Phenol, 2,4-diamino-, dihydrochloride: Human health tier II assessment

30 June 2017

CAS Number: 137-09-7

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.

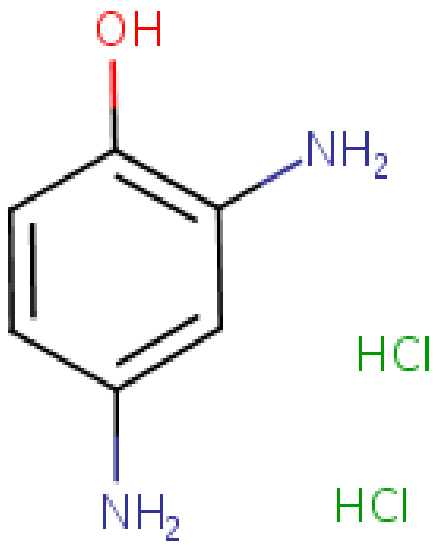
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2,4-diaminophenol HCl Acrol
Structural Formula	
Molecular Formula	C6H8N2O.2ClH
Molecular Weight (g/mol)	197.0
Appearance and Odour (where available)	greyish white solid
SMILES	c1(O)c(N)cc(N)cc1_Cl_Cl

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 Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the National Toxicology Program Report (NTP, 1992); and the Cosmetic Ingredient Review report (CIR, 1994).

The chemical has reported cosmetic use as a hair dye ingredient in oxidative hair dye products. The US Food and Drug Administration (FDA) reported that in 1993, the chemical was used in three hair dyes at concentrations up to 2 % (as a free base) (CIR, 1994).

The chemical has reported commercial use in photographic development.

The chemical has reported site-limited use as an intermediate in the process of dyeing fur.

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products: 2,4-diaminophenol and its dihydrochloride salts;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain—Table 1;
- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products; 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 Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Acute Toxicity

Oral

The chemical has high acute toxicity based on results from animal tests following oral exposure, warranting hazard classification (see **Recommendation** section). The median lethal dose (LD50) in rats is 240 mg/kg bw.

In an acute oral study, groups of five Wistar albino rats were administered single doses of 140, 200, 290, 410, 840 or 5000 mg/kg of the chemical. Mortality was recorded in all treated animals at ≥410 mg/kg bw by the end of day two. Sublethal effects included lethargy, ataxia, diarrhoea, piloerection, ptosis (drooping of the upper eyelid), flaccid muscle tone, prostration, negative righting reflex, vocalisation and staining of the anogenital area. Abnormalities of the lungs, liver, spleen and the gastrointestinal tract were reported at necropsy. Other effects observed included alopecia, emaciation, chromorhinorrhea (the discharge of a pigmented secretion from the nose) and weight gain (CIR, 1994).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is reported to be irritating to the rabbit skin in one animal study. The effects were not sufficient to warrant hazard classification.

In a dermal irritation study, three New Zealand White (NZW) rabbits were topically administered 500 mg per test site of the chemical for four hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48 and 75 hours following exposure. Two rabbits had well defined erythema and slight to moderate oedema, both at one and 24 hours. Erythema was

observed in three rabbits at 72 hours. No other skin reactions were observed. The chemical was reported to be irritating to rabbit skin (CIR, 1994).

In another skin irritation study, ten Hartley guinea pigs were treated with 0.2, 0.5, 1.0, 2.0, 5.0 or 10.0 % of the chemical in petrolatum for 48 hours under occlusive patches. No skin irritation was reported at any concentration tested (Ishihara et al, 1985).

Eye Irritation

Based on the available limited data, the chemical was found to be highly irritating to the eye. Although there is insufficient data to determine an appropriate hazard classification, the potential for eye irritation at low dose of 0.1 mL will be considered in the risk characterisation, as the chemical is used in cosmetic products.

In an eye irritation study conducted in three NZW rabbits, the chemical (0.1 mL) was instilled in the conjunctival sac of one eye of each rabbit. Severe conjunctivitis, iritis, corneal opacity and chemosis were observed in all rabbits at 24, 48 and 72 hours after application (CIR, 1994). The details on reversibility of the effects were not provided.

