1,3-Benzenediol, 4-chloro-: Human health tier II assessment

02 March 2018

CAS Number: 95-88-5

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.

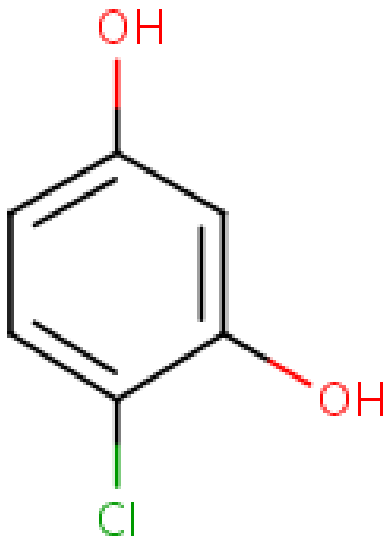
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4-chloro-1,3-benzenediol 4-chlororesorcinol 2,4-dihydroxychlorobenzene p-chlororesorcinol 6-chlororesorcinol
Structural Formula	
Molecular Formula	C6H5ClO2
Molecular Weight (g/mol)	144.56
Appearance and Odour (where available)	beige to brown powder
SMILES	c1(Cl)c(O)cc(O)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).

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the Scientific Committee for Consumer Safety (SCCS).

The chemical has reported:

- cosmetic use as coupler in oxidative hair dye formulations (SCCS, 2010);
- domestic use in leather treatment products (ECHA); and
- site-limited use as an intermediate (Galleria Chemica).

In the US, the chemical was reported to be mostly used at concentrations below 0.1 % in hair dye products (CIR, 1996). However, it was also reported to be used at 0.1–1 % for 10/39 hair dye products (CIR, 1996).

Restrictions

Australian

No known restrictions have been identified.

International

Use of the chemical in cosmetics in the EU is subject to the restrictions described in EU Regulation Annex III. This chemical may be used in hair dyes at a maximum concentration of 2.5 % after mixing under oxidative conditions. The label must mention the following: 'Hair colorants can cause severe allergic reactions' (CosIng).

The chemical is also listed on the ASEAN Cosmetic Directive Annex III Part 1—List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down (Galleria Chemica).

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

Toxicokinetics

In an in vitro dermal percuteaneous study following the Organisation for Economic Cooperation and Development Test Guideline (OECD TG) 428, the chemical was tested for its dermal absorption through dermatomed pig skin in a standard cream formulation and in a water-based formulation at doses of 10 mg/cm^2 (lower than the recommended dose of 20 mg/cm^2 for the test). Dermal absorption from the cream formulation was low with and without oxidative conditions (hydrogen peroxide). A small percentage of the administered dose was bioavailable, 1.5 and 1.95 % with and without hydrogen peroxide, respectively. Dermal absorption was ten times higher for the water-based formulation, with an overall bioavailable proportion of 20.8 % of the administered dose within 48 hours. This study concluded that systemic availability of the chemical was expected to be low and dermal absorption was dependent on the vehicle used (SCCS, 2010).

Acute Toxicity

Oral

The chemical has moderate acute oral toxicity, warranting hazard classification (see **Recommendation** section).

In an acute oral toxicity study, the chemical was administered as a 10 % aqueous solution in sodium sulfite to CFY rats (n=5/sex/dose) at doses of 0, 160, 250, 400 or 640 mg/kg bw by gavage. The median lethal dose (LD50) was calculated to be 369 mg/kg bw. Reported sub-lethal effects included piloerection, lethargy and decreased respiratory rate (SCCS, 2010).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is irritating to the skin, warranting hazard classification (see **Recommendation** section).

In a skin irritation study according to OECD TG 404, the chemical was applied undiluted onto the skin of New Zealand White (NZW) rabbits for 4 hours (n=3). Results included very slight to severe erythema, and moderate to severe oedema in all treated rabbits (scores not provided). These effects had resolved within 14 days in one animal, but were not reversible during the observation period for the other rabbits (SCCS, 2010). Therefore, in this study the chemical is considered as irritating to the skin.

In a US guideline skin irritation test, NZW rabbits (n=3) were exposed to the chemical at 2.5 % (w/v), on intact and abraded skin, and observed for 72 hours. No signs of irritation were reported, and the primary irritation index (PII) was zero (CIR, 1996). Although this study is of limited reliability, it indicates that the chemical is unlikely to be an irritant at concentrations used in hair dyes.

Eye Irritation

Based on the available data, the chemical is corrosive to the eyes, warranting hazard classification (see **Recommendation** section).

In an eye irritation study according to OECD TG 405, the chemical (undiluted) was instilled into the eye of one NZW rabbit. Corrosive effects were observed within 24 hours, including corneal injury (maximum opacity grade of 4 and 100 % epithelial damage on the cornea), redness, chemosis and discharge of the conjunctivae, and necrosis of the eyelids and nictitating membrane (SCCS, 2010).

