Phenol, 4-amino-3-methyl-: Human health tier II assessment

27 November 2014

CAS Number: 2835-99-6

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.

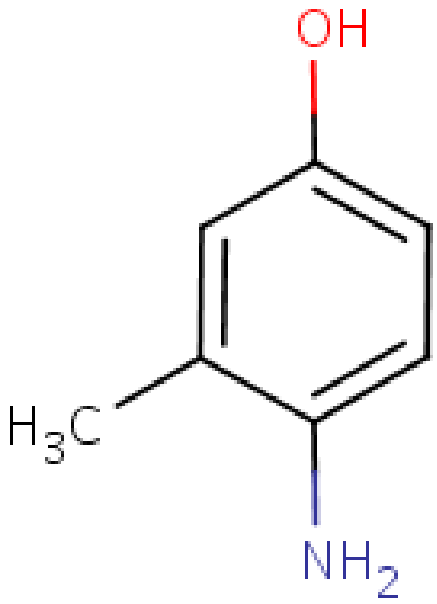
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4-amino-m-cresol 2-amino-5-hydroxytoluene 4-hydroxy-o-toluidine 2-methyl-4-hydroxyaniline 4-hydroxy-2-methylaniline
Structural Formula	
Molecular Formula	C7H9NO
Molecular Weight (g/mol)	123.15
Appearance and Odour (where available)	Crystals
SMILES	c1(N)c(C)cc(O)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).

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 (EU CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal: Organisation for Economic and Co-operative Development High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use as an oxidative coupler in hair dye preparations, and for colouring eyelashes (SCCS, 2012a).

The final concentration in oxidative hair dye formulations is indicated as 1.5 % after mixing with hydrogen peroxide (SCCP, 2005).

Restrictions

Australian

No known restrictions have been identified.

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 restrictions laid down; and
- New Zealand Cosmetic Products Group Standard—Schedule 5: 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

Percutaneous absorption of the radiolabelled chemical was investigated in PVG rats by applying (on 9 cm^2 surface) a 15 % solution in dimethyl sulfoxide (DMSO) or a hair dye formulation containing 1.5 % with hydrogen peroxide, for 24 hours (under occlusive conditions) and 30 minutes, respectively. Total recovery of the applied radioactivity was 95.7 and 97.9 % from the DMSO solution and 86.7 and 89.8 % from the formulation with hydrogen peroxide, for males and females, respectively. Absorption rates were higher from the DMSO solution (with 14.38 % or 231.7 µg/cm^2 absorbed), consistent with the skin-penetration enhancing properties of DMSO. Only 2.73 % (41.4 µg/cm^2) was absorbed from the formulation with hydrogen peroxide. Excretion occurred rapidly and mostly via urine (79.4–88.9 % excreted within 24 hours), and to a lesser extent via the faeces and lungs (SCCP, 2005).

In an in vitro assay, a decrease of 95.2 % and 89.8 % of the parent compound was detected within the 1.5 hour incubation in human and rat hepatocytes, respectively. Metabolite analysis revealed that the chemical undergoes intensive phase II metabolism, with sulfation of the phenol group in humans and rats (SCCP, 2005).

There was nearly 100 % absorption through human intestinal epithelial cells (in vitro study), indicating complete absorption of the chemical following oral administration (SCCP, 2005).

Acute Toxicity

Oral

Based on the limited information available, the chemical is considered to have moderate acute oral toxicity and warrants a hazard classification.

In acute oral toxicity studies conducted according to the OECD Test Guideline (TG) 401, the median lethal dose (LD50) in Wistar rats exposed to the chemical (by gavage) at 10% (in gum arabic) was 870 and 1010 mg/kg bw in males and females, respectively. The LD50 was 908 mg/kg bw in CF1 female mice. Observed sublethal effects included reduction of motor activity (SCCP, 2005).

In a study in which male CD-1 mice were exposed to the chemical at 1000, 1200, 1440, 1728 or 2074 mg/kg bw (method of administration not specified) for two consecutive days, most mice were deceased after two days. The LD50 was reported as 1000 mg/kg bw (CIR, 2004).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Only limited data are available, and therefore, no conclusion can be made on the skin irritation effects of the chemical.

When tested as a 3 % concentration by open application on the clipped skin of guinea pigs for five consecutive days (non guideline study), the chemical did not cause skin irritation (SCCP, 2005).

Eye Irritation

Only limited data are available and, therefore, no conclusion can be made on the eye irritation effects of the chemical.

