Phenol, 5-amino-2-methyl-: Human health tier II assessment

27 November 2014

CAS Number: 2835-95-2

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.

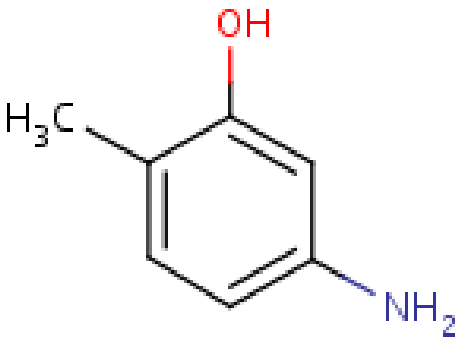
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4-amino-2-hydroxy-1-methylbenzene 4-amino-2-hydroxytoluene 5-amino-o-cresol 2-hydroxy-p-toluidine
Structural Formula	
Molecular Formula	C7H9NO
Molecular Weight (g/mol)	123.154
Appearance and Odour (where available)	Beige to brown crystalline powder
SMILES	c1(C)c(O)cc(N)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 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; US Household Product Database; and eChemPortal: the Organisation for Economic and Co-operative Development High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic uses:

- as an oxidative coupler in permanent hair dye preparations; and
- to colour eyelashes (SCCS, 2012a).

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

The chemical has reported domestic use as a stain remover.

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 provisionnally allowed;
- EU Cosmetics Regulation 1223/2009 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; (b) Products intented for colouring eyelashes; For (a) and (b): After mixing under oxidative conditions the maximum concentration applied to hair or eyelashes must not exceed 1.5%; (b) For professional use only'; 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

The chemical, administered as a single oral dose of 12.5 or 500 mg/kg bw to Wistar rats (according to OECD Test Guideline (TG) 417) was extensively absorbed, distributed and excreted in the urine (79 % and 89 % at high and low doses, respectively). The main metabolic pathway was sulfation. The main metabolites detected in the urine were glucuronide, sulfate and N-acetyl (or N-acetylated and-sulfated metabolite) (SCCS, 2006).

In the same study, dermal application of the chemical at 12.5 or 37.5 mg/kg bw (0.15 or 0.45 mg/cm^2 skin) for 24 hours showed a high dermal absorption rate. The excretion was mainly via urine (18 % and 39 % at high and low doses, respectively). The main metabolic pathway was N-acetylation (SCCS, 2006).

In vitro studies indicated that the chemical is rapidly and completely metabolised in human, rat and mouse hepatocytes (within four hours in both human and rat hepatocytes). The analysis of metabolites indicated extensive phase II metabolic activity with sulfation of the phenol group and, to a lesser extent, via N-acetylation in all three species (SCCS, 2006).

Acute Toxicity

Oral

The chemical has low acute oral toxicity.

The median lethal dose (LD50) in rats is 3600 mg/kg bw (CIR, 1989; SCCS, 2006). Observed sublethal effects included lethargy, piloerection and decreased respiration rate.

Dermal

The chemical has low acute dermal toxicity.

The dermal LD50 in female New Zealand White rabbits was greater than 5000 mg/kg bw. No signs of toxicity were observed (CIR, 1989).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Limited data are available. The chemical is not a skin irritant up to a 10 % concentration.

In a study on three albino rabbits (no guideline indicated), occlusive application of the chemical at a 2.5 % aqueous solution on shaved skin for 24 hours, did not induce signs of skin irritation within 72 hours after patch removal. The primary irritation index was zero (CIR, 1989; SCCS, 2006).

In a combined local lymph node assay (LLNA) and irritancy assay (study not validated by the National Toxicology Program (NTP)), no signs of irritation were observed in mice exposed to the chemical at 0.625 % and 10 % concentrations (NTP, 2006).

Eye Irritation

Limited data are available. The chemical is not an eye irritant up to a 2.5 % concentration.

In a study with three albino rabbits (no guideline indicated), a 2.5 % aqueous solution of the chemical was instilled into one eye of each rabbit for 10 seconds. It induced a slight conjunctival redness (Draize score = 1), but the effect was reversible within 24 hours. As no other effects were observed, the chemical was not considered to be an eye irritant (CIR, 1989; SCCS, 2006).

Sensitisation

Skin Sensitisation

The chemical is considered to be a strong to moderate skin sensitiser, warranting a hazard classification.

Two LLNAs were conducted (OECD TG 429) in female CBA mice (n = five/concentration), using two different vehicles (first assay with water/acetone 1:1 mixed with olive oil at 4:1 and the second assay with dimethyl sulfoxide (DMSO)). All test concentrations of 0.5, 1.5, 3 and 5 % produced a stimulation index (SI) over three (3.2, 5.9, 5.3 and 9.4, respectively) in the first assay; only the 5 % concentration produced a SI over three (SI = 3.9) in the second assay. The positive control, para phenylenediamine at a 1 % concentration, exhibited an SI of 31.2 in the first assay and 12.7 in the second. The effective concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 0.44 % in the first assay and 3.4 % in the second, indicating a strong and moderate sensitising potential, respectively (SCCS, 2006).

