1,3-Benzenediol: Human health tier II assessment

21 April 2016

CAS Number: 108-46-3

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.

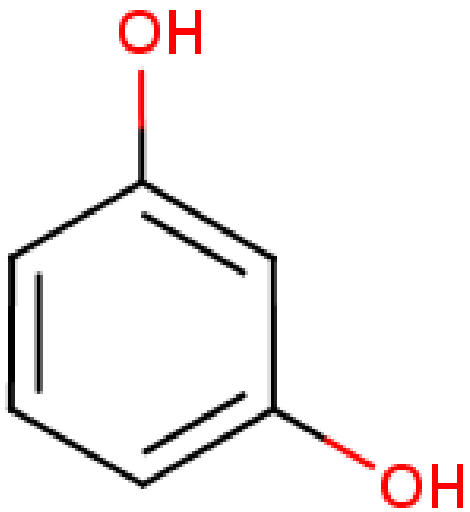
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	resorcinol 1,3-dihydroxybenzene 3-hydroxyphenol 3-hydroxycyclohexadien-1-one m-dihydroxybenzene
Structural Formula	
Molecular Formula	C6H6O2
Molecular Weight (g/mol)	110.11
Appearance and Odour (where available)	light pink flakes
SMILES	c1(O)cc(O)ccc1

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' with reported cosmetic use in permanent hair dye preparations (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 Substances and Preparations in Nordic countries (SPIN) database;
- 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 US Household Products Database; and
- various international assessments (Compilation of Ingredients Used in Cosmetics in the United States (CICUS), 2011; International Fragrance Association (IFRA), 2011; SCCS, 2010).

Resorcinol is used in oxidative hair colouring products at a maximum concentration of 2.5 %. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, which corresponds to a concentration of 1.25 % when applied to hair (SCCS, 2010).

The chemical has reported cosmetic uses:

- as a component of hair dyes, e.g. a colour additive and colourant in personal care products containing up to 1.5 % concentration in foam, liquid or gel form;
- in hair lighteners and hair colour sprays (aerosol);
- as a masking agent and fragrance ingredient (unspecified concentration); and
- in the formulation of other cosmetic products including aftershave lotions, cleansing and other skin products (unspecified concentration).

The chemical has reported domestic uses:

- in adhesives (binding agents), e.g. resorcinol-based resins; and
- as a colouring agent.

The chemical has reported commercial uses in:

- construction materials;
- dyeing and printing textiles;

- process regulators; and
- specialty adhesives and/or as an adhesion promoter for tyres, rubber and wood products.

The chemical has reported site-limited uses, including:

- as an intermediate in the manufacture of chemicals, oxidation hair dyes, light stabilisers for plastics and dyes; and
- as a vulcanising agent.

The chemical has reported non-industrial uses, including in:

- pharmaceuticals as a topical dermatitis treatment of acne and related-skin conditions (2–50% concentration) and bacterial and fungicidal skin ointments; and
- in veterinary medicines as a topical antipruritic and antiseptic.

Restrictions

Australian

No known restrictions have been identified for the chemical.

International

The chemical is listed on the EU Cosmetic Directive 76/768/EEC Annex III Part 1: List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down below (Galleria Chemica): (a) Hair dye substance in oxidative hair dye products for general and professional use—after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.25 % (w/w); and (b) Hair lotions and shampoos— maximum authorised concentration in the finished cosmetic product of 0.5 % (w/w).

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

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down;
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’); and
- Chile list of Cosmetic Ingredients with limited use or concentration.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xn; R22 (acute toxicity); and
- Xi; R36/38 (irritation).

Exposure Standards

Australian

The chemical has an exposure standard of 45 mg/m^3 (10 ppm) time weighted average (TWA) and 90 mg/m^3 (20 ppm) short-term exposure limit (STEL) (Safe Work Australia).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit of 45 mg/m^3 (10 ppm) TWA and 90 mg/m^3 (20 ppm) STEL in various countries such as Canada, Estonia, France, Germany, Iceland, Latvia, Netherlands, Russia, Sweden, United Kingdom and the United States of America (USA).

