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

26 October 2018

CAS Number: 2835-98-5

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.

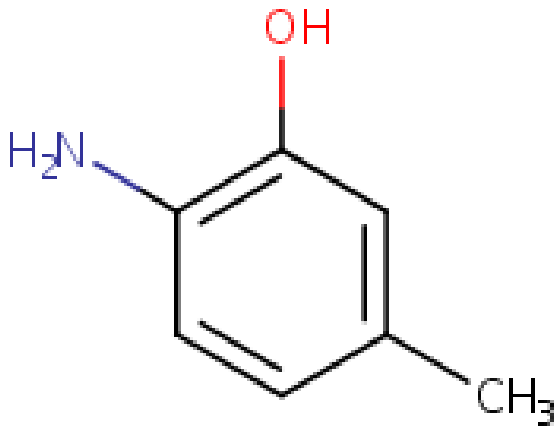
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-amino-5-methylphenol 6-amino-m-cresol
Structural Formula	
Molecular Formula	C7H9NO
Molecular Weight (g/mol)	123.1
Appearance and Odour (where available)	beige to red-brown crystalline powder
SMILES	c1(N)c(O)cc(C)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 Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Cosmetic Ingredients Review (CIR 2004); the OECD High Production Volume chemical program (OECD HPV); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the European (EU) Scientific Committee on Consumer Safety Opinion (SCCS, 2012).

The chemical has reported cosmetic use as an oxidative coupler in hair dye preparations. The maximum concentration in oxidative hair dye formulations is indicated as 1.5 % after mixing with hydrogen peroxide (SCCS, 2012).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’) (Galleria Chemica).

The SCCS opinion states that the chemical has 'genotoxic potential and is not safe for consumers when used in oxidative hair dye formulations with maximum on-scalp concentration of 1.5 % '(SCCS, 2012). The European Commission Scientific Committees Newsletters, 2012 reported that the chemical is not safe for hair dye use.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica).

Exposure limits of 22 mg/m^3 time weighted average (TWA) and 44 mg/m^3 short-term exposure limit (STEL)/MAK in different countries such as Argentina, Austria, Netherlands, Egypt, Denmark and the United States of America (USA) - Idaho.

Health Hazard Information

Toxicokinetics

In a percutaneous absorption conducted in accordance with OECD Test Guideline (TG) 417, radiolabelled chemical was administered to Sprague-Dawley (SD) Crl: CD Br rats as follows: Groups 1 and 5 received the chemical in PEG400/0.9 % saline (40:60) vehicle intravenously (i.v.) at 25 mg/kg bw; Groups 2, 3, 6 and 7 received the chemical in PEG400 at 25 or 400 mg/kg orally; and Groups 4 and 8 received the chemical in acetone/water (1:1) as a dermal application at 10 mg/kg bw (0.3 mg/cm^2), respectively. Total recoveries of 92 % (group 1, i.v. route) and 98 % (group 4, dermal route) of the applied dose were reported. Total absorption was 99 % (25 mg/kg bw) and 96 % (400 mg/kg bw) for oral doses, and 5.1 % (0.019 mg/cm^2) for dermal dose. Excretion after oral dose occurred rapidly via urine (84–91 % and to a lesser extent via the faeces (SCCS, 2012).

In an in vitro bioavailability study using human intestinal epithelial cell line TC-7 nearly 100 % absorption was achieved, indicating complete absorption of the chemical following oral administration (SCCS, 2012).

In an in vitro assay, metabolism of the parent compound at 82.5, 82.8 and 62.4 % was detected within the 1.5 hour incubation period with human, mouse and rat hepatocytes, respectively. Metabolic analysis indicates that the chemical undergoes intensive phase II metabolism, with sulfation of the phenol group in humans and rats (SCCS, 2012).

Acute Toxicity

Oral

Based on the limited information available, the chemical is considered to have moderate acute oral toxicity and warrants hazard classification (see **Recommendation** section).

In an acute toxicity study, the median lethal dose (LD50) in Wistar rats and CF/CBL mice exposed to the chemical by gavage at 10% (in distilled water) was 1225 and 1375 mg/kg bw (female and male rats); and 750-1225 and 1020 mg/kg bw (female and male mice), respectively. Observed sublethal effects included sedation, tremor, accelerated respiration and death (SCCS, 2012).