When the chemical was administered as a 1.5 % concentration (in 50 % propylene glycol) to the left eye of five guinea pigs and not rinsed (non guideline study), it induced conjunctival erythema (score not available; no other macroscopic effects) in one animal according to the Draize scoring system. No irritation effects were noted in other animals at any observation times (0.5, 1, 2, 3, 4, 6 and 7 hours after application). The chemical, at a 1.5 % concentration 'may have minimal ocular irritant potential' (SCCP, 2005).

Sensitisation

Skin Sensitisation

The chemical is a skin sensitiser and warrants hazard classification.

A local lymph node assay (LLNA) with the chemical was conducted in CBA/J mice (OECD TG 429). The chemical was mixed either with water/acetone (1:1) and olive oil (4:1) or with DMSO and administered at the final concentrations of 0.5, 1.5, 3 or 5 % and 0.5, 1.5, 5 or 10 %, respectively. The estimated concentration required to produce a stimulation index of three (EC3) was 2.15 % when water/acetone/olive oil was used as a vehicle, and 1.45 % when DMSO was used as a vehicle. The chemical is, therefore, considered to be a moderate skin sensitiser (SCCP, 2005).

Repeated Dose Toxicity

Oral

Based on the data available for a sulphate salt of the chemical, the chemical is not expected to cause serious damage to health from repeated oral exposure.

In a 90-day study (non-guideline), a salt of the chemical (4-amino-m-cresol sulphate) dissolved in water was administered to Wistar rats (n = 20/sex/dose) by gavage at 0, 15, 60 or 120 mg/kg bw/d. A high-dose recovery group (four weeks following the end of exposure) was also examined. The absolute spleen weight was increased in high-dose females (statistically significant) and high-dose males, but not in the high-dose recovery groups. Other effects observed included discoloured urine at 50 and 120 mg/kg bw/d and a significant increase in creatinine values (but within the normal range) in females at 120 mg/kg bw/d. No mortalities occurred during the study. A no observed adverse effect level (NOAEL) of 60 mg/kg bw/d was established (CIR, 2004; SCCP, 2005).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the negative results reported for all in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

All in vitro studies with the chemical gave negative results:

- a bacterial gene mutation assay (OECD TG 471) using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 (3–5000 µg/plate plate incorporation test; 1–1000 µg/plate preincubation test without metabolic activation; and 3–2500 µg/plate preincubation test with metabolic activation) (SCCP, 2005);
- a bacterial gene mutation assay using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 with or without metabolic activation (up to 600 µg/plate; alone or mixed equally with 6 % hydrogen peroxide) (CIR, 2004);
- a thymidine kinase (tk) gene mutation test (OECD TG 476) with L5178Y mouse lymphoma cells at 0.048–6.25 µg/mL doses without metabolic activation; 0.391–47.5 µg/mL (first experiment) and 0.5–40 µg/mL (second experiment) with metabolic activation. In this study, a slight increase in mutation frequency was reported at 25 and 47.5 µg/mL with metabolic activation in the first experiment and a marginal effect at 40 µg/mL in the second, but these findings were not considered sufficient to demonstrate a 'clear and/or reproducible induction of gene mutations at the *tk*-locus' (SCCP, 2005); and
- two unscheduled DNA synthesis (UDS) tests (non-guidline) using rat hepatocytes (up to 100 µg/mL) (SCCP, 2005; CIR, 2004).

All in vivo studies with the chemical gave negative results:

- a micronucleus assay (OECD TG 474) in bone marrow cells of NMRI mice exposed to the chemical (dissolved in sodium chloride) by intraperitoneal (i.p.) injections at 20, 100 or 200 mg/kg bw (SCCP, 2005);
- a micronucleus assay (non-guideline) in which NMRI mice were exposed by gavage to the chemical (dissolved in DMSO) at 100, 333 or 1000 mg/kg bw (SCCP, 2005; CIR,2004);
- a sister chromatid exchange (SCE) assay in which Chinese hamsters were dosed with the chemical in aqueous solution, either orally at 100, 300, 1000, 1500 or 2000 mg/kg bw or, i.p. at 10, 30, 100, 300 or 400 mg/kg bw (CIR, 2004);
- an UDS test (non-guideline) in which Wistar rats were orally administered a single dose of the chemical at 60 or 600 mg/kg bw (for 16 hours) and at 1000 mg/kg bw (for four hours), prior to culturing hepatocytes for analysis after four hours (CIR, 2004; SCCP, 2005).

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of the chemical. Based on the available genotoxicity data and information available from Quantitative Structure Activity Relationship (QSAR) modelling, the chemical is not considered to be carcinogenic.