Sensitisation

Skin Sensitisation

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

In a Beuhler dermal sensitisation study, 1.0 % of the chemical in petrolatum (approximately 50 mg) was applied to the nape of ten Hartley guinea pigs for 48 hours under occlusive conditions, during induction. The treatment was repeated three times, weekly. After two weeks of no treatment period, challenge doses of approximately 0.1 % and 1.0 % were then applied to the flanks for 48 hours under occlusive conditions. No signs of local irritation or skin sensitisation were observed at 24 or 48 hours after patch removal (CIR, 1994; Ishihara et al, 1985).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical can cause serious damage to health (kidney damage) following repeated oral exposure, warranting hazard classification (see **Recommendation** section).

In a 16-day study, groups of Fischer 344 (F344/N) rats (n=5/sex/dose) were orally administered the chemical at doses of 6, 13, 25, 50 or 100 mg/kg bw/day. Treatment was given on days 1–5 and days 8–12. The animals were euthanised on day 16. No mortalities were recorded. Mild to moderate renal tubular cell necrosis was observed in four males and five females at the highest dose tested (100 mg/kg bw/day); three males and one female at 50 mg/kg bw/day and three males and five females at 25 mg/kg bw/day. The lowest observed adverse effect level (LOAEL) was 25 mg/kg bw/day (CIR, 1994; NTP, 1992).

In a similar 16-day study in B6C3F1 mice, groups of mice (n=5/sex/dose) were administered the chemical at 13, 25, 50, 100 or 200 mg/kg bw/day on days 1-5 and 8-12. Mortalities were recorded at 200 mg/kg bw/day (all males and five females); 100 mg/kg bw/day (all males and three females) and 50 mg/kg bw/day (two females). Relative liver weights were increased in all treated females, and absolute liver weights were increased in 50 and 100 mg/kg bw/day in both sexes. All treated animals at 100 mg/kg bw/day were reported to show renal tubular necrosis (CIR, 1994; NTP, 1992).

In a 13-week study, groups of F344/N rats (n= 10/sex/group) were orally administered the chemical in corn oil at doses of 0, 12, 25, 50, 100 or 200 mg/kg bw/day. Mortalities were reported at 200 mg/kg bw/day (all females and nine males) and at 100 mg/kg bw/day (four males and one female). Reduction in body weights by 11, 21 and 4 % were reported in males at 50 and 100 mg/kg bw/day and in females at 100 mg/kg bw/day, respectively. Significant increase in the relative kidney weights were observed in all

treated males and four females each at 50 and 100 mg/kg bw/day. Males at ≥25 mg/kg bw/day and females at ≥100 mg/kg bw/day showed significantly increased, dose-dependent renal cortical tubular necrosis. Severity of the necrosis was also dose-dependent. Ulcers of the nonglandular stomach, associated with severe acute inflammation, and epithelial hyperplasia were observed in male rats at ≥50 mg/kg bw/day, and in female rats at ≥100 mg/kg bw/day. Acanthosis, hyperkeratosis of the squamous epithelium, foci of spongiosis in the stratum corneum, and black-brown pigment in the macrophages of the duodenal lamina propria were observed in few animals at higher doses. Dose-dependent increases in the severity of splenic myeloid hyperplasia in treated male rats and splenic haemosiderosis (iron overload disorder) in female rats at ≥100 mg/kg bw/day, were reported. All male rats at ≥100 mg/kg bw/day showed significant splenic lymphoid depletion (CIR, 1994; NTP, 1992).

In a mouse study, B6C3F1 mice (n= 10/sex/group) were orally administered the chemical in corn oil at doses of 0, 5, 9, 19, 38 or 75 mg/kg bw/day for 13 weeks. Mortalities were reported in all treatment groups. Absolute and relative liver and kidney weights were increased in all treated females and in males at ≥19 mg/kg bw/day. Females dosed at ≥19 mg/kg bw/day showed increased absolute heart weight. All treated mice in the 75 mg/kg bw/day dose group showed multifocal and diffuse renal cortical tubular regeneration; with greater severity of these lesions in females. Acanthosis and hyperkeratosis on the non-glandular stomach were observed in male and female mice at 38 and 75 mg/kg bw/day, respectively. Female mice at ≥38 mg/kg bw/day had swollen Kupffer's cells with brown pigment. Increased haemosiderosis was also observed in all treated groups (CIR, 1994; NTP, 1992).