Health Hazard Information

The chemical 1,3-benzenediol, is a water soluble aromatic phenol (*meta*-isomer of benzenediol) commonly known as resorcinol (CAS No. 108-46-3). It is produced through sulfonation of benzene followed by fusion with an anhydrous caustic or through hydroperoxidation of 1,3-diisopropylbenzene (CAS No. 99-62-7) (OECD, 2008).

Toxicokinetics

Studies in rats and rabbits reported that the orally-administered chemical is rapidly absorbed, metabolised and excreted in the urine primarily as a monoglucuronide conjugate. Minor metabolites included a monosulphate conjugate, a mixed sulfate-glucuronide conjugate, and a diglucuronide conjugate. In rats, repeated oral doses of the chemical were reported to increase the rate of metabolism. Dermal absorption of the chemical was reported to be slow in humans but showed the same urinary excretion pathway and metabolites as those in orally-treated rats and rabbits (HSDB; REACH; OECD, 2008).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in HSIS (Safe Work Australia). The available data support this classification.

The chemical is of moderate acute oral toxicity based on results from key studies (equivalent to OECD TG 401 and 420) and a non-guideline animal study in rats following oral exposure. The median lethal doses (LD50) were reported to be 200, 510 and 980 mg/kg bw/day in female Sprague Dawley (SD) rats, male and female SD rats and male albino rats, respectively. In the first study, reversible treatment-related effects in all SD rats at the 200 mg/kg bw/day dose included: respiratory effects, lethargy, abnormal gait, hypoactivity, dyspnoea, tremors, convulsions and salivation (OECD, 2008; SCCS, 2010). Treatment-related effects in rats reported in the other two studies included behavioural and clinical abnormalities, gross lesions, body-weight changes, hyperaemia, and distention of stomach and intestines in animals that died (REACH; OECD, 2008).

Dermal

The chemical (flaked, industrial grade or in paste form of unspecified purity) has low acute dermal toxicity based on results from three non-guideline animal studies in male rabbits (three unspecified strains) following dermal exposure. The LD50 was reported

to be >2000 mg/kg bw/day (2830, 3360 and 3830 mg/kg bw). In two studies (flaked and industrial grade chemical), necrosis of the skin, and clinical signs including salivation, tremors, and convulsions prior to death were reported. Overt neurological effects were reported; however, the effects were considered to be associated with bolus dosing (refer to **Repeat dose toxicity: oral** section) (REACH; OECD, 2008).

Inhalation

The chemical has low acute inhalation toxicity based on results from two non-guideline animal studies in Harlan Wistar rats following inhalation exposure (aerosol). The median lethal concentrations (LC50s) were reported to be >7800 mg/m^3/1–hour (equivalent to 7.8 mg/L or 1732 ppm) and >2800 mg/m^3/8–hours (equivalent to 2.8 mg/L or 622 ppm), respectively. No lesions attributable to inhalation of the aerosol were reported at gross necropsy (REACH; OECD, 2008).

Corrosion / Irritation

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). While the available data do not support this classification, in the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend this classification.

The chemical is considered to be slightly to severely irritating to skin when administered in solution or in semi-solid state (flaked or industrial grade) (OECD, 2008).

In a non-guideline (Federal Hazardous Substance Labelling Act (FHSLA)) skin irritation study, 500 mg (0.5 g) of the chemical (flaked grade) in a physiological saline vehicle was applied to the clipped belly skin (abraded and intact) of albino rabbits (six males) for 24 hours under occlusive patches. Observations were made at 24 and 72 hours post-treatment, and animals were kept under observation for a maximum of two weeks. Treatment-related effects were moderate irritation on intact skin and necrosis on abraded skin. Effects were more pronounced at 72 hours post-treatment. In the two week recovery period, necrotic areas were still encrusted or scarred. The primary dermal irritation index (PDII) was reported to be 4.4 (REACH; OECD, 2008).