Experimental genotoxicity data (see **Genotoxicity** section) show that the chemical is not genotoxic, but QSAR modelling, using OASIS–TIMES, resulted in positive predictions for in vitro genotoxicity and negative predictions for in vivo genotoxicity. However, it should be noted that the chemical structure was out of the applicability domain of the model. If a prediction is out of the applicability domain of the model, it indicates that there is a greater uncertainty about the models's reliability since the performance statistics of the data in the model may not be applicable to the chemical. Thus, QSAR model predictions were considered to not outweigh the negative test results for genotoxicity within 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 pro-carcinogenic nitrenium ions. The highly reactive nitrenium ions can covalently bind to DNA, provided that they are sufficiently stabilised so as not to undergo further reactions. The stability of the nitrenium ions is correlated with mutagenicity, for example in the Ames test, with metabolic activation (Benigni & Bossa, 2011). However, the presence of two or more electron-donating groups, particularly in the *ortho*- and/or *para*-positions, reduces the metabolic N-hydroxylation and inhibits the formation of the

nitrenium ions (Vance and Levin, 1984; Shimizu and Yano, 1986; Serafimova et al., 2007). This is the case with the chemical due to the presence of the hydroxyl group in the *para*-position and another electron-donating group (methyl) at the *ortho*-position.

Reproductive and Developmental Toxicity

Based on a single prenatal developmental toxicity study available, the chemical is not expected to cause reproductive or developmental toxicity at the doses tested. However, the SCCP (2005) opinion stated that this study did not use the dose selection according to the OECD TG and therefore, 'a possible hazard is not adequately identified'.

In a prenatal developmental toxicity study (OECD TG 414), groups of 24 pregnant Wistar rats received the chemical (in water) at 0, 10, 40 or 80 mg/kg bw/d by gavage from gestation day (GD) 5–15. No deaths and no clinical signs of toxicity were observed. No significant differences were noted in the reproductive parameters such as the uterus and placenta weights, number of corpora lutea, number of foetuses, sex ratio, body weights, live birth index and postimplantation losses. One foetus with hydrocephaly (build-up of cerebrospinal fluid in the ventricles of the brain) at 40 mg/kg bw/d and two foetuses with minor visceral abnormalities (increased renal pelvic cavitation) at 80 mg/kg bw/d were observed (CIR, 2004). There were no statistically significant skeletal and visceral abnormalities of the foetuses compared with the controls, and therefore, a NOAEL of 80 mg/kg bw/d was established for maternal and developmental toxicity (CIR, 2004; SCCP, 2005).

According to SCCP (2005) opinion, the dose levels indicated in the above study were calculated based on the use concentration of a dye formulation (maximum concentration of chemical in dye = 3 %). The internal dose of 0.072 mg/kg bw was calculated considering the external exposure as 36 mg/person and using 0.2 % absorption.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects (skin sensitisation).

Data on acute or repeated dose dermal and inhalation toxicity are lacking. Systemic toxicity from dermal exposure is not expected to be significant due to the anticipated low concentration of the chemical in hair dyes and low dermal absorption rate (2.73 % at 1.5 % concentration; see **Toxicokinetics**).

Public Risk Characterisation

The chemical is reported to be used in permanent hair dye preparations in Australia. The chemical may also be in products to colour eyelashes (SCCS, 2012a).

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 (CosIng).

If the chemical is included in cosmetic products containing N-nitrosating agents, carcinogenic compounds could be formed (SCCP, 2012b).

Currently, there are no restrictions in Australia on using this chemical in hair dyes and eyelash colouring products. In the absence of any regulatory controls, the characterised critical health effects (skin sensitisation) have the potential to pose an unreasonable risk to public under the uses identified.

Occupational Risk Characterisation

During dye manufacture, exposure of workers to the chemical may occur, particularly where manual open processes are used. Inhaling the chemical dust from crystals may be possible for workers at dye formulation plants. The level and route of exposure will vary depending on the work practices employed.

Exposure to the chemical at low concentrations may occur while using formulated products (hair dyes, eyelash products) containing the chemical at hair salons and beauty parlours.

Given the systemic acute and local health effects, the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise dermal and ocular exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products 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 Schedule 5 of the *Poisons Standard* (the *Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) with an appropriate concentration cut-off (exemption) for hair dyes and eyelash colouring products.

Consideration should be given to the following:

- the chemical is a moderate skin sensitiser;
- limited data on eye and skin irritation; with a 1.5 % concentration the chemical may have a minimal eye irritation potential;
- lack of data on acute or repeated dose dermal and inhalation toxicity; and
- maximum concentration allowed in the European Union in hair dyes and eyelash products is 1.5 %.

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]
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 consumers

Products containing the chemical should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and 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:

- 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.

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