1,2-Benzenediol: Human health tier II assessment

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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.

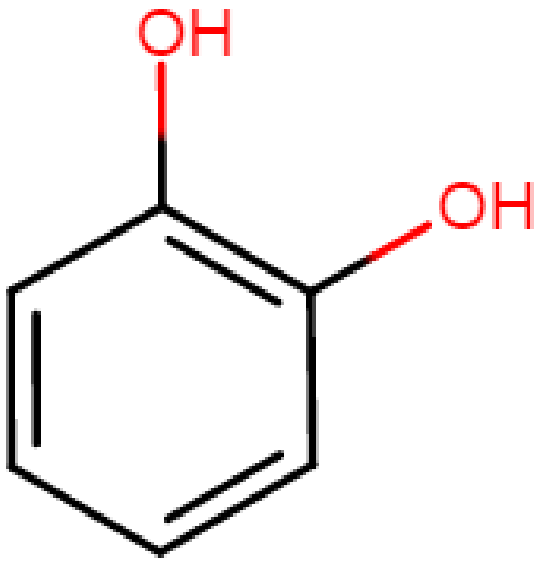
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1,2-Dihydroxybenzene Pyrocatechin Pyrocatechol Benzene-1,2-diol Catechol
Structural Formula	
Molecular Formula	C6H6O2
Molecular Weight (g/mol)	110.1
Appearance and Odour (where available)	Colourless crystals, discolours to brown on exposure to air and light, especially when moist. Faint characteristic (phenolic) odour and sweet and bitter taste.
SMILES	c1(O)c(O)cccc1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified via the Cosmetic Ingredients and Substances (CosIng) database, Registration Evaluation and Authorisation of Chemicals (REACH) Dossiers, Canadian Priority Substance List Assessment Report, Galleria Chemica, the Substances and Preparations in the Nordic countries (SPIN) database and eChemPortal (Hazardous Substances Data Bank (HSDB)).

The chemical has reported cosmetic use as:

- historical use in hair dyes, perfumes, and essential oils.

The chemical has reported domestic/commercial use including:

- surface treatment.

The chemical has reported commercial use including:

- photographic developer;
- developer in fur dyes;
- as an ingredient in epoxy coatings, adhesives, speciality inks;
- electroplating agents;
- process regulators; and
- colouring agents.

The chemical has reported site-limited use including:

- intermediate for antioxidants in rubber and lubricating oils and in polymerisation inhibitors.

Restrictions

Australian

No known restrictions have been identified.

International

Cosmetics

EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the Composition of Cosmetic Products.

EU List of substances banned for use in hair dye products.

Canadian List of Prohibited and Restricted Cosmetic Ingredients (The Cosmetic Ingredient Hotlist).

New Zealand Cosmetic Products Group Standard - Schedule 4: Components Cosmetic Products Must Not Contain.

Food Packaging

Europe Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food - Annex I: Substances: specific migration limit (SML) = 6 mg/kg (expressed as 1,2-dihydroxybenzene)

Existing Work Health and Safety Controls

Hazard Classification

The chemical is currently classified on the Hazardous Substances Information System (HSIS) (may be accessed at http://hsis.safeworkaustralia.gov.au/HazardousSubstance) with following risk phrases:

Xn; R21/22 (Acute toxicity)

Xi; R36/38 (Irritation)

Exposure Standards

Australian

Time Weighted Average (TWA): 23 mg/m³ (5 ppm)

International

TWA: 5 ppm (20 mg/m³) [Austria, France, Greece, Ireland, South Korea, Mexico, Norway, South Africa, Sweden]

TWA: 5 ppm (23 mg/m³) [Canada, China, Indonesia, Malaysia, New Zealand, Peru, Singapore, Switzerland]

TWA: 5 ppm (22 mg/m³) [Finland]

Short-Term Exposure Limit (STEL): 10 ppm (45 mg/m³) [Canada, Finland]

STEL: 9 ppm (40 mg/m³) [Germany]

STEL: 10 ppm (40 mg/m³) [Sweden]

Health Hazard Information

Toxicokinetics

It is reported in OECD (2003a) that the chemical is absorbed by oral and dermal routes, as well as by the respiratory tract. The chemical is metabolized to o-benzoquinone by enzymatic oxidation. After oral administration the chemical is conjugated with glucuronic acid and sulfuric acid and eliminated mainly and rapidly via urine.