In similar non-guideline (FHSLA) studies, a 24-hour occluded application of the chemical (flaked and industrial grade) at 0.5 g to the bellies of male albino rabbits produced moderate irritation on intact skin and necrosis on abraded sites. The chemical (industrial grade) was reported to cause slight to severe irritation of the intact areas, and from severe irritation to necrosis of the abraded areas, 24 hours after exposure. In the two week post-recovery period, necrotic areas were still encrusted or scarred. The primary dermal irritation index (PDII) for the chemical was reported to be 4.4 (flaked grade) and 5.4 (industrial grade) (REACH; OECD, 2008).

In a study conducted according to OECD TG 404 (acute dermal irritation/corrosion), 0.5 mL of the chemical (2.5 % aqueous solution) (98.8 % purity) was applied to the clipped back skin of New Zealand White rabbits (three males/group) for four hours under semi-occlusive patches. Observations were made at one, 24, 48 and 72 hours post-treatment. No treatment-related effects (cutaneous reactions) were reported at this low concentration (REACH; SCCS, 2010; OECD, 2008).

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). Data from one study using the chemical (flaked and industrial grade in dissolved and semi-solid state, respectively) indicated that the chemical should be considered a severe eye irritant.

In a non-guideline (FHSLA) study, 0.1 g of the chemical (flaked and industrial grade) was instilled into the eyes of albino rabbits (six males). Treatment-related effects upon administration included inflamed conjunctivae, opaque corneas and discomfort in animals. At 24 hours post-exposure, observations included severe conjunctivitis, iritis, corneal opacity occluding most of the iris and corneal ulcerations. Irreversible effects on the eyes were reported and by day 14, all treated eyes had kerataconus (thinning

of and irregularly shaped cornea) and pannus (abnormal layer of fibrovascular tissue or granulation tissue over the cornea) formation. Total mean eye irritation Draize scores were reported to be 105/110 at 24, 48 and 72 hours and the chemical was considered as a severe eye irritant (REACH; OECD, 2008).

The chemical was mildly irritating in six albino rats administered 100 mg of the chemical (dry powder). Reported mean irritation scores are 56.3, 45.0 and 39.9 out of 110 over the observation period at 24, 48 and 72 hours, respectively. No further study details were available (REACH; OECD, 2008).

In a study conducted according to OECD TG 405 (acute eye irritation/corrosion), 0.1 mL of the chemical (2.5 % solution in water (98.8 % purity)) was instilled into the eyes (conjunctival sacs) of New Zealand White rabbits (three males) and left for 72 hours. Mean scores of zero were reported for chemosis, iris lesions and corneal opacity over 24, 48 and 72 hours. For redness of the conjunctivae, a mean score of 0.1 was reported (REACH; SCCS, 2010; OECD, 2008).

Sensitisation

Skin Sensitisation

Based on the available animal and human data (refer to **Sensitisation: Observation in Humans** section), the chemical is considered to be a moderate to strong contact skin sensitiser and is recommended for classification (refer to **Recommendation** section).

In a guinea pig maximisation test (GPMT) conducted in accordance with OECD TG 406, Pirbright white guinea pigs (treatment group 10 animals, control group 5 animals and accompanying group 20 animals used for range finding) were administered 2 % (w/v) solution of the chemical (99.9 % purity as white flakes in sodium chloride) by intradermal injection followed by occlusive, epicutaneous application of 25 % the chemical. At the challenge exposure using 25 % of the chemical (occlusive epicutaneous application), no clinical signs were reported. However, at first challenge, very slight to distinct erythema was observed on the skin of two or three animals at 24 and 48 hours observation periods. At the second challenge, very slight to distinct erythema was reported in seven animals at 24 hours and on 5 animals at 48 hours and minor swelling was also observed in one animal at 24 hours after patch removal. The relative incidence of the positive reactions in animals was over the threshold value of 30 % and the chemical was considered to be a skin sensitiser (REACH; OECD, 2008).

