1,2,3-Benzenetriol: Human health tier II assessment

03 July 2015

CAS Number: 87-66-1

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.

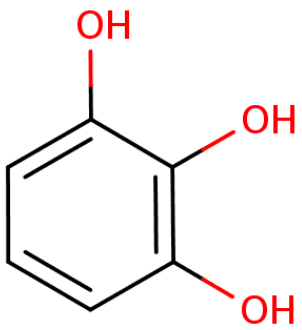
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	pyrogallol pyrogallic acid 1,2,3-trihydroxybenzene
Structural Formula	
Molecular Formula	C6H6O3
Molecular Weight (g/mol)	126.1104
Appearance and Odour (where available)	odorless, white to gray solid
SMILES	c1(O)c(O)c(O)ccc1

Import, Manufacture and Use

Australian

No specific Australian industrial use, import, or manufacturing information has been identified under previous mandatory and/or voluntary calls for information.

The chemical has been used in Australia as a topical therapy for chronic plaque psoriasis, but the usage has declined since the 1960s (Willsteed & Regan, 1985).

International

The following uses were identified through Galleria Chemica, European Commission Health Cosmetic Ingredients and Substances (CosIng), Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI), the Substances in Preparations in Nordic Countries (SPIN), the United States (US) National Toxicology Program (US NTP, 2013), Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011), US Occupational Health Database (HazMap), Handbook of Preservatives (Ash & Ash, 2004), the National Health Surveillance Agency (ANVISA, 2013), and Combined Chemical Dictionary Online (ChemNetBase).

The chemical has reported cosmetic uses, including in:

- dyes including hair dyes and colours;
- fragrances; and
- hair straighteners.

The chemical has reported domestic uses, including in:

- paints, lacquers and varnishes (e.g. rust inhibitors); and
- adhesives.

The chemical has reported commercial uses, including as:

- a developer in the photo industry;
- an ingredient in manufacturing pharmaceuticals and pesticides
- a mordant for wool;
- an ingredient in staining leather and fur; and
- an antioxidant in lubricating oils.

The chemical has reported site-limited uses including:

- as an intermediate (e.g. in producing fluorinated surfactants and/or fluorinated urethanes);
- in process engraving;
- as an oxygen absorber for gas analysis; and
- as an active reducer for gold, silver, and mercury salt.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria):

- the 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;
- Canada Cosmetic Ingredient Hotlist: List of ingredients that are prohibited for use in cosmetic products;
- European Union (EU) Commission Regulation (EC) No 1223/2009 on cosmetic products - annex II – List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard – Shedule 4: Components cosmetic products must not contain – table 1;
- China – List of banned sbstances for use in cosmetics;
- Philippines restricted ingredients for use in cosmetics – List of substances which cosmetics products must not contain except subject to the restrictions and conditions specified. Conditions: (a) Do not use to dye eyelashes or eyebrows. Rinse eyes immediately if product comes into contact with them. (b) For professional use only; and
- Thailand Cosmetic Act – specially controlled substances: Permanent hair dyeing products, 5 %.

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; R20/21/22 (acute toxicity)
- Muta. Cat 3; R68 (mutagenicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

Protective Action Criteria (PAC) Rev 27 (United States)

PAC-1: 0.15 mg/m^3

PAC-2: 1.6 mg/m^3

PAC-3: 31 mg/m^3

Health Hazard Information

Toxicokinetics

Limited information is available for the toxicokinetics of the chemical.

Albino rats (sex not specified) were administered 100 mg/kg body weight (bw) pyrogallol either via gavage or intraperitoneally (i.p.). Pyrogallol and its metabolites including 2-*O*-methyl pyrogallol and resorcinol (1,3-dihydroxybenzene) were detected in the urine 24 hours after dosing (CIR, 1991; US NTP, 2013).

In another study, following oral (gavage) administration of 100 mg pyrogallol/kg bw to male albino rats, 6.2 % of the dose was detected in the urine 48 hours after dosing as 2-*O*-methyl pyrogallol (US NTP, 2013).

In another study, the chemical was detected in the brain. The maximum concentration of pyrogallol in the brain of male mice (strain not reported) was detected 10 minutes after i.p. administration of 120 mg/kg bw (Rogers et al., 1968). In female mice (strain not specified) receiving 60 mg pyrogallol/kg bw i.p., the maximum concentration in the brain was detected 10 minutes after administration, but the chemical was not detectable in the brain after 15 minutes (Angel et al., 1969). Following an intraventricular dose of 2 mg of pyrogallol in male Wistar rats, metabolites were detected in the brain (CIR, 1991; US NTP 2013).

