Phenol, 4-methoxy-: Human health tier II assessment

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CAS Number: 150-76-5

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

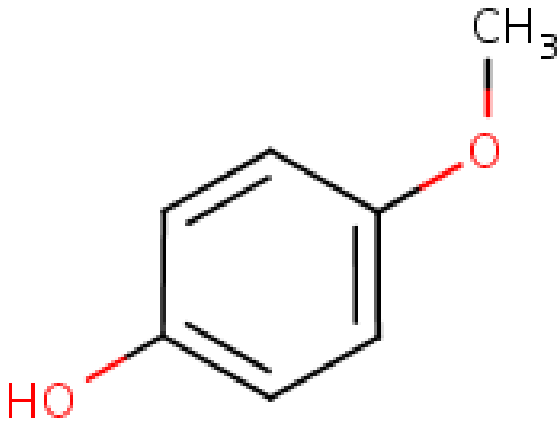
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	hydroquinone monomethyl ether hydroquinone, monomethyl ether p-hydroxyanisole p-methoxyphenol mequinol
Structural Formula	
Molecular Formula	C7H8O2
Molecular Weight (g/mol)	124.14
Appearance and Odour (where available)	Colourless to pale yellow appearance with a caramel/phenol-like odour
SMILES	c1(O)ccc(OC)cc1

Import, Manufacture and Use

Australian

The chemical has reported commercial use in industrial threadlockers (adhesives).

The chemical has reported site-limited use as an inhibitor in monomers such as acrylic monomers.

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening information data set International Assessment Report (OECD SIAR); 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 OECD High Production Volume chemical program (OECD HPV); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (Cosmetic Ingredient Review (CIR), 1985; Scientific Committee on Cosmetic Products and non-Food Products (SCCNFP),

2002; European Food Safety Authority (EFSA), 2006; US Food and Drug Administration (FDA), 2008; the Health Council of the Netherlands, 2011; CIR, 2015).

The chemical has reported cosmetic uses, including as:

- a component in artificial nail gels at concentrations between 0.01–0.04%;
- a reducing agent;
- an antioxidant at concentrations up to 1%; and
- a fragrance ingredient.

The chemical has reported domestic and commercial uses in washing or cleaning agents (SPIN). The SPIN database did not clearly indicate if the chemical or a reaction product produced from the chemical is used as cleaning or washing agents.

The chemical has reported commercial uses, including:

- in coating products;
- in adhesives and sealants;
- in inks and toners;
- in leather treatment products;
- as a solvent;
- in photo-conductors;
- as a textile lubricant; and
- in paints, lacquers and varnishes.

The chemical has reported site-limited uses, including as:

- an intermediate in the manufacture of antioxidants, plastics, plasticisers, and dyestuffs;
- an inhibitor in monomers such as acrylic monomers and acrylonitrile;
- a stabiliser at concentrations of 0.05–0.3% to inhibit thermal degradation of polyether polyols; and
- a component in cement.

This chemical has non-industrial uses:

- as a pharmaceutical agent including in the medication for dyschromia (alteration of skin and nail colour) at concentrations of up to 20%;
- as a component in depigmentation creams;
- in food additives (flavourings); and
- in pesticides (inert ingredient).

The US FDA (2008) identified the maximum level of the chemical present in fruit flavoured drinks as 100 ppb (0.00011 µg/kg bw).

Clark & Brunch (1996) identified the chemical as being present in cigarette smoke at concentrations ranging from 0.15 ±0.05 to 0.26 ±0.11 µg/cigarette.

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 4 (SUSMP, 2016) as 'MONOBENZONE and alkyl ethers of hydroquinone for human therapeutic use or cosmetic use **except** in cosmetic nail preparations containing 0.02 per cent or less of monobenzone or alkyl ethers of hydroquinone'.

Schedule 4 chemicals are described as 'Prescription Only Medicine, or Prescription Animal Remedy – Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription' (SUSMP, 2016).

This restriction limits use of the chemical in cosmetics to use only in cosmetic nail preparations, and only at concentrations of 0.02% (200 ppm) or less.

International

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

- EU Regulation (EC) No 1223/2009 Annex III - List of Substances which cosmetic products must not contain except subject to the restrictions laid down;
- New Zealand Cosmetic Products Group Standard - Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down;
- Health Canada List of restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist'); and
- ASEAN Cosmetic Directive Annex III Part 1: List of substances which cosmetics must not contain except subject to the restrictions and conditions laid down.

The International Fragrance Association (IFRA) standard has prohibited the use of the chemical in fragrances (IFRA, 2009).