In a study conducted in accordance with OECD TG 429, positive skin sensitisation was reported in mouse local lymph node assay (LLNA) studies in two independent experiments. A positive control of α-hexylcinnamaldehyde (HCA), a moderate sensitiser, at the concentration of 25 % (v/v) in dimethylformamide (DMF) was used. In the first experiment (range finding), female CBA/J mice (four animals/dose including negative and positive controls) were administered 25 µL of the chemical (in vehicle dimethylformamide at 2.5, 5, 10, 25 or 50 %) applied to the dorsal surface of each ear, once daily for three consecutive days. Stimulation indices (SI) of 3.83, 4.14, 3.97, 3.51 and 3.30 were reported, respectively. Positive lymphoproliferative responses (SI > 3) were reported at all concentrations, but no clear dose-response relationship was observed. In the second experiment, mice (four/dose) were administered daily applications of 0.1, 0.5, 1, 5 or 25 % chemical (w/v). Treatment resulted in stimulation indices of 1.58, 2.87, 1.97, 3.51 and 5.74, respectively. A dose-related increase in SI was seen and the threshold positive value of 3 was exceeded. The effective concentration at which a three-fold increase in stimulation index was achieved (EC3) was reported to be 1.4 % and the chemical was reported to be a moderate skin sensitiser (REACH; OECD, 2008; SCCS, 2010).

The chemical (purity unspecified) was not reported to be sensitising according to two non-guideline skin sensitisation (LLNA) studies in mice (concentrations of up to 2.5 % and 25 % w/v were tested, respectively). No further study details were available and the reliability of both studies was questioned due to outdated study methods (OECD, 2008). However, the chemical was reported to be a sensitiser in mice in a LLNA study (OECD TG 429). A group of CBA/Ca female mice (four/dose) were treated at daily concentrations of 0, 1, 5, 10, 25 and 50 % (w/v) of the chemical (purity unspecified) in acetone/olive oil (ratio of 4:1). Stimulation indices of 1.0, 0.7, 2.2, 5.2, 8.4 or 10.4 were measured respectively, and an EC value of 6.3 % was determined (REACH; OECD, 2008).

Observation in humans

Human patch-testing using the chemical elicited allergic skin reactions in 0.7–0.8 % of 1694 dermatitis patients. In further case histories of 34 dermatitis patients, the chemical was reported cause reactions after epicutaneous testing (REACH; OECD, 2008).

No dermatitis of the hands was reported for 42 workers from a tyre factory after an epicutaneous test with the chemical (REACH; OECD, 2008).

In human patch tests with the chemical (2 % in petrolatum), four out of 302 hairdressers suffering from contact dermatitis reported a positive reaction. No further details were available. In another case, one patient who developed contact dermatitis after application of paint to the skin was patch tested with the chemical (5 % in petrolatum) and showed a positive result after 48 hours. In a third case, three female patients suffering from acne and contact dermatitis gave a positive patch test for the chemical (2 % in petrolatum) after 48 and 72 hours (REACH; OECD, 2008).

Repeated Dose Toxicity

Oral

Based on weight-of-evidence, the chemical is not considered to cause serious damage to health from repeated oral exposure.

Several studies were conducted by National Toxicology Program (NTP) in rats and mice for 17 days, and 13 and 104 weeks through the oral bolus (gavage). The NTP review panel concluded neurological effects of the chemical were due to the dosing method (OECD, 2008).