In another LLNA study (not validated by the NTP), BALB/c mice exposed to the chemical at concentrations of 0.625, 1.25, 2.5, 5 and 10 % (in acetone:olive oil) exhibited a significant increase of lymphocyte proliferation at 5 % and 10 % concentrations, but only the highest dose induced a three-fold increase. The chemical was reported to be weakly sensitising (NTP, 2006).

In an open epicutaneous test with albino guinea pigs, the chemical at a 3 % concentration (in a vehicle containing 2 % Natrosol 250HR, 2 % Tween 80, 0.05 % sodium sulfite, 82.95 % deionised water and 10 % isopropanol) induced positive reactions in 4/19 animals (CIR, 1989).

In a Magnusson Kligman study in female Hartley guinea pigs, the chemical was used at 1 % and 25 % in propylene glycol for intradermal and epidermal induction applications, respectively. Challenge with epidermal application of the chemical at a 25 % concentration produced a positive reaction in 4/10 guinea pigs (CIR, 1989; SCCS, 2006).

Repeated Dose Toxicity

Oral

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

A 13-week oral study (no test guideline indicated) was conducted in Him:OFA rats with the chemical at 0, 300, 900 or 2700 mg/kg bw/d. Reported toxic effects included irritated stomach mucosa, hepatotoxicity and effects on red blood cells at all doses, although the effects were less severe at 300 mg/kg bw/d (SCCP, 2006).

In another study, Him:OFA rats were administered the chemical by oral gavage doses of 0, 20, 60 or 180 mg/kg bw/d for 90 days (no test guideline indicated). No significant toxic effects were observed and the no observed adverse effect level (NOAEL) was reported to be 180 mg/kg bw/d (SCCP, 2006).

In a 90-day study (no test guideline indicated) Sprague Dawley (SD) rats were administered the chemical at 0, 0.3, 1 or 3 % in the diet (mg/kg bw/d doses not available). The treatment-related effects observed in rats were discoloured fur, decreased body weight, a hypothyroid state marked by decreased thyroxine (T4) hormone level, increased cholesterol concentration, sporadic microfollicular goitre, and anaemia. There were no deaths and no signs of serious toxicity. Following the end of treatment and examination periods, the rats were continued on the study for another three months. No additional effects related to treatment were observed (CIR, 1989).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the negative results observed in several in vivo genotoxicity studies, the chemical is not expected to be genotoxic.

Positive results were observed in most in vitro genotoxicity studies:

- a bacterial gene mutation test (OECD TG 471) in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA102 produced negative results (35–5000 µg/plate) with or without metabolic activation (SCCP, 2006);
- a bacterial gene mutation test in *S. typhimurium* strains TA100 (from 1000 µg/plate), and TA97 and TA98 (from 333 µg/plate) showed positive results with metabolic activation (CIR, 1989);
- a gene mutation test with mouse lymphoma cells (OECD TG 476) produced positive results with metabolic activation (from 50–1500 µg/plate) or without metabolic activation (2.5–500 µg/plate) (SCCP, 2006);
- a micronucleus test with human lymphocytes (OECD draft TG 487) was positive at 206.7 µg/plate without metabolic activation, and at 788.5 µg/plate with metabolic activation (SCCP, 2006); and
- a Comet assay with Chinese hamster V79 cells showed a clear dose-dependent increase in DNA damage of cells from 308 µg/plate; the metabolite 4-acetylamino-2-hydroxytoluene did not induce any DNA damage at 413 µg/plate (SCCP, 2006).

All in vivo genotoxicity studies gave negative results:

- two bone marrow micronucleus tests (OECD TG 474) conducted in NMRI mice were negative at oral doses of 125, 250 or 500 mg/kg bw and intraperitoneal doses of 20, 100 or 200 mg/kg bw (SCCP, 2006);
- a micronucleus test in CFY rats with two oral gavage doses of the chemical at 4000 mg/kg bw induced signs of toxicity (convulsions, agitation, lethargy), but no induction of micronuclei (CIR, 1989);
- an unscheduled DNA synthesis (UDS) test (OECD TG 486) in SD rats with oral doses of the chemical at 500, 1000 or 2000 mg/kg bw showed no significant increase in the mean number of nuclear grain counts (SCCP, 2006);
- a Comet assay in Wistar rats administered (gavage) the chemical twice at 500, 1000 or 2000 mg/kg bw had inconclusive results; rats dosed again (twice) with the highest dose of 2000 mg/kg bw did not show genotoxic effects in the the stomach or the urinary bladder (SCCP, 2006); and
- a dominant lethal assay in SD rats receiving the chemical in the diet at 0.3, 1 or 3 % for about 20 weeks did not show any toxic or dominant lethal effects (CIR, 1989).