Pyrogallol is detected in human urine and faeces, but is assumed to be a metabolite of tea polyphenols (Daykin et al., 2005; CIR, 2009; Schantz et al., 2010).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available information (both animal and human data; see ***Observation in humans***) supports this classification.

In a non-guideline gavage study, the acute oral toxicity of technical synthetic pyrogallol (TS pyrogallol; 92.2 % w/w) and technical natural pyrogallol (TN pyrogallol; 98.8 % w/w) was assessed in male and female Sprague Dawley (SD) rats. Males were exposed to 800, 1131, 1600, or 2261 mg TN pyrogallol/kg bw or to 566, 800, 1131 or 1600 mg TS pyrogallol/kg bw (six/group). Females were exposed to 566, 800, 1131, or 1600 mg TN pyrogallol/kg bw or to 283, 400, 566, 800, or 1131 mg TS pyrogallol/kg bw (six/group). Acute oral median lethal dose (LD50) values (Weil method) were 1270 mg/kg in males and 800 mg/kg in females for TS pyrogallol, and 1270 mg/kg in males and 848 mg/kg in females for TN pyrogallol. The symptoms were similar for both TS and TN pyrogallol and included cyanosis, reduced activity, reduced muscle tone, body tremors, ataxia, lacrimation, salivation, piloerection, coolness to the touch, hunched posture, pale extremities and general soiling. Gross necropsy revealed cyanosis, dark and/or enlarged spleen, dark kidneys, brown or pale liver and lungs, distension of the stomach and bladder, and fluid in the intestines (US EPA, 1984; CIR, 1991; US NTP, 1998).

The acute oral toxicity of a 50% solution of pyrogallol (in DMSO) was evaluated in ten male SD rats. The LD50 was 1800 mg/kg bw. No other details were provided for this study (CIR, 1991).

In a non-guideline study in rabbits, the oral LD50 was reported as 1600 mg/kg bw following exposure to 750–2000 mg/kg pyrogallol by gavage. The effects involved gastrointestinal changes, hepatotoxicity and chronic pulmonary oedema (US NTP, 1998; 2013).

Dermal

The chemical is classified as hazardous with the risk phrase 'Harmful in contact with skin' (Xn; R21) in the HSIS (Safe Work Australia). The available human data (see ***Observation in humans***) support this classification.

In a non-guideline study, the dermal toxicity of TS pyrogallol and TN pyrogallol was evaluated in male and female SD rats (six/group) with application via occlusive dermal patches at 2100 mg/kg bw for 24 hours. An LD50 could not be determined for either test substance at the administered dose (dermal LD50 >2100 mg/kg bw) (CIR, 1991).

Survival was not affected in guinea pigs when 25 mg/site of pyrogallol was applied via occlusive dermal patches to two separate sites for 24 hours. However, slight local skin irritation was detected (US NTP, 1998). No other study details were provided.

Inhalation

The chemical is classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in the HSIS (Safe Work Australia).

No data are publicly available that assess inhalation toxicity. However, lungs are reported as the target organ following acute oral and subcutaneous exposure in humans as well as following oral exposure in rats (ChemID Plus).

Therefore, in the absence of any substantial information, no amendment to the classification is recommended.

Observation in humans

Pyrogallol ingestion or excessive skin application can cause severe poisoning and ultimately death in humans (Gosselin et al., 1984). Poisoning through skin absorption or ingestion has been reported to produce a range of symptoms and outcomes, including local pain/oedema, malaise, nausea, vomiting, diarrhoea, organ congestion, haemorrhage, parenchymatous degeneration of the liver, somnolence, coma, convulsions, cardiac failure, and death (CIR, 1991). Pyrogallol is mildly caustic to skin and mucous membranes (US NTP, 1998).

Reports of accidental poisoning include a psoriatic male patient who covered two-thirds of his body with an ointment containing pyrogallol. The man collapsed within five minutes and died 24 hours later. The patient was estimated to absorb 10 g of pyrogallol, which corresponds to a 143 mg/kg bw dose based on 70 kg bw (US NTP, 2013).

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

Mixed findings are reported for the skin irritation potential of the chemical.

Skin irritation potential was assessed in a non-guideline study in albino rabbits. Each rabbit had 500 mg of pyrogallol powder applied to abraded and intact skin sites and each site was covered for 24 hours with an occlusive patch. Reactions were scored 24 and 72 hours after patch application. A primary irritation index of 0.5 was reported, indicating a low irritation potential (US NTP, 1998).