In Fischer 344 (F344) rats, NOAELs of 27.5 and 110 mg/kg bw/day (for females and males, respectively) were reported in a 17-day (range finding) repeated dose oral study based on overt neurological effects (hyperexicitability and tachypnoea) at doses of 55 mg/kg bw/day and higher in females and at doses of 225 mg/kg bw/day and higher in males. Decreased absolute and relative thymus weights in female rats were reported at 450 mg/kg bw/day (highest dose tested) (REACH; OECD, 2008; SCCS, 2010).

In B6C3F1 mice, NOAELs of 75 and 150 mg/kg bw/day (for males and females, respectively) were reported in a 17-day (range finding) repeated dose oral study based on overt neurological effects (prostration and tremors) in males at doses of 150 mg/kg bw/day and higher and females at doses of 300 mg/kg bw/day and higher. Mortality in males was reported in 20 % and 80 % of animals at the 300 and 600 mg/kg bw/day doses, respectively. Mortality was reported in all females at 600 mg/kg bw/day (highest dose tested) (REACH; OECD, 2008; SCCS, 2010).

In a 90-day repeated dose oral toxicity study (OECD TG 408), SD rats (20/sex/dose) were administered the chemical (>95 % purity) through oral gavage at doses of 0, 40, 80, or 250 mg/kg bw/day for five days/week. At 250 mg/kg bw/day, intermittent convulsive movements and excessive salivation were observed along with loud breathing in two males. However, the functional observational battery did not show treatment-related neurological effects. Female animals showed reduced body weight gains from weeks 4–8. The NOAEL for both sexes was reported to be 80 mg/kg bw/day (OECD, 2008; REACH).

In F344 rats, NOAELs of 32 and 65 mg/kg bw/day (for females and males, respectively) were reported in a 13-week repeated dose oral study (similar to OECD TG 408) based on increased absolute and relative liver weights in females at 65 mg/kg bw/day and increased absolute liver weights in males at 130 mg/kg bw/day and higher. The neurological effect (tremor) was reported in both sexes at 520 mg/kg bw/day (highest doses tested). In males, the absolute and relative adrenal weights were significantly increased in all surviving animals (REACH; OECD, 2008; SCCS, 2010).

In B6C3F1 mice, a NOAEL of 225 mg/kg bw/day for both sexes was reported in a 13-week repeated dose oral study based on neurological effects (dyspnoea, prostration and tremors). Mortality was reported in both sexes at 420 mg/kg bw/day (highest dose tested) (REACH; OECD, 2008; SCCS, 2010).

In F344 rats, a NOAEL of 50 mg/kg bw/day (for females only) was reported in a 104-week repeated dose oral study based on neurological effects (ataxia, prostration, salivation and tremors at 100 mg/kg bw/day). A NOAEL for male rats was not established. A LOAEL of 112 mg/kg bw/day was reported for males rats based on neurological effects similar to those seen in females. The lowest dose tested in males and females were 112 and 50 mg/kg bw/day, respectively. Decreased body weights and increased mortalities were reported at 150 and 225 mg/kg bw/day (highest doses tested) in females and males, respectively (REACH; OECD, 2008; SCCS, 2010).

In B6C3F1 mice, a NOAEL for both sexes was not established in a 104-week repeated dose oral study using the chemical at doses of 0, 112, 225 mg/kg bw/day. However, a LOAEL of 112 mg/kg bw/day based on neurological effects (ataxia and tremors) in males and females was reported. Decreased body weight in females was reported at 225 mg/kg bw/day (REACH; OECD, 2008; SCCS, 2010).

A number of systemic effects reported included adrenal weight changes and liver weight changes in the 17-day, 13 and 104-week studies in rats and mice. However, these effects were not observed in a subsequent reproductive study (OECD TG 416) conducted in rats at concentrations up to 3000 mg/L (calculated doses of 304 mg/kg bw/day during premating and gestation; and 660 mg/kg bw/day during lactation) (refer to **Reproductive & Developmental Toxicity** section).The reproductive study also included a detailed evaluation of the thyroid endpoints where no significant effects on the thyroid were observed in rats administered with up to 233 mg/kg bw/day (males) or 304 mg/kg bw/day (females) of the chemical in drinking water (REACH; OECD 2008).

