;
- The European Union (EU) Regulation (EC) No 344/2013 Annex III— List of substances which cosmetic products must not contain except subject to the restrictions laid down: ‘(a) hair dye substance in oxidative hair dye products; (a) after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 3.0 %; (b) hair dye substance in non-oxidative hair dye products; (b) the maximum concentration in ready for use preparation is 1.85 %; and for (a) and (b): — do not use with nitrosating agents, — maximum nitrosamine content: 50 µg /kg, — keep in nitrite-free containers’; and
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: ‘(a) the maximum authorised concentration in the finished cosmetic product as a hair dye substance in non-oxidative hair dye products is 1.85%; (b) in combination with hydrogen peroxide the maximum use concentration upon application is 3.0%; (c) do not use with nitrosating systems; (d) maximum nitrosamine content: 50 µg/kg; and (e) keep in nitrate-free containers’.

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

The chemical is minimally absorbed following dermal exposure.

An in vitro percutaneous absorption study was conducted according to the Organisation for Economic Co-operation and Development Test Guideline (OECD TG) 428 using human skin. The chemical (20 mg/cm^2) was applied to human skin at concentrations of 3 % in an oxidative hair dye formulation or 1.85 % in a semi-permanent hair dye formulation. Following 24 hours of application, the total amount of the chemical removed from the skin was 97.09 % under oxidative conditions and 98.11 % under semi-permanent conditions. The dermal absorption was 2.5 and 0.45 µg/cm^2 under oxidative and semi-permanent conditions, respectively (SCCP, 2006; CIR, 2009).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The effects observed were not sufficient to warrant hazard classification.

In an acute oral toxicity study, a median lethal dose (LD50) of >2000 mg/kg bw was established in Sprague Dawley (SD) rats. Observed sub-lethal effects included hypoactivity, piloerection, lateral recumbency and dyspnoea. Death was observed in 2/5 animals at 2000 mg/kg bw within four hours of treatment (SCCP, 2006; CIR, 2009).

In a separate acute oral toxicity study the chemical, administered at 3000 mg/kg bw, resulted in a 10 % mortality rate in albino Wistar rats and no mortalities in Swiss mice (CIR, 2009).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is not considered to be a skin irritant.

In a study conducted according to OECD TG 404, 0.5 mL of an aqueous solution of the chemical at a 6 % concentration was applied to a male New Zealand White rabbit on the anterior left flank, anterior right flank or posterior right flank for three minutes, one hour or four hours, respectively. Two additional animals were treated with the chemical for four hours when the first treated animal displayed persistently red discoloured skin. The two additional animals were euthanised 72 hours after treatment and skin samples were analysed microscopically. Red discoloured skin was observed in all animals and could have masked erythema. However, no skin dryness, crusts or oedema were observed in any of the animals. Microscopic examination did not show signs of skin irritation. The chemical was concluded to not have skin irritation properties in this study (SCCP, 2006; CIR, 2009).

In a separate skin irritation study, 0.5 mL of the chemical at a 4 % concentration was applied to both flanks of six male New Zealand White rabbits. Skin biopsies were performed 24 and 72 hours after application on three animals each. No signs of skin irritation were observed on microscopic examination (CIR, 2009).

Eye Irritation

The chemical is considered to be a slight eye irritant. The effects observed were not sufficient to warrant hazard classification.

In a study conducted according to OECD TG 405, 0.1 mL of an aqueous solution of the chemical at a 6 % concentration was instilled into the left conjunctival sac of three male New Zealand White rabbits. The eyes were not rinsed following instillation. Slight chemosis and very slight conjunctival redness (irritation scores were not provided) were observed in all animals on days 1–4 after instillation. The effects were reversed by day five. The chemical is concluded to be a slight eye irritant in this study (SCCP, 2006; CIR, 2009).

In a separate eye irritation study, 0.1 mL of an aqueous solution of the chemical at a 4 % concentration was instilled into the right conjunctival sac of six male New Zealand White rabbits. Chemosis, slight discharge and slight conjunctival enanthema (irritation scores were not provided) were observed when checked one hour after instillation. These effects were reversed within 48 hours. Folded irises were also observed but that effect was reversed within 24 hours. The chemical is concluded to be a slight eye irritant in this study (CIR, 2009).

Sensitisation

Skin Sensitisation

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

In a local lymph node assay (LLNA) conducted according to OECD TG 429, the chemical was applied to the dorsal surface of both ear lobes of female CBA/J mice (four animals/group) once daily for three consecutive days. The chemical, at test concentrations of 0.03, 0.09, 0.28, 0.83 or 2.5 %, produced stimulation indices (SI) of 2.18, 3.54, 6.36, 7.61 or 11.22, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 0.07 %, indicating extreme skin sensitisation potential (SCCP, 2006; CIR, 2009).