In another non-guideline study, six female Dunkin Hartley guinea pigs were applied with 25 mg pyrogallol to two sites (in 0.5 mL of distilled water/site) on the back of each animal with patches made of lint. The exposure sites were covered for 24 hours. Sites were then washed with soap and water, rinsed, and dried. Slight erythema was observed at one site treated with TN pyrogallol (three guinea pigs), and at one site treated with TS pyrogallol (two guinea pigs) (US NTP, 1998).

A non-guideline skin irritancy assay was conducted in BALB/c mice using exposure levels of 0.125 %, 0.25 %, 1.0 %, 5 %, and 10 % pyrogallol. The results suggested that pyrogallol is a skin irritant at the lowest concentration of 0.125 % (US NTP, 2006;

Guo et al., 2013).

Eye Irritation

The eye irritation potential of the chemical has not been sufficiently assessed. The available data suggest that the chemical could be an eye irritant. However, the limited information is not sufficient to warrant a hazard classification.

The ocular irritation of the chemical was evaluated in male New Zealand White rabbits (six/group). Pyrogallol was applied as powder (100 mg) into the conjunctival sac, or 0.1 ml of a 1 % pyrogallol solution in propylene glycol was instilled into the left eye. The eyes were not rinsed after instillation in either treatment group. Untreated eyes served as controls. Pyrogallol (powder form) induced ocular irritation, although the 1 % solution was not an ocular irritant (CIR, 1991).

Sensitisation

Respiratory Sensitisation

No data are available.

Skin Sensitisation

Based on the available information (both animal and and human data; see ***Observation in humans***), pyrogallol is considered to be a skin sensitiser, warranting hazard classification.

A local lymph node assay (LLNA) was conducted with BALB/c mouse following dermal application of pyrogallol in acetone:olive oil (4:1). The chemical was applied at 0.25, 0.5, 1, 2.5, 5, and 10 % dilutions. All dilutions except 0.25 % exhibited a significant increase (stimulation index (SI) >3) in the proliferation of lymph node cells when compared with vehicle controls. The SI 3 value was calculated as a ratio of proliferating lymph node cells in pyrogallol exposed mice compared with the vehicle treated controls (Guo et al., 2013).

The skin sensitisation potential of pyrogallol (purity not specified) was evaluated in female Hartley guinea pigs. On three consecutive days, 0.1 mL of 0.01 M pyrogallol or 0.05 M pyrogallol were injected subcutaneously into the feet of 21 guinea pigs. During the same week, a fourth injection was made at a site near the neck. During the challenge, test solutions were injected subcutaneously four weeks after the first injection. Of the 21 guinea pigs tested, seven and 14 animals showed positive reactions to 0.01 M pyrogallol and 0.05 M pyrogallol, respectively (CIR, 1991).

In a similar study, eight guinea pigs were injected subcutaneously with 0.01 or 0.1 M pyrogallol according to the induction procedure above. The challenge used topical sealed cloth applications of test solutions. At 0.01 M and 0.1 M pyrogallol, three and six animals showed positive reactions, respectively (CIR, 1991).

In another study, 0.05 mL of 1 % pyrogallol (in water) was injected intradermally in 10 female Hartley albino guinea pigs. A week later, 25 % solution of the test substance (in propylene glycol) was applied topically. Each site was covered with an occlusive patch for 48 hours. No further experimental details were reported. After a two-week non-treatment period, the animals were challenged with a single topical application of the 25 % solution. There was no evidence of sensitisation in any of the animals tested (US NTP, 1998).

Observation in humans

Pyrogallol is a contact sensitiser in humans, particularly in individuals exposed to hairdressing chemicals (US NTP, 2013).

Patch tests were conducted in hairdressers and their customers who reported contact dermatitis. The volunteers were administered 1 % (79 mM) pyrogallol in petrolatum by occlusive patch for 2–3 days. Depending on the study, 0.76–2.3 % of participants had positive reactions. Two other studies compiled medical record data from patients undergoing patch testing (1 %

pyrogallol) for suspected allergies to hairdressing chemicals. Positive reactions were detected in 5.4 % (Hillen et al., 2007) or 9.1 % (Wang et al., 2011) of patients tested.