Dermal

No data are available for the chemical.

Inhalation

Based on the limited data available, there is insufficient evidence to support hazard classification for repeated dose inhalation toxicity.

A sub-acute inhalation study (range study to determine appropriate concentrations for a 90-day study) reported no treatment-related systemic effects when Wistar rats (five/sex) were exposed to the chemical at a concentration of 220 ppm (calculated dose of 993 mg/kg bw/day), eight hours/day for 14 days. It was reported at the 220 ppm dose, only one male had slight haemorrhagic spotting on the lungs while the remaining tissues appeared normal. No further study details were available as the subsequent 90-day study was not conducted (REACH).

Genotoxicity

Based on the available weight-of-evidence, the chemical is not considered to be genotoxic (OECD, 2008).

Several in vitro assays using the chemical gave predominantly equivocal results (REACH; OECD, 2008; SCCS, 2010) in the following studies:

- negative results for bacterial mutation assays (various *Salmonella typhimurium* strains) with and without metabolic activation at doses of up to 5000 µg/plate;
- negative results in two gene mutation assays using mouse lymphoma (L5178Y hprt (hypoxanthine-guanine phosphoribosyl transferase) locus) cells with and without metabolic activation at doses of up to 1101 µg/mL (10 mM);
- mixed results for gene mutation assay in mouse lymphoma (L5178Y tk locus) cells (negative result with metabolic activation and a positive result without metabolic activation) at doses of up to 1101 µg/mL (10 mM);
- a positive result for gene mutation assays in mouse lymphoma (L5178Y thymidine kinase locus) cells without metabolic activation only, at doses up to 10 mM.
- mixed results in two mammalian micronucleus tests using human peripheral lymphocyte cells (equivocal results with metabolic activation and positive result without metabolic activation) at doses of up to 1100 µg/mL. The positive result was not reproduced in a second test;
- a negative result for unscheduled DNA synthesis in F344 rat hepatocytes at doses up to 1000 nmoles/mL;
- a negative result in Syrian hamster embryo cell morphological transformation assay at doses up to 138 µg/mL; and

- positive results for sister chromatid exchange in Chinese hamster ovary (CHO) cells with and without metabolic activation at doses up to 1670 µg/mL.

The chemical gave predominantly negative results in the following in vivo studies (REACH; OECD, 2008; SCCS, 2010):

- a negative result in a mammalian erythrocyte micronucleus tests in rat (various strains) bone marrow cells at doses of up to 500 mg/kg bw;
- a negative result in a transgenic mouse model for activation of RasH2;
- negative results for inducing bone marrow chromosomal aberrations in SD rats at doses up to 300 mg/kg bw;
- a negative and equivocal result for a sex-linked recessive lethal test in *Drosophila melanogaster* (doses up to 11940 ppm); and
- a negative result for a sex-linked recessive lethal test in *Drosophila melanogaster* (doses up to 50 mM).

Carcinogenicity

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

In a non-guideline study, F344/N male rats and B6C3F1 female mice were orally administered doses of 112 or 225 mg/kg bw/day; and 50, 100 or 150 mg/kg bw/day of the chemical (> 99 % purity), respectively for five days a week over two years. No treatment-related effects in clinical pathology parameters or statistically significant increase in the incidence of tumours in rats or mice were reported (REACH; OECD, 2008; SCCS, 2010).

Reproductive and Developmental Toxicity

The chemical is not considered to be a reproductively or developmentally toxic.