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 the chemical was applied as a 1 % aqueous solution on the clipped abraded skin of albino guinea pigs (SPF) (n=10 females), 3 times/day, for two consecutive days (non guideline study), the chemical did not cause skin irritation (SCCS, 2012).

Eye Irritation

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

When the chemical was administered as a 1 % aqueous solution (0.1 mL) to the left eye of Pirbright guinea pigs (SPF) (n=5 females) and not rinsed (non guideline study), the chemical did not cause eye irritation (SCCS, 2012).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is a skin sensitiser and warrants hazard classification (see **Recommendation** section).

In a local lymph node assay (LLNA) (OECD TG 429), the chemical was mixed with either DMSO (vehicle 1) or acetone:water (1:1) mixed with olive oil (3:1) (vehicle 2) at concentrations of 0.5, 1.5, 5.0 or 10 % (in vehicle 1) or 0.5, 1.5, 3.0 or 5.0 % (in vehicle 2). The stimulation indices for the chemical concentrations in vehicle 1 were 1.3, 1.5, 4.2 and 8.0 and for chemical in vehicle 2 were 0.9, 2.0, 29.3 and 33.9 %, respectively. The estimated concentration required to produce a stimulation index of three (EC3) was 3.44 % (vehicle 1) and 1.55 % (vehicle 2). The chemical is considered to be a moderate skin sensitiser (SCCS, 2012).

Repeated Dose Toxicity

Oral

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

In a 90-day study (non-guideline), the chemical was administered as 10 % suspension (in 5% gum arabic) to Wistar rats (n= 20/sex/dose) by gavage at 800 mg/kg bw/day (reduced to 500 mg/kg bw/day from week 6 onwards). Significant reduction in food consumption, body weight and body weight gain were reported. Other effects observed included tyrosine crystal sedimentation in the urine; increased mean liver, kidney and spleen weight; elevated bilirubin (both sexes) and reduced iron levels in males. No mortality was recorded. A no observed adverse effect level (NOAEL) could not be determined (SCCS, 2012).

In a 28-day non-guideline study, the chemical dissolved in 0.5 % carboxymethylcellulose was administered to Wistar BOR:WisW (SPF/TNO) rats (n = 120/sex/dose) by gavage at 0, 50, 250 or 500 mg/kg bw/day. Reduced body weight gain, increased water consumption and increased urine excretion were observed in the first two weeks of treatment. Other effects observed included reduction in erythrocyte counts, and haemoglobin, haematocrit and iron levels; increase in reticulocyte counts, haematocrit, mean corpuscular volume (MCV) and prothrombin time. No mortality was observed during the study. Autopsy findings included significant increases in liver, kidney and spleen weights. A NOAEL of 50 mg/kg bw/day was reported (CIR, 2004; SCCS, 2012).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is considered to be genotoxic, warranting hazard classification (see **Recommendation** section).

Several in vitro assays conducted using the chemical showed both positive and negative results. These included:

- bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA100, TA 1535, TA 1537 and TA 102 (0–5000 µg/plate incorporation test); positive results were seen in TA100, with and without metabolic activation (CIR, 2004; SCCS, 2012);
- thymidine kinase (tk) gene mutation test (OECD TG 476) in L5178Y mouse lymphoma cells at 0.1–25 µg/mL doses (first experiment) and 10–160 µg/mL doses (second/verification experiment) without metabolic activation; 0.5–100 µg/mL doses with metabolic activation. In this study, a concentration dependent statistically significant increase in mutation frequency was observed in both experiments with metabolic activation. The occurrence of increases in small colonies demonstrate a 'clastogenic rather than a direct mutagenic effect' of the chemical. Negative results were observed in the absence of metabolic activation (SCCS, 2012);
- micronucleus test (draft OECD TG 487) in human lymphocytes at 8.59–26.21µg/mL (first experiment) and 17.18–26.84 µg/mL (second experiment) without metabolic activation; 34.68–67.73 µg/mL (first experiment) and 25–50 µg/mL (second experiment) with metabolic activation. An increase in lymphocytes with micronuclei was seen at 26.21 µg/mL (first experiment) and a concentration dependent statistically significant increase in micronucleus formation was observed in the second experiment, without metabolic activation. No relevant increases were observed in experiments with metabolic activation. These findings were considered sufficient to demonstrate that the chemical is "genotoxic (clastogenic and/or aneugenic) in cultured human peripheral blood lymphocytes (SCCS, 2012); and
- positive results were seen in the absence of metabolic activation in an *in vitro* alkaline comet assay with Chinese hamster lung (V79) cells (CIR, 2004; SCCS, 2012).