Five out of eight individuals known to be sensitive to resorcinol (1,3-benzenediol, CAS No. 108-46-3) showed mild reponses to treatment with 2 % (159 mM) pyrogallol in alcohol by occlusive patch (exposure length not provided; US NTP, 2013).

In another study, 25 patients with leg ulcers were patch tested with pyrogallol. Positive reactions to pyrogallol were observed in three patients (CIR, 1991).

No positive reactions to pyrogallol (1 %) were reported when a total of 8230 patients with allergic contact dermatitis were patch tested with cosmetic ingredients over a period of 15 years (1968–1983) (CIR, 1991).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

Based on available data, repeated dermal dosing does not cause severe systemic toxicity.

In a non-guideline study, New Zealand White rabbits (six animals/sex) were treated with a hair dye formulation containing 0.4 % pyrogallol mixed with an equal volume of 6 % hydrogen peroxide (H_2O_2) applied to the skin of for one hour, twice a week, for 13 weeks. Skin was washed and dried after the treatment. After 13 weeks, slight thickening of the skin was observed only at sites where the dye had been applied. No gross or microscopic changes related to administration of the dye were observed (CIR, 1991).

In a study conducted in compliance with good laboratory practice (GLP), groups of 10 male and 10 female F344/N rats were treated with 0, 9.5, 18.75, 37.5, 75, or 150 mg/kg bw/day (in 95 % ethanol) five days per week for 14 weeks. Additional groups of 10 male and 10 female rats were administered the same doses, five days per week for 23 days. The exposure did not cause lethality or affect body weight. Chemical-related clinical findings included brown staining and irritation of the skin at the site of application. Haematology, serum clinical chemistry, thyroid hormone values or organ weights were not affected (Mercado-Feliciano et al, 2013).

In another GLP study, groups of 10 male and 10 female B6C3F1/N mice received dermal applications 0, 38, 75, 150, 300, or 600 mg/kg bw/day (in 95 % ethanol), five days per week for 14 weeks. No chemical-related lethality or effects on body weight were reported. Clinical findings included brown staining and irritation at the site of application. No treatment-related changes in haematology or organ weights were observed (Mercado-Feliciano et al, 2013).

In another non-guideline study, dermal exposure of rabbits to 5–50 % of pyrogallol applied to the ear twice a week for their lifetime did not affect survival (Stenback, 1977).

In another non-guideline study, no significant treatment-related changes in mice were reported following a lifetime application of up to 0.01 mg pyrogallol in acetone twice per week (Stenback & Shubik, 1974). Application of an oxidative hair dye formulation containing 0.49 % pyrogallol (mixed with 6 % H_2O_2) to the shaved skin of mice once per week for nine or 20 months did not affect average body weight gain or survival (Jacobs et al., 1984).

A calculated dose of 8 mg/kg per day applied to the shaved skin of rats (exposure duration not specified, but probably less than 21 days) led to skin irritation (Burnett et al., 1976).

In a two-year follow up GLP study, 50 male and 50 female F344/N rats received dermal applications of pyrogallol in 95 % ethanol at doses of 0, 5, 20, or 75 mg/kg bw/day, five days per week for up to 104 weeks. No chemical-related lethality or effects on body weight were reported (Mercado-Feliciano et al, 2013).

In a two-year follow up GLP study, groups of 50 male and 50 female B6C3F1/N mice received dermal applications of 0, 5, 20, or 75 mg pyrogallol/kg bw/day (in 95% ethanol), five days per week for up to 105 weeks. Exposure to 75 mg/kg/day significantly reduced survival in females; most early deaths in this group were due to ulcers at, or adjacent to, the application site. The body weights of the 75 mg/kg/day-exposed female mice were generally reduced by over 10% compared with controls. Sebaceous gland hyperplasia was significantly increased in the female mice dosed with 75 mg/kg/day. Survival of male mice was not affected (Mercado-Feliciano et al, 2013).

Inhalation

No data are available.

Observation in humans

A psoriasis patient who applied an aqueous solution of 10 % pyrogallol (793 mM) to his hands daily for 40 years developed ulcerated lesions on the back of the hand. These lesions could not be explained by exposure to other substances or UV radiation (Willsteed & Regan, 1985).

Genotoxicity

The chemical is classified as a Category 3 mutagen with the risk phrase ‘Possible risk of irreversible effects’ (Xn; R68) in the HSIS (Safe Work Australia). The classification is supported by the weight of evidence from in vitro and in vivo experiments.