A study was conducted in 10 human volunteers by applying a hair dye formulation containing the chemical (concentration not available) mixed with 3–6 % hydrogen peroxide at a 1:1 ratio (0.5–4 g of active substance/person). The application was repeated 13 times every 3–5 weeks. There was no evidence of sister chromatid exchange in the chromosomes of peripheral lymphocytes (CIR, 1989).

Carcinogenicity

No animal carcinogenicity data are available.

Based on the available genotoxicity data for the chemical and its N-acetylated metabolites, and information available from Quantitative Structure Activity Relationship (QSAR) modelling, the chemical is not considered to be carcinogenic.

The experimental genotoxicity data with the chemical (see **Genotoxicity** section) show positive results in the in vitro tests and negative results in the in vivo tests. QSAR modelling using OASIS–TIMES resulted in equivocal predictions for the in vivo models. The applicability domain of the models was satisfied, indicating that the performance statistics of the data in the models were applicable to the chemical.

Primary aromatic amines can be metabolically activated to reactive electrophiles as an initial step in a carcinogenic mechanism of action. This usually involves the activation of N-hydroxylamine metabolites with enzymatic reaction and eventual formation of pro-carcinogenic nitrenium ions. The highly reactive nitrenium ions can covalently bind to DNA, provided that they are sufficiently stable to not undergo further reactions. The stability of the nitrenium ions is correlated with mutagenicity, for example in an Ames test with metabolic activation (Benigni and Bossa, 2011). For the chemical, an Ames test, conducted in accordance with OECD TG 471, showed negative results, indicating a lower likelihood of carcinogenic potential.

N-acetylation of the chemical is one of the metabolic pathways observed in human, rat, and mouse hepatocytes (see **Toxicokinetics**). The N-acetylated metabolites of the chemical were found to give negative results in Ames tests and in vivo micronucleus tests with cultured human lymphocytes (Zeller and Pfuhler, 2014).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not expected to have reproductive and developmental toxicity. However, some reproductive and developmental effects were reported at very high doses in rats (at 1000 mg/kg bw/d), probably due to severe maternal toxicity effects.

In a one-generation reproductive toxicity study (OECD TG 415), Wistar rats were administered the chemical during the pre-mating (70 days for males and 14 days for females), mating, gestation and lactation periods, by oral gavage at doses of 0, 40, 200 or 1000 mg/kg bw/d. There were no treatment-related effects at 40 mg/kg bw/d. Discolouration of the urine was the only effect observed in both males and females at 200 mg/kg bw/d. Increased mean duration of gestation, birth difficulties, and decreased number of pups at birth were observed at the highest dose. Increased post-natal loss in dams, an increased incidence of clinical signs and decreased body weights in the offspring were also noted at 1000 mg/kg bw. An increased incidence of mortality was reported at the highest dose (2/24 males and 5/24 females). The NOAEL for reproductive toxicity was

reported to be 200 mg/kg bw. The effects on reproductive function and development at the highest dose could be linked to the severe toxic effects in parental animals (SCCP, 2006).

In a teratogenicity study, female SD rats were orally administered the chemical at doses of 0, 20, 60 or 180 mg/kg bw/d, from day 6 to day 15 post coitum. No treatment-related effects were observed in dams or in foetuses. A NOAEL of 180 mg/kg bw/d was established for both maternal and embryo toxicity (SCCP, 2006).

Risk Characterisation

Critical Health Effects

The critical health effect identified for risk characterisation is skin sensitisation.

Only limited data are available for eye and skin irritation, indicating that concentrations up to 2.5 % are not irritating to the eyes and concentrations up to 10 % are not irritating to the skin. Data on acute or repeated dose inhalation toxicity are lacking.

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, 2012 a).

Many countries, including New Zealand and the European Union, have restricted the use of this chemical in cosmetics. Following a safety evaluation, the SCCP (2006) concluded that the use of the chemical 'as an oxidative hair dye substance at a maximum concentration of 1.5 % in the finished cosmetic product (after mixing with hydrogen peroxide) does not pose a risk to the health of the consumer, apart from its sensitising potential'.

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

Currently, there are no restrictions in Australia on using this chemical in cosmetics/hair dyes or 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 manufacture, exposure of workers to the chemical may occur, particularly where manual or open processes are used. Inhaling the chemical dust from crystals may be possible for workers at formulation plants.

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

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

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 hair dye preparations and eyelash colouring 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 6 of the *Poisons Standard* (the *Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) for use in hair dyes and eyelash colouring products.

Consideration should be given to the following:

- the chemical is a strong to moderate skin sensitiser;
- limited data on eye and skin irritation;
- lack of data on acute or repeated dose inhalation toxicity and repeated dose dermal toxicity;
- overseas restrictions for use of this chemical in hair dyes. The maximum concentration allowed in an oxidative hair dye substance is 1.5 % (after mixing with hydrogen peroxide) (SCCP, 2006); and
- that as many hair dye formulations come under Schedule 6 due to p-phenylenediamine content, inclusion in Schedule 6 with a cut-off is not likely to give an effective upper concentration limit for the chemical.

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]
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 the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation 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;
- 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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