Acute Toxicity

Oral

The chemical is currently classified with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in Australia (Safe Work Australia – HSIS). The data available support this classification.

The chemical was reported to cause acute toxicity via the oral route (median lethal dose (LD50) in rats = 300 mg/kg bw). The animals that died during the observation period revealed hyperaemia of the stomach and intestine (OECD 2003a).

Dermal

The chemical is currently classified with the risk phrase 'Harmful in contact with skin’ (Xn; R21) in Australia (Safe Work Australia – HSIS). The data available support this classification.

The chemical was reported to cause acute toxicity via the dermal route (LD50 in rats = 600 mg/kg bw). At doses of 1125 mg/kg bw and 875 mg/kg bw rats presented with marked tremor after 5 minutes of treatment. They died after clonic convulsions during the first 30 minutes after dosing (OECD 2003b).

Inhalation

The chemical was reported to cause low acute toxicity via the inhalation route (median lethal concentration (LC50) in rats is >2800 mg/m³ in rats).

An 8 hour inhalation (aerosol) exposure to 1500 mg/m³ of the chemical did not cause any signs of toxicity in rats (Environment & Health Canada 2008). However following exposure to 2000 mg/m³ or 2800 mg/m³ irritation, persistent tremors after 24 hours and loss of toes or tail ends were noted (OECD 2003b).

Corrosion / Irritation

Skin Irritation

The chemical is currently classified with the risk phrase ‘Irritating to skin’ (Xi; R38) in Australia (Safe Work Australia – HSIS). The data available support this classification.

The chemical on intact skin of rabbits produced slight to moderate erythema, and slight oedema after 24 h. After 14 days, the exposed areas were free of irritation (OECD 2003b).

Eye Irritation

The chemical is currently classified with the risk phrase ‘Irritating to eyes’ (Xi; R36) in Australia (Safe Work Australia – HSIS). The data available support this classification.

In an eye irritation study in rabbits the chemical was found to be highly irritating with conjunctivitis and marked to dense corneal opacity was observed after application, at 24, 48 and 72 h (OECD 2003b).

Sensitisation

Skin Sensitisation

The chemical is a potential skin sensitiser. In one dermal sensitisation study using a modified split adjuvant test the chemical caused a positive reaction in less than 30% (2 out of 9) of the Hartley guinea pigs (ECHA 2012). In another modified adjuvant type study the majority (number not specified) of 8 to 12 Hartley guinea pigs were sensitised by the chemical (ECHA 2012).

A case study of occupational contact dermatitis from exposure to pyrocatechol has been reported (Morelli 1989). A 33 year old woman showed a strong positive reaction to pyrocatechol, a photographic developer.

Repeated Dose Toxicity

Oral

In the only available reliable repeated dose oral toxicity study in rats (Wistar) following the guideline OECD 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test), the substance was administered via gavage to 10 animals/sex/dose at 0, 30, 80 and 160 mg/kg bw/day for 4 weeks to males and 7 weeks to females. Mortality was observed at the highest dose in 2 males and 1 female (ECHA 2012). Tremors were observed at the highest dose. From the robust study summary description it is not clear whether tremors were observed at 80 mg/kg bw/day. At the highest dose tremors persisted throughout treatment in all animals in both sexes. Other clinical observations were hind legs stretched out and ventral recumbency in 1 female and 3 males, and chromodacryorrhea in 3 males at the highest dose. At the highest dose, diffuse hepatocellular hypertrophy was recorded at minimal severity in 3 males and 2 females. Given that there were no further indicators of liver injury, this lesion was considered to be of metabolic nature and of adaptive character. At the two highest doses the incidence and severity of squamous hyperplasia in the stomach were increased in animals of both sexes. This lesion was considered to be due to a local irritant effect of the test material. No other significant histopathology changes were noted. At the highest dose food consumption was statistically significantly higher between days 8 - 14 of the pre-pairing period. A no observed adverse effect level (NOAEL) of 30 mg/kg bw/day can be derived based on squamous hyperplasia in the stomach.