The chemical was tested in guinea pigs in a non-standard adjuvant test. In this study, erythema could not be scored due to red discoloured skin. The chemical was concluded to be non-sensitising to the skin in this study (CIR, 2009).

Repeated Dose Toxicity

Oral

Limited data are available. The available data suggest that the chemical has low repeated dose toxicity, based on results from an animal test following oral exposure.

In a sub-chronic oral toxicity test, SD rats (10 animals/sex/group) were administered the chemical at concentrations of 0, 40, 200 or 1000 mg/kg bw/day by gavage, seven days a week for three months. Red discolouration was observed in the fur and urine of the animals due to the dyeing properties of the chemical. In the 1000 mg/kg bw/day group, excessive salivation was observed from week seven of treatment. A slight yellow-orange discolouration of the choroid, with no alteration to the appearance of the choroid vessels, was observed in the animals of this group. Seven of the 10 males in the 1000 mg/kg bw/day group had dark discolouration of the thyroids due to finely granular lipofuscin or melanin pigment in the thyroid follicles. A no observed adverse effect level (NOAEL) of 200 mg/kg bw/day was established in this study (SCCP, 2006; CIR, 2009).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

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

In vitro studies

A bacterial point mutation assay was conducted according to OECD TG 471 in five *Salmonella typhimurium* strains (TA98, TA100, TA102, TA1535 and TA1537) up to a maximum concentration of 5000 µg/plate of the chemical, in the absence and presence of a rat liver metabolic activation system. Negative results were obtained in this study (SCCP, 2006; CIR, 2009).

A bacterial point mutation assay was conducted in five *S. typhimurium* strains (TA98, TA100, TA1535, TA1537 and TA1538) up to a maximum concentration of 1000 µg/plate of the chemical, in the absence and presence of a rat liver metabolic activation system. Negative results were obtained in this study (CIR, 2009).

A bacterial point mutation assay was conducted in five *S. typhimurium* strains (TA98, TA100, TA1535, TA1537 and TA1538) up to a maximum concentration of 500 µg/plate of the chemical, in the absence and presence of a rat liver metabolic activation system. The initial assay showed unusually high spontaneous mutation. The assay was repeated in TA100 and TA1538 in the presence of metabolic activation and negative results were obtained (CIR, 2009).

A mammalian cell gene mutation assay was conducted according to OECD TG 476 in the mouse lymphoma L5178Y cell line (tymidine kinase (tk) locus). The chemical was tested up to maximum concentrations of 9 or 10 mM in the absence or presence of a rat liver metabolic activation system, respectively. Significant increases in mutation frequency were observed in both the absence and presence of metabolic activation. The chemical is considered to possess clastogenic potential in this study (SCCP, 2006; CIR, 2009).

A mammalian cell gene mutation assay was conducted according to OECD TG 476 in the mouse lymphoma L5178Y cell line (hypoxanthine-phosphoribosyl-transferase (hprt) locus). The chemical was tested up to maximum concentrations of 1200 and 1600 µg/mL in the absence and presence of a rat liver metabolic activation system, respectively. Negative results were obtained in this study (SCCP, 2006).

An in vitro micronucleus assay was conducted according to OECD TG 487 in human lymphocytes from two healthy, non-smoking female donors. The chemical was tested up to maximum concentrations of 900 and 1980 µg/mL in the absence and presence of a rat liver metabolic activation system, respectively. Dose-dependent increases in the frequencies of micronucleated

binucleated (MNBN) cells were observed in both the absence and presence of metabolic activation. The chemical is considered to be genotoxic in this study (SCCP, 2006; CIR, 2009).

A chromosomal aberration test was conducted in the Chinese hamster ovary (CHO) cell line. The chemical was tested up to a maximum concentration of 0.4 mg/mL. No increases in the frequency of chromosomal aberrations were observed in the study (CIR, 2009).

In vivo studies

In an in vivo micronucleus assay in bone marrow cells conducted according to OECD TG 474 in SD rats (five animals/sex/group), the chemical was administered at concentrations of 0, 500, 1000 or 2000 mg/kg bw by oral gavage. Bone marrow cells were collected 24 or 48 (for the 0 and 2000 mg/kg bw groups only) hours after administration of the chemical and the polychromatic erythrocytes (PCEs) for each rat were examined. No increases in micronucleated PCEs were found and the chemical was concluded to be non-mutagenic in this study (SCCP, 2006; CIR, 2009).

In an in vivo micronucleus assay in bone marrow cells in male Swiss random-bred mice (four animals/group), the chemical was administered at concentrations of 0, 37.5, 75, 150 or 300 mg/kg bw by a single intraperitoneal (i.p.) injection. No increases in the frequency of micronuclei were observed in the animals. However, it is noted that the concentrations of the chemical applied in this study were not sufficient for an observation to be made (CIR, 2009).