The chemical gave the following positive results in inducing DNA strand breaks in acellular tests (metabolic activation status not provided; US NTP, 1998):

- in purified ? phage DNA (250 µM),
- in pBR322 plasmid DNA (1 mM), and
- in calf thymus DNA in the presence of Fe^{2+} (0.18 mM).

In vitro studies conducted on the chemical gave the following positive results (CIR, 1991; US NTP, 2013):

- in a bacterial gene mutation assay using *Salmonella typhimurium* strains TA97 (200 or 500 µg/plate), TA98 (4–3600 µg/plate), TA100 (5–5000 µg/plate), TA104 (200 or 500 µg/plate) and TA1537 (15–5000 µg/plate) with or without metabolic activation (S9) and strain TA102 (200 µg/plate) without metabolic activation (S9) only;
- in its ability to induce colicin E2 or umu gene in *Salmonella typhimurium* strains REN or TA1535/Psk1002, respectively;
- in a mitotic gene conversion assay in *Saccharomyces cerevisiae* strain D7 (2380 µM at pH10, metabolic activation status not provided);
- in inducing chromosomal aberrations in human lymphocytes (100–793 µM) and Chinese hamster ovary (CHO) cells (793 µM) with or without metabolic activation (S9);
- in inducing mutations in L5178Y mouse lymphoma cells (32–634 µM) with or without metabolic activation (S9); and
- in inducing induced sister chromatid exchanges in Chinese hamster V79 (up to 25 µM) cells (metabolic activation status not provided).

In vitro studies on the chemical gave the following negative results (CIR, 1991; US NTP, 2013):

- In a bacterial gene mutation assay using *Salmonella typhimurium* strains TA100 (4–378 µg/plate), TA1535 (1.25–5000 µg/plate), TA1538 (15–5000 µg/plate) with or without metabolic activation (S9); strains TA98 (1.25–5000 µg/plate), TA102 (1.25–500 µg/plate), TA1537 (378–3600 µg/plate) with metabolic activation (S9) only; and strains TA98 (5–5000 µg/plate), TA1537 (378 µg/plate) without metabolic activation (S9) only;

- in a mitotic gene conversion assay in *Saccharomyces cerevisiae* strain D7 (2380 µM at pH7, metabolic activation status not provided); and
- in inducing chromosomal aberrations in CHO K1 cells (20–79 µM, metabolic activation status not provided).

The chemical gave the following results for in vivo studies (CIR, 1991; US NTP, 2013):

- in the mouse micronucleus test, 252 mg/kg pyrogallol was administered (i.p.) to four mice at 0 and 24 hours. An untreated group of four mice served as the control. Bone marrow smears were prepared at 30 hours. Pyrogallol significantly increased the percentage of micronucleated polychromatic erythrocytes (CIR, 1991); and
- in the mouse in vivo chromatic break test, mice were injected i.p. with 0.01 M, 0.02 M, and 0.03 M solutions of pyrogallol. At 24 hours after administration, chromatid breaks were observed only in bone marrow cells from mice dosed at 0.02 M and 0.03 M (CIR, 1991).

Carcinogenicity

The available evidence is not sufficient to demonstrate the carcinogenic potential of the chemical. No data on carcinogenicity in humans were found in the literature.

In the most recent GLP carcinogenicity studies, F344 rats (50 animals/sex/dose) and B6C3F1/N mice (50 animals/sex/dose), were dermally applied pyrogallol (in 95 % ethanol) at doses of 0, 5, 20 or 75 mg/kg bw/day. The following effects were reported (Mercado-Feliciano et al., 2013):

- male and female rats showed skin irritation and significant increases in incidence of non-neoplastic changes at the 20 and 75 mg/kg bw/day dose; and
- male and female mice showed skin irritation and/or ulceration at the site of application predominantly in the 20 and 75 mg/kg bw/day groups;
- females showed a significant increase in the incidence of squamous cell carcinoma at the site of application at the highest dose;
- some males at the highest dose had squamous cell papillomas; and
- an increased incidence of non-neoplastic lesions at the site of application were detected at all dose levels.

Additonally, the application of pyrogallol increased the incidences of bone marrow hyperplasia in males and females and lymphoid hyperplasia of the axillary, inguinal, and mandibular lymph nodes; adrenal cortical haematopoietic cell proliferation; and mammary gland hyperplasia in females.