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

An epidemiology study reported exposure of 13 workers in a chemical factory in Japan to catechol (2 to 72 ppm) and phenol (55 to 260 ppm) vapours during 2 years (OECD 2003b). The clinical examinations and physical responses of workers indicated significant cough, sputa, throat and eye irritation.

Genotoxicity

The genotoxic potential of the chemical is summarised from the conclusion of the OECD (2003a). The chemical appeared to show generally negative results in point mutation studies but uniformly positive result in clastogenicity studies.

Eight *in vitro* reverse mutation assays with *Salmonella typhimurium* were negative with and without metabolic activation. In one assay with *Escherichia coli,* a positive result was obtained without metabolic activation and the result was negative with metabolic activation. Addition of metabolic activation inhibited the mutagenicity of the chemical. Four gene mutation assays in

cultured mammalian cells without metabolic activation were positive. In chromosome aberration assays *in vitro*, the chemical induced positive results without metabolic activation, and with S9 the toxicity of the chemical was decreased. *In vitro* tests on damaging effects of the chemical were positive only without metabolic activation in different cell lines. Positive results were obtained in a sister chromatid exchange assay, without metabolic activation, at concentrations that were not cytotoxic (10 and 30 µM). Additional testing on cell transformation *in vitro* indicated that the chemical at the concentration levels of 1 and 3 µM may induce morphological transformation in Syrian Hamster Embryo cells. An *in vivo* genetic toxicity spot test in mice was negative. *In vivo* micronucleus assays with mice were positive, indicating that administration of the chemical at doses of 40 mg/kg by gavage and by intraperitoneal route at 10, 20, and 30 mg/kg bw induced chromosomal aberrations. Results from an i*n vivo* replicative DNA synthesis test were positive. Two unscheduled DNA synthesis (UDS) tests gave opposite results and a test on DNA breaks was negative.

There is sufficient evidence to classify the chemical as causing possible mutagenic effects.

Carcinogenicity

Classified by the International Agency for Research on Cancer (IARC) as Group 2B (possibly carcinogenic to humans) based on sufficient evidence of carcinogenicity in experimental animals (IARC 1999).

The chemical was tested for carcinogenicity by oral administration in one study in mice and in two studies in rats. No increase in the incidence of malignant tumours was found in mice (IARC 1999). In rats, it induced adenocarcinomas in the glandular stomach in several strains. In one study (ECHA 2012, Environment and Health Canada, 2008) administration of 0.1, 0.2, 0.4 or 0.8% (33, 65, 141, or 318 mg/kg bw/day) of the chemical in the diet in male F344 rats for 34 weeks caused hyperplasia and adenomas of the pyloric gland (glandular hyperplasia) at 141 or 318 mg/kg bw/day. Very weak hyperplasia was noted at 33 and 65 mg/kg bw/day. However, after a 2-year exposure, adenomas and submucosal hyperplasia of the glandular stomach were found in nearly all animals at 33 mg/kg bw/day and higher doses.

Environment and Health Canada (2008) reported that as the chemical was genotoxic in several *in vitro* and *in vivo* assays, in the absence of a fully elucidated mode of induction of tumours, it cannot be precluded that the tumours observed in experimental animals resulted from an interaction with genetic material. The OECD (2003a) also states that while only studies by the oral route are available, concerns for carcinogenicity at other sites of first contact cannot be dismissed.

Reproductive and Developmental Toxicity

Any reproductive and developmental effects were only observed secondary to maternal toxicity, so the chemical is not a specific reproductive or developmental toxin.

In a reproductive toxicity screening study in rats [OECD TG 422] the chemical was administered via oral gavage to 10 animals/sex/dose at 0, 30, 80 and 160 mg/kg bw/day for 4 weeks to males and 7 weeks to females. Mortality was observed at the highest dose in 2 males and 1 female, two in the pre-pairing period and one in the pairing period (ECHA 2012). As described under repeated dose toxicity clinical observations were described at the highest dose and a NOAEL of 30 mg/kg bw/d was derived based on squamous hyperplasia in the stomach. Hence the NOAEL for maternal toxicity was 30 mg/kg bw/d. The NOAEL for reproduction/ developmental toxicity was considered to be 160 mg/kg/day, the highest dose tested without observed effects.