In an in vivo micronucleus assay in bone marrow cells in CD-1 mice (five animals/sex/group), the chemical was administered at concentrations of 0, 2500, 5000 or 10000 mg/kg bw by oral gavage in two equal doses separated by 24 hours. No increases in the frequency of micronuclei were observed in the PCEs and the chemical was concluded to be non-mutagenic in this study (CIR, 2009).

Carcinogenicity

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

The weight of evidence from experimental in vitro and in vivo genotoxicity data (see **Genotoxicity** section) did not indicate the chemical to be genotoxic. However, 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. 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 a greater uncertainty about the reliability of the models since the performance statistics from the training set might not be applicable to the chemical. There are no existing expert rules based on the chemical stucture and reaction mechanism for carcinogenicity that can be used to identify with greater certainty whether this chemical is carcinogenic or not. Therefore, the available genotoxicity studies are used in the overall weight of evidence analysis to ascertain the carcinogenic potential of the chemical.

Reproductive and Developmental Toxicity

Limited data are available. The available data indicate that the chemical might be a developmental toxicant following oral exposure, warranting hazard classification.

In a prenatal development toxicity study conducted according to OECD TG 414, pregnant SD rats (20 animals/group) were administered 0, 100 or 1000 mg/kg bw/day of the chemical daily by oral gavage on gestational days (GDs) 6–15. All rats were euthanised on GD 20. Red discoloured urine was observed in all animals due to the dyeing properties of the chemical. In the 1000 mg/kg bw/day group, the number of viable foetuses was slightly decreased and the post-implantation loss was slightly increased. Two foetuses in this group had malformations including external astomia (congenital absence) of the face and brain, and polydactyly of the digits. External astomia is known to occur spontaneously in rats of this strain at a low incidence and the presence of polydactyly could not be confirmed by a re-examination of the specimen; therefore, the effects were considered as artifactual events. No other adverse effects were observed (SCCP, 2006; CIR, 2009). The SCCP (2006) considered ‘the NOAEL for developmental toxicity to be 100 mg/kg/day and the NOAEL for maternal toxicity 1000 mg/kg/day, which means that it can not be ruled out that teratogenic (external astomia) and embryotoxic (decreased number of live foetuses and increased post-implantation loss) effects occurred at dose levels which were not toxic to the pregnant dams’.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include skin sensitisation and developmental toxicity (i.e. possible risk of harm to the unborn child).

Public Risk Characterisation

The chemical is reported to be used in permanent and semi-permanent hair dye preparations in Australia (NICNAS, 2007).

The ASEAN, EU and New Zealand regulation agencies have restricted the use of this chemical in cosmetics. Following a safety evaluation, the SCCP (2006) concluded that the chemical ‘as an oxidative hair dye substance at a maximum concentration of 3.0% in the finished cosmetic product (after mixing with hydrogen peroxide) or as an ingredient in semi-permanent hair colouring products at a maximum concentration of 1.85% does not pose a risk to the health of the consumer, apart from its sensitising potential’.

Currently, there are no restrictions in Australia for using this chemical in cosmetic products. The risks could be mitigated by implementing concentration limits for use in hair dyes to address the risk of skin sensitisation.

Occupational Risk Characterisation

During product formulation, dermal exposure may 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 chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal exposure 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 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

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 cosmetic products (hair dye preparations) be managed through changes to the Poisons Standard, 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 be included in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons) with an appropriate concentration cut-off (exemption) for use in hair dye products.

Consideration should be given to the following:

- the chemical is an extreme skin sensitiser with a LLNA EC3 value = 0.07 %;
- the chemical meets the criteria for classification as a developmental toxin under the WHS framework (see **Work Health and Safety** section);
- the chemical is a secondary amine and is thus prone to nitrosation;
- overseas restrictions (refer to **International Restrictions** section) for use of the chemical in hair dyes are currently under review (SCCS, 2013) to take into account the sensitisation potential of the chemical;
- the chemical is listed in the SCCS Memorandum, which states that 'the assessment of the safety of hair dyes has been in terms of general toxicology rather than sensitization potential. Hence, "hair dye chemical X is safe for use at Y % in hair dyes intended for the consumer apart from its potential to cause skin sensitization"...hair dye substances which fulfil the criteria for classification as R43 (now Skin Sens 1 H317 according to CLP) may not be safe for consumers and that this is particularly so for hair dye substances categorised as extreme and strong sensitizers' (SCCS, 2013); and
- risk could be controlled by including appropriate SUSMP warning statements on labels for hair dye formulations containing the chemical at all concentrations. This statement could be similar to that specified under the EU Cosmetic Regulation (EC) No 344/2013 for phenol, 4-[(2-hydroxyethyl)amino]-3-nitro- (CAS No. 65235-31-6; reference number 248).

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]
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)	Suspected of damaging the unborn child - Cat. 2 (H361d)

[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 instructions 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:

- 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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