In a carcinogenicity study in rats, groups of F344/N rats (n=60/sex/dose) were administered with the chemical in corn oil at 0, 12.5 or 25 mg/kg bw/day, by gavage, five days a week for 103 weeks. After 15 months of treatment, 10 male and female rats were sacrificed and evaluated for clinical pathology and histopathology. No adverse effects were observed in the haematology or clinical chemistry parameters at 15-months evaluation. Females had a greater survival rate at the termination of the study. At 25 mg/kg bw/day, 7-16 % and up to 11% reduction in the mean body weights were reported for males and females, respectively. Increases in the incidence and severity of nephropathy in both female and male rats (at 12.5 and 25 mg/kg bw/day) were reported to be dose-related. In all treated animals, a golden brown, iron-positive pigment (hemosiderin) was present in the cytoplasm of the proximal renal tubule epithelial cells and, occasionally, in the lumen of the proximal renal tubules. Ulcers (low dose: 2/23; high dose 5/50) associated with severe acute inflammation were observed in the non-glandular stomachs of all treatment groups. The epithelial hyperplasia, acanthosis (low dose: 10/23; high dose: 13/50) and hyperkeratosis (thickening of the stratum corneum) reported in the study were associated with the ulcers. The incidence and description of tumours in this study are summarised in the Carcinogenicity section of this report (see Carcinogenicity section) (CIR, 1994; NTP, 1992).

In a 103-week mouse study, groups of B6C3F1 mice (n=60/sex/dose) were administered the chemical in corn oil at 0, 19 or 38 mg/kg bw/day, by gavage, five days a week for 103 weeks. After 15 months of treatment, 10 male and female mice were sacrificed and evaluated for clinical pathology and histopathology. No significant differences in the survival of the treated and control groups were noted. Significant reductions in haematocrit, haemoglobin and erythrocyte counts, and significant increases in the leukocyte and neutrophil counts were observed in the high dose male and females at 15-months. All treated groups showed renal tubular necrosis and regeneration; golden brown pigment in the cytoplasm of proximal renal tubule epithelial cells; and pigment in the duodenum, liver and mesenteric lymph nodes. Treated males had dose-related increases in ulceration (low dose: 2/23; high dose: 5/50) and acanthosis (low dose: 10/23; high dose: 13/50) of the forestomach. The incidence and description of tumours in this study are summarised in the carcinogenicity section of this report (see **Carcinogenicity** section) (CIR, 1994; NTP, 1992).

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 not considered to be genotoxic.

In vitro studies

In an Ames test in *Salmonella typhimurium* strain TA98, the chemical was mutagenic with metabolic activation at up to 3 µg/plate, but showed negative results without metabolic activation. The chemical was not mutagenic in *S.typhimurium* strains TA100, TA1535 and TA1537 (NTP, 1992).

In a Chinese hamster ovary (CHO) cell assay, the chemical did not induce chromosomal aberrations at concentrations of 0.09–0.9 µg/plate with or without metabolic activation (CIR, 1994).

In another CHO assay, the chemical was not mutagenic at concentrations of 0.27–2.7 µg/plate without metabolic activation and at 0.9–9 µg/plate with metabolic activation (CIR, 1994).

In a mammalian cell gene mutation test, positive results were reported in *L5178Y tk $^{+}$/tk $^{-}$* mouse lymphoma cells at a concentration of 2 µg/ml, in the absence of S9 metabolic activation. The chemical caused 1.8-fold increase in forward mutations (CIR, 1994; NTP, 1992).

In vivo study

In a sex-linked recessive lethal test in *Drosophila melanogaster, e*quivocal results were reported at a concentration of 125 ppm (CIR, 1994; NTP, 1992).