The chemical gave some positive results for in vivo genotoxicity assays. These included:

- the chemical gave a positive result in a mammalian erythrocytes micronucleus test (OECD TG 474) in polychromatic erythrocytes of Crl:CD (SD) BR rats exposed to the chemical (5-methyl ortho-aminophenol) in 2.5 % aqueous hydroxypropylcellulose (HPC) by intraperitoneal (i.p.) injection at 100, 200 or 400 mg/kg bw. Dose-dependent increases in the number of cells with micronuclei were observed in all treated animals, but were significant only in males at 400 mg/kg bw. Clinical observations included irregular respiration, hypoactivity, recumbency, paleness, salivation, cyanosis, squinted eyes, flattened posture, urine staining, tremors/convulsions and piloerection (SCCS, 2012); and
- the chemical tested negative in an unscheduled DNA synthesis test (UDS) (draft OECD 486) in male Wistar HanIbm:WIST (SPF) rats orally treated with the chemical at 0, 150 or 1500 mg/kg bw in 0.5 % aqueous solution of carboxymethylcellulose. No relevant increases in the mean net nuclear grain count was observed in the cultured hepatocytes for 2 and 16 hour treatment periods (CIR, 2004; SCCS, 2012).

The metabolite, N-acetyl-2-amino-5-methylphenol, was genotoxic in an *in vitro* micronucleus assay. It caused a significant, concentration-dependent increase in the number of cells containing small nuclei (SCCS, 2012).

Although the chemical does not induce gene mutations in vivo, its genotoxic potential was evident by positive clastogenic and/or aneugenic effects in the in vivo micronucleus test (SCCS, 2012).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Based on a single teratogenicity study, the chemical is not expected to cause reproductive or developmental toxicity at the doses tested.

In a teratogenicity study (non-guideline), groups of 23 pregnant female SD rats received the chemical in water at 0, 5, 50 or 200 mg/kg bw/day by gavage during gestation days (GD) 6–15. No deaths and no clinical signs of toxicity were observed. No significant differences in body weights; body weight gains; or any reproductive or developmental effects were observed. A NOAEL of 200 mg/kg bw/day was established for maternal and developmental toxicity (CIR, 2004; SCCS, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (mutagenicity), systemic acute effects (acute toxicity from oral exposure) and local effects (skin sensitisation).

Public Risk Characterisation

The chemical is reported to be used in permanent hair dye preparations in Australia. Canada has restricted the use of this chemical in cosmetics. The SCCS Opinion, 2012 has reported that the chemical is not safe when used in oxidative hair dye formulations with a maximum concentration of 1.5 % on the scalp.

The chemical and its metabolite, N-acetyl-2-amino-5-methylphenol are found to be genotoxic (SCCS, 2012).

Currently, there are no restrictions in Australia on this chemical when used in hair dye products. In the absence of any regulatory controls, the characterised critical health effects (skin sensitisation and genotoxicity) have the potential to pose an unreasonable risk to the public under the identified use. The risk could be mitigated by implementing restrictions for the use of the chemical in hair dyes.

Occupational Risk Characterisation

During product formulation, oral and dermal exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. The level and route of exposure will vary depending on the work practices employed.

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

Given the critical systemic long-term; acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral and 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 HCIS (Safe Work Australia) (see **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 cosmetics and/or domestic products be managed through changes to poisons scheduling, 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

Due to the toxicity profile at concentrations reported to be potentially in use, the chemical is recommended for scheduling for inclusion in the Australian Poison Standard with the objective of prohibiting the sale, supply and use in cosmetic products.

Matters to be taken into consideration include:

- the known use of the chemical in permanent hair dye preparations in Australia;
- the chemical is acutely toxic by oral route, genotoxic and a moderate sensitiser;
- limited data on eye and skin irritation; the chemical may have irritation potential when used at the reported use concentration of 1.5 %, which is higher than the concentration tested in the available data;
- lack of data on acute or repeated dermal and inhalation toxicity; and
- the chemical is restricted for cosmetic use overseas. The restrictions on the use of the chemical in cosmetic products in Canada and those proposed in the European Union (see **International restrictions** section) are considered appropriate in Australia, to mitigate the risk.

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1A (H317)
Genotoxicity	Not Applicable	Suspected of causing genetic defects - Cat. 2 (H341)

[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 oral and 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 that 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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