Reproductive toxicity

In a two-generation reproductive toxicity study (OECD TG 416), Crl:CD rats (30/sex/group) were orally administered the chemical (99.8 % purity) in drinking water at concentrations of 0, 120, 360, 1000 or 3000 mg/L for both the F0 and F1 generations, at least 70 days prior to mating. The chemical concentrations of approximately 0, 11, 31, 86 and 233 mg/kg bw/day were administered to males over the entire generation; 0,16, 48, 126 and 304 mg/kg bw/day for females during premating and gestation; and 0, 28, 85, 225 and 660 mg/kg bw/day for females during lactation, respectively. There were no treatment-related effects on reproductive parameters, offspring growth, or developmental toxicity at any exposure level. The NOAEL for male reproductive toxicity (F0) was determined to be 3000 mg/L (calculated dose of 233 mg/kg bw/day). The maternal NOAEL was 3000 mg/L (calculated doses of 304 mg/kg bw/day during premating and gestation; and 660 mg/kg/day during lactation). The NOAEL for reproductive toxicity (fertility and development) was 3000 mg/L (calculated dose of 245 and 295 mg/kg bw/day in F1 males and females, respectively) (REACH; OECD, 2008; SCCS, 2010).

Developmental toxicity

In a developmental toxicity study (OECD TG 414), Wistar rats were orally administered with the chemical (99.8 % purity) in drinking water at daily doses of 40, 80, 250 mg/kg bw/day on gestation days (GD) 6–19. In the high dose group, decrease in maternal body weight was reported. No significant treatment-related effects in the offspring were reported. The maternal NOAEL was 80 mg/kg bw/day based on statistically significantly decrease in body weight gains at 250 mg/kg bw/day (the highest dose tested). The developmental NOAEL was determined as 250 mg/kg bw/day (REACH; OECD, 2008; SCCS, 2010).

In a supporting developmental toxicity study, teratogenicity was not reported in SD rats that were administered the chemical by oral gavage at doses of 0, 125, 250 or 500 mg/kg bw/day on GD days 6–15. No significant treatment-related effects were reported in foetal parameters (anomalies and weights or on resorptions). The maternal and developmental NOAELs were 500 mg/kg bw/day (the highest dose tested) (REACH; OECD 2008).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral exposure) and local effects (skin and eye irritation, and skin sensitisation).

Public Risk Characterisation

The chemical was reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007) and in overseas hair lotions and shampoos (refer to **Import, Manufacture and Use** section).

The EU has restricted the use of this chemical in oxidative hair colouring products at a maximum concentration of 2.5 %. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, which corresponds to a concentration of 1.25 % when applied to hair (SCCS, 2010). Restricted use in hair lotions and shampoos was also reported to be the maximum authorised concentration in the finished cosmetic product of 0.5 % (refer to **International restrictions section**).

Currently, there are no restrictions in Australia on using this chemical in hair dyes, hair lotions and shampoos. In the absence of any regulatory controls, the characterised critical health effects (skin and eye irritation, and skin sensitisation) have the potential to pose an unreasonable risk under the identified uses. The risk could be mitigated by implementing concentration limits for use in hair dyes, hair lotions and shampoos.

Occupational Risk Characterisation

Given the critical local 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 (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support hazard classification in the HSIS (Safe Work Australia) (refer to **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

Given the risk characterisation, it is recommended that the chemicals should be included in Schedule 6 and 10 (Appendix C) of the *Poisons Standard* (the *Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) with an appropriate concentration cut-off (exemption) for hair dye use.

Consideration should be given to the following:

- the chemical has moderate acute oral toxicity;
- the chemical is a severe eye irritant and is classified as a skin irritant;
- the chemical is a moderate skin sensitiser;
- overseas restrictions for use of this chemical in hair dyes. The maximum concentration in oxidative hair colouring products is 2.5 %. It is mixed with hydrogen peroxide in a 1:1 ratio just prior to use, which corresponds to a concentration of 1.25 % when applied to hair (SCCS, 2010); and
- overseas restrictions for use of this chemical in hair lotions and shampoos. The maximum authorised concentration in the finished cosmetic product is 0.5 % (COSIng).

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 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)* 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)

[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 which can 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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.

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