In a US guideline eye irritation test, NZW rabbits (n=3) were exposed to the chemical at 2.5 % instilled in to the eye for 10 seconds before the eye was rinsed with water. Transient mild conjunctival inflammation, reversible within 24 hours, was reported. No more details were provided but the study concluded that the chemical was 'essentially non-irritating to the eyes of rabbits' (CIR, 1996). Although this study is of limited reliability, it indicates that the chemical could cause irritation to the eyes at concentrations used in hair dye formulations.

Sensitisation

Skin Sensitisation

The chemical is considered as a skin sensitiser based on the results of a local lymph node assay (LLNA), warranting hazard classification (see **Recommendation** section).

In a LLNA according to OECD TG 429, groups of female CBA mice (n=5/group) were dermally exposed to the chemical at concentrations of 0, 2.5, 5, 10, 25 or 50 % in acetone:olive oil (4:1 v/v), applied daily for 3 consecutive days. At the highest concentration, 4/5 animals died on day 3. Stimulation index (SI) values of 1.1, 1.5, 10.1 and 16.4 were reported at 2.5, 5, 10 and 25 %, respectively. The estimated concentration required to produce a 3-fold increase in lymphocyte proliferation (EC3) was 5.8 %. The chemical was therefore considered to be a moderate skin sensitiser in this study (SCCS, 2010).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not considered to be harmful following repeated oral exposure.

In a repeated dose toxicity study according to OECD TG 407, groups of Wistar rats (n=5/sex/dose) were treated by gavage with the chemical at doses of 0, 30, 150 or 300 mg/kg bw/day for 28 days. No deaths ocurred, but clinical signs of toxicity included sedation, tremor, ruffled fur, convulsions, abnormal gait, muscle twitching and laboured breath at the highest dose. Bilateral pelvic dilation and unilateral hydronephrosis were observed in one female rat at mid dose and one male rat at high dose. No other effects were reported (SCCS, 2010).

In a subchronic toxicity study according to OECD TG 408, groups of Wistar rats (n=10/sex/dose) were treated by gavage with the chemical at doses of 0, 35, 70 or 210 mg/kg bw/day for 90 days. Additional groups of rats (n=5/sex/dose) were treated with 0 or 210 mg/kg bw/day and assessed for recovery for 4 weeks after the end of the treatment. A total of 4 female rats died at the highest dose. Clinical signs of toxicity included spasms, tremors, hunched posture, abnormal gait and salivation in the high-dose group for both sexes. At the highest dose, other effects included reduced forelimb grip in male rats, depressed red blood cell count in female rats, changes in reticulocyte count and in lipid metabolism (not detailed) in male rats. A no observed adverse effect level (NOAEL) of 70 mg/kg bw/day was determined based on the mortality, clinical signs and haematotoxicity observed at the high dose (SCCS, 2010).

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

In a bacterial gene mutation assay (OECD TG 471), the chemical was found negative in *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537 when tested at concentrations up to 5000 µg/plate (SCCS, 2010).

In a mammalian cell gene mutation test (OECD TG 476), the chemical tested negative in L5178Y mouse lymphoma cells, when used at concentrations up to 46.9 µg/mL and 562.5 µg/mL with and without metabolic activation, respectively (SCCS; 2010).

In a mammalian chromosome aberration test (OECD TG 473), the chemical gave positive results in Chinese hamster V79 cells at concentrations of 2.5–10 µg/mL and 200–400 µg/mL, with and without metabolic activation, respectively. It induced statistically significant and biologically relevant increases in the number of cells with structural aberrations, with more than 10-fold increase observed (concentration not stated) compared to controls. More than half of the chromosomal aberrations were identified as chromatid or chromosome breaks (SCCS, 2010).

In vivo

In a micronucleus test according to OECD TG 474, NMRI mice (n=6/sex/dose) were treated intraperitoneally (i.p.) with the chemical at single doses of 25, 50 or 100 mg/kg bw. There were no statistically significant increases in the frequency of micronuclei in erythrocytes (SCCS, 2010).

Carcinogenicity

Only limited information is available, suggesting the chemical is not expected to be carcinogenic at doses used in hair dye formulations. However, potential for carcinogenicity cannot be ruled out, based on structural alerts for this class of chemicals.

In a non-guideline chronic toxicity study, groups of Swiss mice (n=50/sex) were dermally exposed to a hair dye fomulation containing 2 % of the chemical, mixed equally with hydrogen peroxide prior to application, for 21 months (frequency of application not stated). No carcinogenic effects were reported (CIR, 1996).

