Phenol, 2-amino-4-nitro-: Human health tier II assessment

11 April 2014

CAS Number: 99-57-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

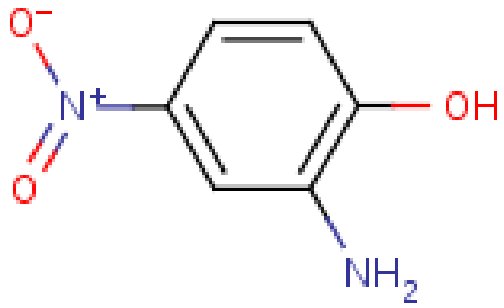
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-amino-4-nitrophenol 1-amino-2-hydroxy-5-nitrobenzene 1-hydroxy-2-amino-4-nitrobenzene 1-nitro-3-amino-4-hydroxybenzene 2-hydroxy-5-nitroaniline
Structural Formula	
Molecular Formula	C6H6N2O3
Molecular Weight (g/mol)	154.124
Appearance and Odour (where available)	Orange odourless solid
SMILES	c1(O)c(N)cc(N(=O)=O)cc1

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; Galleria Chemica; the Substances and Preparations in the Nordic countries (SPIN) database; 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 eChemPortal: OECD 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 use:

- as an oxidative coupler in permanent hair dye preparations.

The chemical has reported site-limited use including as:

- an intermediate in manufacturing mordant and acid dye (for dyeing leather, nylon, silk, wool and fur);
- an intermediate in manufacturing certain azo dyes (IARC, 1993);
- an antioxidant and light stabiliser in butyl rubber; and
- a catalyst in manufacturing hexadiene.

Restrictions

Australian

This chemical is not listed in the Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)).

There is a group entry in Schedule 6 of the SUSMP for 'NITROPHENOLS, ortho, meta and para', but this chemical is not considered to be covered under that entry.

International

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

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

In a study in Sprague Dawley (SD) rats, percutaneous absorption was investigated using two hair dye formulations containing the radiolabelled chemical at 1.54 % and 0.77 % concentrations. In each case, less than 2 % of the applied dose was absorbed within five days. Twenty-four hours after the initial application, most of the absorbed dose was excreted through the urine, indicating a low potential for bioaccumulation (REACH; IARC, 1993).

In the same study, 2 mL of the chemical at a 0.2 % concentration (in saline) was administered orally. The majority of the radiolabel was excreted within five days, with 68.3 % found in the urine and 25.4 % in the faeces, indicating rapid excretion. About 4 % of the administered dose was eliminated in the

bile within three hours of administration (REACH; IARC, 1993).

Acute Toxicity

Oral

The chemical has low to moderate acute oral toxicity in rats and mice, respectively. A hazard classification is recommended based on the available data in mice, even though the median lethal dose (LD50) available for the preferred species, the rat, is slightly above the classification cut-off.

The LD50 is 2400 mg/kg bw in rats and 850 mg/kg bw in mice (IARC 1993).

An LD50 of 1840 mg/kg bw in rats was established by quantitative structure-activity relationship (QSAR), to classify the chemical as 'harmful if swallowed' (REACH).

Dermal

No data are available.

An LD50 of 2192 mg/kg bw in rabbits was predicted using QSAR, indicating low acute dermal toxicity (REACH).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Only limited data are available.

The chemical, tested at 2.5 % concentration on three New Zealand White rabbits, produced no skin irritation during the 72-hour observation period (REACH).

Eye Irritation

The available data indicate the chemical is an eye irritant, warranting a hazard classification.

In a standard Draize test, the chemical was found to moderately irritate the eyes of rabbits, 24 hours after exposure to the chemical (100 mg—maximum standard dose recommended in OECD Test Guideline (TG) 405), (REACH). This result was supported by QSAR, in which a modified maximum average score (MMAS) of 40.5 was predicted for the chemical, meeting the criteria for eye irritation (REACH).

Sensitisation

Skin Sensitisation

The available data indicate the chemical to be a skin sensitiser, warranting a hazard classification.