The OECD (2003a) reported that in one developmental study with rats (one generation) with a single day administration by gavage on gestation day 11, maternal toxicity was observed at all doses tested (333, 667, 1000 mg/kg bw). Reduced body weight gains and mortality was observed at all three doses. Mortality in the dams at 1000 mg/kg was 67%. Litter size decreased at 667 mg/kg bw on postnatal day 6 and at 1000 mg/kg on postnatal day 1. Litter biomass decreased on postnatal day 1 at 667 mg/kg bw. A syndrome of malformation involving the limb, tail and urogenital system was observed. The litter incidence regarding hindlimb paralysis and/or short kinky tails was 21.4%, 66.7% and 80.0% for 333, 667 and 1000 mg/kg, respectively. Observed developmental effects were only in the presence of maternal toxicity.

Risk Characterisation

Critical Health Effects

The critical effects for risk characterisation are carcinogenicity, mutagenicity and skin sensitisation. The chemical is also expected to be acutely toxic via the oral and dermal routes, and is irritating to the skin and eyes.

Public Risk Characterisation

Considering the health effects, and the bioavailability of the chemical through the oral and dermal routes there is a concern in the use of this chemical as a ingredient in cosmetics or domestic products. As the chemical is carcinogenic and may also cause mutagenic effects, in the absence of a fully elucidated mode of induction of tumours, there is some concern whether the tumours observed in experimental animals resulted from direct interaction with genetic material. Furthermore, while only studies by the oral route are available, concerns for carcinogenicity at other sites of first contact cannot be dismissed. The chemical may also cause sensitisation if used regularly in contact with the skin. Hence, overall there is a concern in the potential use of this chemical in cosmetics or domestic products in the absence of any regulatory controls.

Canada, New Zealand and the European Union have restricted the use of this chemical in cosmetics. Currently there are no restrictions on the use of this chemical in Australia.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered high if adequate control measures to minimise occupational exposure to the chemical are not implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking, or an employee at a workplace has adequate information to determine appropriate controls.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend the chemical to be risk managed for public safety from the potential use in cosmetics and/or domestic products through scheduling, and occupational health and safety through classification and labelling.

The chemical is sufficiently assessed at the Tier II level subject to implementation of risk recommendations.

Regulatory Control

Public Health

The chemical is recommended for scheduling to prohibit its sale, supply and use in cosmetic products. Appropriate scheduling and labelling to be undertaken to mitigate risk for use in domestic products.

Matters to be taken into consideration include the carcinogenicity and potential mutagenicity of the chemical and, in the absence of a fully elucidated mode of induction of tumours, there is some concern whether the tumours observed in experimental animals resulted from an interaction with genetic material. Furthermore, while only studies by the oral route are available, concerns for carcinogenicity at other sites of first contact cannot be dismissed. Risk of skin sensitisation should also 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 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 in contact with skin (Xn; R21)*	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)

[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 label instructions.

Advice for industry

Work Health and Safety (WHS) legislation in each Australian state and territory imposes obligations on manufacturers and importers of hazardous chemicals to ensure that the chemicals are correctly classified, correctly labelled and (material) safety data sheets ((m)SDS) are prepared for those chemicals. These include:

- the (m)SDS for the chemical, or products and mixtures containing the chemical, must contain accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of a chemical, as well as instructions on the safe storage, handling, use and disposal of the chemical (a review of physical hazards of the chemical has not been undertaken as part of this assessment); and
- a copy of the (m)SDS must be easily accessible to employees.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals to meet duties under the WHS Regulations are provided in the *Preparation of Safety Data Sheets for Hazardous Chemicals—Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively.

To comply with the WHS legislation, a person conducting a business or undertaking (PCBU) at a workplace must manage risks arising from storage, handling and use of a hazardous chemical. Other duties may apply to a PCBU involved in the storage, handling and use of hazardous chemicals at a workplace. Refer to the WHS legislation in the relevant jurisdiction for further information.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice*.

It is recommended that a PCBU should ensure that:

- equipment be designed, constructed, and operated so that, the person handling the chemical does not come into contact with the chemical and is not exposed to a concentration of the chemical that is greater than the workplace exposure standard for the chemical;
- equipment used to handle the chemical retains the chemical, without leakage, at all temperatures and pressures for which the equipment is intended to be used and dispenses or applies the substance, without leakage, at a rate and in a manner for which the equipment is designed.

References

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