In a non-guideline chronic toxicity study, groups of Sprague Dawley rats (n=60/sex) were topically exposed twice a week to a hair dye formulation containing 2 % of the chemical, mixed equally with hydrogen peroxide prior to application, for 24 months. There was a significant increase in pituitary adenomas in female rats, but this type of tumour was considered common in this

strain of rats. There was a significant increase in mammary gland adenomas in female rats compared to one control group, but it was not statistically significant compared to the overall control groups. No conclusion could be made on the carcinogenicity of the chemical in this study (CIR, 1996).

The chemical contains structural alerts for carcinogenicity according to quantitative structure-activity relationship (QSAR) modelling (QSAR Toolbox 3.4). Halogenated benzene rings are prone to 'exert carcinogenic action via non-genotoxic mechanisms rather than by direct action on DNA', via 'inhibition of intercellular communication' (Woo & Lai 2005; Woo et al., 1995). Therefore, a potential for carcinogenicity cannot be excluded for the chemical.

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not expected to be toxic to reproduction or development.

In a prenatal development toxicity study according to OECD TG 414, groups of mated female Wistar rats (n=5/dose) were treated orally with the chemical at doses of 0, 75, 150 or 300 mg/kg bw/day, from day 6 to day 20 post-coitum. At the highest dose, 3 animals died before the end of the treatment. Spasms and tremor were observed in all treated groups. Mean body weight gain was statistically reduced at 150 and 300 mg/kg bw/day. There were no effects on the reproductive parameters (number of foetus per dam, incidence of post-implantation loss) and foetal parameters (sex ratio, foetal weight, external examination) in this study (SCCS, 2010).

In another study according to OECD TG 414, groups of mated female Wistar rats (n=22/dose) were treated orally with the chemical at doses of 0, 50, 100 or 200 mg/kg bw/day, from day 6 to day 20 post-coitum. At 200 and 100 mg/kg bw/day, tremor was observed in all female rats but no other clinical signs were reported. At 100 and 50 mg/kg bw/day, slightly higher incidences of post-implantation loss were noted (8.6 and 8.5 %, respectively) when compared with the control group (4.3 %). No other treatment-related effects were observed. Based on these results, NOAELs of 50 mg/kg bw/day for maternal toxicity and 200 mg/kg bw/day for developmental toxicity were determined (SCCS, 2010).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

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

Public Risk Characterisation

The chemical was reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007) and in oxidative hair dye formulations overseas (see **Import, Manufacture and Use** section). Considering the range of domestic (leather treatment) and cosmetic products that may contain the chemical, the main route of public exposure is expected to be through the skin.

In the EU, this chemical may be used in hair dyes at a maximum concentration of 2.5 % after mixing under oxidative conditions. The SCCS (2010) calculated a margin of safety (MOS) of 625 under oxidative conditions and 472 without oxidative conditions, based on a NOAEL of 50 mg/kg bw/day (see **Reproductive and Developmental Toxicity** section) and dermal absorptions of 8.31 µg/cm^2 and 10.99 µg/cm^2, with and without hydrogen peroxide, respectively (SCCS, 2010). These MOS values indicate that the use of the chemical in hair dyes at a maximum concentration of 2.5 % after mixing with hydrogen peroxide should be safe, apart from the sensitising and irritant potential.

Currently, there are no restrictions in Australia on using this chemical in cosmetics or domestic products. In the absence of any regulatory controls, the characterised critical health effects have the potential to pose an unreasonable risk under the identified uses.

The risk could be mitigated by implementing concentration limits and restricting use in hair dye products. The restrictions on this chemical in cosmetic products in the EU (see **International restrictions** section) are considered appropriate to mitigate the risk.

Occupational Risk Characterisation

During product formulation, oral, dermal 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 health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal and ocular exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking 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

Appropriate scheduling and labelling should be undertaken to mitigate risk when the chemical is used in domestic and cosmetic products. Due to the toxicity profile at the concentrations reported to be potentially in use, this chemical should be considered for listing in the SUSMP, consistent with the *Scheduling Policy Framework* guidelines. Matters to be taken into consideration include:

- the chemical being used in cosmetic products (hair dye preparations) in Australia, and in cosmetic and domestic products overseas;
- the chemical has moderate acute oral toxicity;
- the chemial is a skin irritant and severe eye irritant;
- the chemical is a moderate skin sensitiser;
- overseas restrictions for use of this chemical in hair dyes. The maximum concentration corresponds to 2.5 % after mixing under oxidative condition in hair dye products (CosIng); and
- the current scheduling of related chemicals 1,3-benzenediol (CAS No 108-46-3) and 1,3-benzenediol, 2-methyl- (CAS No 608-25-3), with similar toxicological profile and use (TGA, 2017).

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)
Irritation / Corrosivity	Not Applicable	Causes serious eye damage - Cat. 1 (H318) Causes skin irritation - Cat. 2 (H315)
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1B (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 instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal and ocular exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures 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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