In a modified Buehler and Klecak method (similar to OECD TG 406), guinea pigs were exposed to the chemical at a 1 % concentration (induction phase) and challenged using the chemical at 0.25, 0.5 and 1 % concentrations. A positive challenge response was recorded for the highest concentration only (Dinardo et al., 2007).

A QSAR prediction based on local lymph node assay (LLNA) data indicated the chemical to be a strong sensitiser in humans with a predicted EC3 (effective concentration needed to produce a three-fold increase in lymphocyte proliferation) of 2.81 % (REACH).

Repeated Dose Toxicity

Oral

The chemical caused renal toxicity in rats and mice at high doses (500 mg/kg bw/d and above). Considering that there were no renal effects reported at lower doses, the chemical is not considered to cause serious damage to health sufficient to warrant a hazard classification.

In an oral gavage study (OECD TG 408), groups of F344/N rats and B6C3F1 mice (n = 10/sex/dose), were administered the chemical in corn oil at doses of 0, 62.5, 125, 250, 500 or 1000 mg/kg bw/d, five days a week for 13 weeks. All rats and mice in the highest dose groups and a few rats in the 500 mg/kg bw/d group were deceased (2/10 males and 2/10 females) before the end of the study. The effects observed in rats at 500 and 1000 mg/kg bw/d included diarrhoea, lethargy, reduced body weight (in males) and, most importantly, mild to severe mineralisation of the renal cortex and degeneration of renal tubular epithelium. In mice, degeneration and necrosis of renal tubular epithelium were observed at 1000 mg/kg bw/d (in 5/10 males and 3/10 females), but with signs of regeneration in some animals. No other treatment-related clinical signs were reported in mice (NTP, 1988).

Dermal

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

In New Zealand White rabbits the chemical, equally mixed with hydrogen peroxide, was applied to the skin at a dose of 1000 mg/kg bw (1 mL/kg bw), twice a week for 13 weeks. No treatment-related systemic effects were recorded (REACH).

Inhalation

No data are available.

Genotoxicity

The in vitro genotoxicity studies have shown some evidence of genotoxicity, but all in vivo studies indicated negative results. Therefore, based on the results of in vivo genotoxicity studies, the chemical is not expected to be genotoxic.

Most in vitro genotoxicity tests with the chemical indicated some genotoxic potential (Shahin et al., 1982; NTP, 1988; Burnett et al., 2009):

- mutagenic in bacterial gene mutation tests (Ames) with *Salmonella typhymurium* strain TA1538 and TA98 with and without metabolic activation;
- mutagenic in *S. typhymurium* strains TA98 and TA100 with metabolic activation and not mutagenic in strains TA1535 or TA1537 with and without metabolic activation;
- induced chromosome aberrations in Chinese hamster ovary cells with and without metabolic activation;
- induced sister chromatid exchanges in a sister chromatid exchange assay with and without metabolic activation;
- mutagenic in L5178 mouse lymphoma cell mutation assay (from 25 µg/mL) without metabolic activation (not tested with metabolic activation); and
- the chemical (dissolved in DMSO and diluted with ethanol) tested at 6.1 to 305.1 µg/mL doses on bacteriophages TD4, induced only a weak mutagenic activity at 11.9 µg/mL (IARC, 1993).

All in vivo genotoxicity studies indicated negative results (Burnett et al., 2009):

- intraperitoneal (i.p.) injection of the chemical (dose not provided) in CFW male mice showed no significant damage to bone marrow cells 24 hours after administration;
- in a micronucleus test, CFY rats were orally administered a suspension of the chemical at 5000 mg/kg within 24 hours; examination of bone marrow smears for micronucleated polychromatic erythrocytes showed no difference between the treated and untreated animals;
- in a dominant lethal mutagenicity study, groups of 20 sexually mature Charles River CD male rats were administered the chemical (i.p. injection) at 20 mg/kg bw, three times a week for eight weeks before mating; there was no evidence of an increase in postimplantation foetal loss in females mated with exposed males.