The following earlier dermal carcinogenicity studies reported no significant increases in the incidence of neoplastic changes:

- in female Swiss mice (50/group) treated with 5, 25, or 50 % solution of pyrogallol (in acetone) applied to dorsal shaved skin twice per week (CIR, 1991);
- in Swiss Webster mice treated with a hair dye formulation containing 0.49 % pyrogallol and H_2O_2 in an aqueous solution (once per week for 20 months) (Stenback & Shubik, 1974);
- in New Zealand White rabbits (five/group)treated with 5, 25, or 50 % pyrogallol solution (in acetone or methanol) applied to shaved skin, twice per week (Stenback, 1977); and
- in F344 rats treated with a subcutaneous injection of pyrogallol (100 mg/kg per day for eight weeks followed by 14 mg/rat per day for 50 weeks) (CIR, 1991).

The chemical could be a co-carcinogen. On the skin of female ICR/HA Swiss mice, pyrogallol (5 mg in acetone) was an active co-carcinogen when applied with benzo[a]pyrene on the skin three times weekly for 440 days. Ten of the 50 mice treated with benzo[a]pyrene developed squamous carcinomas, whereas 33/50 mice co-treated with benzo[a]pyrene and pyrogallol developed squamous carcinomas. No neoplastic changes were observed in the mice treated with pyrogallol alone (CIR, 1991; US NTP, 2013).

Reproductive and Developmental Toxicity

Based on available information, the chemical does not have reproductive or developmental toxicity potential.

Female SD rats were treated orally (gavage) with 100, 200, or 300 mg pyrogallol/kg bw/day on gestation days (GD)s 6–15. A significant reduction in mean maternal weight gain, increase in resorption, and decreased foetal body weight was observed at the highest dose. No chemical-related differences in gross, visceral, or skeletal anomalies or variations were found when compared with controls (CIR, 1991).

In a multigeneration reproduction study, a total of 40 male and 40 female Charles River CD rats were tested with a hair dye formulation that contained 0.4 % pyrogallol. The dye was mixed with an equal volume of 6 % hydrogen peroxide and applied at 0.5 ml to the skin twice per week throughout mating, gestation, and during lactation to weaning of the F1, F2, and F3 litters of the respective generations. There were no treatment-related changes in general behaviour and appearance, body weight, or survival in parents or offspring. Fertility, gestation and viability indices were comparable between control and experimental groups. Additionally, there were no treatment-related gross or microscopic lesions observed in F1 parental rats or F3 weaning rats. However, mild skin reactions, in the treated animals, were noted intermittently throughout the study (CIR, 1991).

In another study, 20 pregnant Charles River CD female rats were treated with a calculated dose of 8 mg/kg per day (hair dye formulation containing 0.4 % pyrogallol) applied to the shaved skin on days 1, 4, 7, 10, 13, 16, and 19 of gestation; more frequent application led to skin irritation in a pilot study. The mean numbers of corpora lutea, implantation sites, and live foetuses in experimental groups were not significantly different from those in control groups. No significant differences in the number of females with resorption sites and the mean number of resorptions per pregnancy were observed. No foetal toxicity was detected (CIR, 1991).

Other Health Effects

Neurotoxicity

Pyrogallol was detected in the brain (see ***Toxicokinetics***) and is a substrate of catechol-O-methyltransferase (COMT) and a potent COMT inhibitor in vitro; no sufficient data exist for its neurotoxicity. Some, but not all experimental studies suggest that pyrogallol treatment can change catecholamine levels in various regions of the brain in mice, rats, and rabbits. In addition, convulsions were observed in 50 % of mice after i.p. exposure to 720 mg/kg pyrogallol. However, the convulsions were also concurrent with distinct cyanosis, and therefore anoxia could not be ruled out as the cause (US NTP, 2013).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (mutagenicity) and local effects (skin sensitisation). It also has systemic acute effects (acute toxicity from oral, dermal, and inhalation).

Public Risk Characterisation

The public health risks for the general population are considered low, based on the low probability of exposure considering that:

- the chemical is not on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007);
- there is only one reported use in cosmetic products in the US (CIUCUS, 2011).

- the chemical is not found on the US Household Products Database indicating that it is not common in domestic use (US HPD); and
- the use in photoprocessing has declined.

Occupational Risk Characterisation

The most probable route of exposure fo the chemical by a worker is by dermal contact or inhalation during manufacture and use of this chemical (e.g. end product formulations and application of paints). Oral exposure is possible but can be prevented by good hygiene practices.

Given the critical systemic and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, inhalation and oral 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 an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

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

Regulatory Control

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 in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
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)

[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, inhalation and oral 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 could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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 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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