Carcinogenicity

Based on the available data, the chemical is not expected to be carcinogenic.

In a carcinogenicity study in rats and mice, groups of F344/N rats (n=60/sex/dose) were orally administered the chemical in corn oil at 0, 12.5 or 25 mg/kg bw/day and groups of B6C3F1 mice (n=60/sex/dose) were orally administered with the chemical in corn oil at 0, 19 or 38 mg/kg bw/day, five days a week for 103 weeks. After 15 months of treatment, 10 male and female rats and mice, were sacrificed and evaluated for clinical pathology and histopathology. At two year examination, increased incidences of focal renal tubular cell hyperplasia were reported in all treated rats at 25 mg/kg bw/day. Three high-dose males and one high-dose female rat showed renal tubular cell adenomas. No renal tubular cell carcinomas were observed. In mice, renal tubular cell focal hyperplasia (9/50 in males and 3/60 in females) and renal tubular cell adenomas (6/50 in males and 1/50 in females) were reported at the highest dose (38 mg/kg bw/day). Renal tubular cell carcinoma was recorded in 1/39 female mice in the 19 mg/kg bw/day group (CIR, 1994; NTP, 1992).

The authors concluded there are no evidence of carcinogenicity in rats and female mice. There was some evidence of carcinogenic activity in male mice based on the significantly increased incidence of renal tubular cell adenomas (NTP, 1992).

Reproductive and Developmental Toxicity

Based on the limited information available, the chemical is not considered a developmental toxin in rats dermally exposed to the chemical.

In a developmental toxicity study, pregnant Charles River CD rats (n=20) were treated with 2 mL/kg formulation containing 0.2 % of the chemical. The chemical formulation was applied to the shaved area on the back on days 1, 4, 7, 10, 13, 16 and 19 of gestation. No significant differences in the mean number of corpora lutea, live foetuses and resorptions per pregnancy were reported. No significant changes were observed in the soft-tissue or skeletal anomalies in the foetuses of treated rats compared with the control groups (CIR, 1994; NTP, 1992).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are systemic acute and systemic long-term toxicity (the kidney as a target organ).

The chemical is a potential eye irritant.

Public Risk Characterisation

New Zealand, ASEAN countries, Canada and the European Union have restricted the use of this chemical in cosmetics, whereas currently there are no restrictions in Australia on using this chemical in cosmetic products.

While Australian use information is not available, the chemical has reported international use in cosmetics including as a hair dye ingredient in oxidative hair dye products at concentrations up to 2% (as a free base). Considering the use of the chemical in cosmetics, the main routes of exposure are expected to be through dermal, ocular and possibly oral exposures.

In the absence of any regulatory controls, the characterised critical health effects (acute toxicity, repeat dose toxicity and possible eye irritation) have the potential to pose an unreasonable risk under the uses identified.

Based on the CIR, 1994 expert panel conclusion, the chemical and its parent are safe for use in hair dyes at concentrations up to 0.2 % (as a free base).

Overall, there is sufficient uncertainty regarding the safety of this chemical in hair dye products and; therefore, a Tier III assessment to determine the risk of systemic toxicity is required (see **NICNAS Recommendation** section). In the absence of additional information, including an acceptable MOE, a conservative assessment will be undertaken and relevant recommendations will be made.

Occupational Risk Characterisation

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

Given the critical systemic acute and long term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, oral and ocular 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 a new entry 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 for workplace health and safety be managed through changes to classification and labelling.

The chemical is recommended for Tier III assessment to determine :

- the extent to which this chemical is used in hair dye preparations in Australia, considering the prohibitions and/or restrictions overseas;
- any other uses of the chemical in Australia;
- the availability of toxicological information, including a MOE to better characterise the systemic hazards of the chemical; and

- whether risk management controls are required.

Regulatory Control

Public Health

The need for regulatory control for public health will be determined as part of the Tier III assessment.

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)
Repeat Dose Toxicity	Not Applicable	May cause damage to organs (kidney) through prolonged or repeated exposure - Cat. 2 (H373)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

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

Advice for industry

Control measures

Control measures to minimise the risk from dermal, oral 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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- 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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