Carcinogenicity

Based on the carcinogenicity studies available, the chemical is considered to have some carcinogenic activity in male rats, and mice. However, the information available is not sufficient to classify the chemical as a carcinogen.

Most notifications to the Classification and Labelling Inventory from the industries in the European Union indicated the chemical as carcinogenic (ECHA).

The International Agency for Research on Cancer (IARC) has classified the chemical as 'Not classifiable as to its carcinogenicity to humans (Group 3)', based on inadequate evidence for carcinogenicity in humans and limited evidence for carcinogenicity in animals (IARC, 1993). This finding is based on the rat and mice studies described below.

In a two-year carcinogenicity study (NTP, 1988), Fischer 344/N rats and B6C3F1 mice (n = 50/sex/dose) were administered the chemical by gavage (in corn oil) at 0, 125 or 250 mg/kg bw/d, five days per week for 103 weeks. Survival of male rats decreased markedly at the high dose group (10/50 compared with 32/50 and 24/50 in the control and low dose groups, respectively). Survival rates were comparable across all groups in female rats and in male and female mice.

Non-neoplastic effects such as pigmentation of small and large intestines of all treated rats; and ulcers and erosive lesions of the digestive tract in male rats at both doses (to a lesser extent in the low dose group) were reported. These effects were not observed in mice. Severe nephropathy was observed in treated male rats, with lesions indicative of reduced kidney function. Renal cortical (tubular cell) adenomas were observed in male rats (0/50, 11/48 and 3/50 in the control, low and high dose groups, respectively). One male rat receiving the high dose had a carcinoma of the colon and there were no other neoplastic effects in the gastrointestinal tract of rats. Secondary hyperparathyroidism (with parathyroid hyperplasia), mineralisation of various organs and fibrous osteodystrophy (abnormal development of bone) were reported in treated male rats (NTP, 1988). 'Two liver-cell neoplastic nodules and one hepatocellular carcinoma were observed in high-dose male rats' (IARC, 1993). The historical incidence at the study laboratory for such effects was reported as 3/149 (2 ± 3 %) (IARC, 1993).

There were some incidences of preputial gland adenomas or carcinomas, or both, in the low dose male rats (10/48 compared with 3/50 for control and high dose groups). Haemangiomas or haemangiosarcomas, or both, occurred in treated male mice at different sites (0/50, 11/50 and 5/50 in the control, low and high dose groups, respectively). The historical control rates for these effects/tumours were provided as 11 % at the study laboratory and 6 % in 2-year NTP studies (NTP, 1988). Based on these studies in rats and mice, the NTP (1988) concluded that there was 'some evidence of carcinogenic activity' ('Some Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence' (NTP, 1988)).

Reproductive and Developmental Toxicity

Only limited data are available. No conclusion can be made on the reproductive and developmental toxicity of the chemical.

In a multigeneration study on SD rats, hair dye formulations containing the chemical at 0.4 % were mixed equally with hydrogen peroxide and applied topically (0.5 mL) on the skin twice a week, starting 100 days before mating until day 21 of lactation. No adverse effects on reproduction or teratogenic effects were reported (Burnett et al., 1988).

In a developmental toxicity study, hair dye formulations containing the chemical at 0.4 % (according to the REACH dossier) were topically applied to groups of 20 pregnant Charles River CD rats on days 1, 4, 7, 10, 13, 16, and 19 of gestation. No significant changes were recorded for mean numbers of corpora lutea, implantation sites, live foetuses, and resorptions per pregnancy, as well as numbers of litters with resorptions. Teratogenic effects (changes in soft and skeletal tissues) were not observed (Burnett et al., 1976).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- local effects (skin sensitisation and eye irritation); and
- systemic acute effects (acute toxicity by oral exposure).

The data available are not sufficient to draw a conclusion on carcinogenicity, reproductive or developmental toxicity of the chemical.

Public Risk Characterisation

The chemical is not on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

Many countries including Canada, New Zealand and the European Union have prohibited the use of this chemical in cosmetics. Currently, there are no restrictions in Australia on using this chemical in cosmetics or hair dye preparations. If the chemical is used in hair dyes, in the absence of any regulatory controls, the characterised critical health effects (skin sensitisation and eye irritation) have the potential to pose an unreasonable risk. The chemical is not genotoxic and the evidence for carcinogenicity is not conclusive. If this chemical is included in cosmetic products containing N-nitrosating agents, carcinogenic N-nitrosamine compounds could be formed (SCCS, 2012).

Based on the main use of the chemical internationally as an intermediate to manufacture other chemicals, it is unlikely that the public will be exposed to the chemical.

Occupational Risk Characterisation

Given the critical health effects identified, 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

Assessment of the chemical is considered to be sufficient, provided that the recommended classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

While there is no identified use of this chemical in Australia based on a review of voluntary surveys, should the chemical be used for hair dying in the future, it could potentially cause unreasonable risks to consumers and public risk management measures would need to be considered.

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

Control measures

Control measures to minimise the risk from oral and dermal exposure to the chemical(s) 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.

References

Ames BN, Kammen HO and Yamasaki E 1975. Hair dyes are mutagenic: identification of a variety of mutagenic ingredients. Proc Natl Acad Sci U S A. 1975 June; 72(6): 2423–2427.

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

Burnett C, Goldenthal EI, Harris SB, Wazeter FX, Strausburg J, Kapp R and Voelker R. 1976. Teratology and percutaneous toxicity studies on hair dyes. J Toxicol Environ Health 1976 Jul;1(6):1027-40. Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/966314

Burnett C, Loehr R and Corbett J. 1977. Dominant lethal mutagenicity study on hair dyes. J Toxicol Environ Health. 1977 Jan;2(3):657-62. Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/846013?dopt=AbstractPlus

Burnett CL, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW and Alan Andersen F. 2009. Final report on the safety assessment of amino nitrophenols as used in hair dyes. International Journal of Toxicology 2009 28(Suppl 3) 217S-251S.

Burnett CM and Goldenthal EI. 1988. Multigeneration reproduction and carcinogenicity studies in Sprague-Dawley rats exposed topically to oxidative hair-colouring formulations containing p-phenylenediamine and other aromatic amines. Food Chem Toxicol. 1988 May;26(5):467-74. Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/3391471?dopt=Abstract

ChemIDplus Advanced, CAS No. 99-57-0. Accessed February 2014 athttp://chem.sis.nlm.nih.gov/chemidplus/

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

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

Galleria Chemica. Accessed February 2014 at http://jr.chemwatch.net/galleria/

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed on January 2014 at http://toxnet.nlm.nih.gov.

International Agency for Reseach on Cancer (IARC) 1993. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 57 Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. Accessed at http://monographs.iarc.fr/ENG/Monographs/vol57/mono57.pdf

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

National Toxicology Program (NTP) 1988. Toxicology and carcinogenesis studies of 2-amino-4-nitrophenol (CAS No. 99-57-0) In F344/N rats And B6C3F1 mice (gavage studies). Technical Report Series No. 339. US Department Of Health And Human Service.

Registration, Evaluation and Authorisation of Chemicals (REACH) Dossier. 2-amino-4-nitrophenol (CAS No. 99-57-0). Accessed February 2014 at http://echa.europa.eu/information-on-chemicals/registered-substances.

Scientific Committee on Consumer Safety (SCCS) 2012. Opinion on Nitrosamines and Secondary Aminesin Cosmetic Products. Adopted at its 14th plenary meeting of 27 March 2012. Accessed at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_090.pdf

Shahin MM, Bugaut A and Kalopissis G. 1982. Mutagenicity of aminonitrophenol compounds in Salmonella typhimurium: a study of structural-activity relationships. Int J Cosmet Sci. 1982 Feb;4(1):25-35. Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/19469946

Last update 11 April 2014

Share this page