The use of the chemical was restricted by the Scientific Committee on Cosmetic Products and non-Food Products (SCCNFP) to 200 ppm (after mixing) when used in artificial nail systems (SCCNFP, 2002).

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 oral toxicity)
- Xi; R36 (eye irritation)
- Xi; R43 (sensitisation)

Exposure Standards

Australian

The chemical has an exposure standard of 5 mg/m^3 time weighted average (TWA) (Safe Work Australia).

International

The following exposure standards are identified (Galleria Chemica):

TWA:

- 0.5 – 5 mg/m^3 in different countries such as Russia, Canada, Denmark, Greece, Iceland, Indonesia, Ireland, Malaysia, Norway and Poland, South Africa, Singapore, Spain, Taiwan and the USA (California, Minnesota, Tennessee, Vermont and Washington)

Short-term exposure limit (STEL):

- 10 mg/m^3 in Canada (Saskatchewan) and the USA (Washington)

Health Hazard Information

Toxicokinetics

The chemical has been reported to follow a two-compartment model with rapid absorption into the body following intra-arterial administration (Belcher et al., 1990). Metabolism of 4-methoxyphenol has been studied in animals and humans, with several conjugated metabolites almost entirely excreted in

the urine within 24 hours after administration. However, the chemical has been reported to be metabolised to a limited extent via demethylation or oxidation to produce reactive oxygen species (ROS), which are responsible for the cytotoxicity of the chemical in the body.

In an *in vitro* study conducted according to the Organisation for Economic Co-operation and Development (OECD) Testing Guideline (TG) 428, the chemical (volume not specified) was applied to skin sections of human abdomen (200–400 µm thick; n=12). The test was conducted in three phases: phase 1 measured the permeability of the skin sample to titrated water (mean absorption: 1.21±0.57 mg/cm^2/hr); phase 2 measured the permeability of the skin sample after exposure to the chemical (mean absorption: 0.326 ±0.099 (n=6)); and phase 3 measured the permeability of the skin sample to titrated water after chemical exposure (mean absorption: 1.07 mg/cm^2/h). The ratios of the damage in skin samples were determined by dividing phase 3 by phase 1. The mean calculated ratio for the treated group was 1.24±0.28 mg/cm^2/h, compared to 1.03±0.22 mg/cm^2/h for the control. Absorption rate of the test substance was found to be 0.33±0.1 mg/cm^2/h with a permeability constant of 9.39 ± 3x10^{-3} cm/h (REACH).

In a study conducted in human patients (n=10 females), the chemical (10 g dissolved in 500 mL saline solution—concentration of 0.16 M) was infused into the femoral artery via catheter twice per day for four days. Blood samples were collected and serum concentrations were analysed after the first and fourth administration. The serum concentrations of the chemical decreased significantly between the two observations. There was a significant increase in the volume of distribution between the first (65.3 ± 5.4) and fourth (83.0 ± 8.4) administration. There was no significant change in the half-life or clearance rates of the chemical between the first and fourth infusion (Belcher et al., 1990).

The chemical was administered to three melanoma patients and five healthy human subjects by intra-arterial infusion at a concentration of 20 mg/mL in isotonic saline at a rate of 40 g/24 h, for four days. Urine samples were collected. In the melanoma patients, the chemical along with the following metabolites were detected 3,4-dihydroxyanisole (85–90%), 3-hydroxy-4-methoxyanisole and 4-hydroxy-3-methoxyanisole (10–15%) and hydroquinone. These compounds were not detected in the urine of the healthy subjects. All metabolites in the urine of the melanoma patients were excreted both as sulphates and glucuronides with a small percentage found in the unconjugated form. Hydroquinone was found in the melanoma patients at “considerable amounts” compared to minute quantities in the healthy patients (EFSA, 2011).

In a study conducted in male and female CBA mice (number not specified), radiolabelled chemical in saline solution was adminsitered via (1) intraperitoneal (i.p). route at doses 25, 50, 100, 150 or 200 mg/kg bw in males and 25, 100, 150, 200 or 300 mg/kg bw in females; and (2) intravenous (i.v.) route at doses =150 mg/kg bw. Urine and faeces were collected 24 and 48 hours after administration. The bioavailability of the chemical administered via i.p. injection was 100% with no significant difference in half-lives between the i.v. and i.p. injections. After i.p. injection, free radio-labelled chemical was not detected in the urine or faeces. After 48 hours, 96.54% of the administered dose was detected in the urine and faeces, with 86% of metabolites present in the urine. The rate of elimination in the male mice by i.p. injection was linear at all dose levels. In contrast, the initial rate of elimination in male mice by i.v. injection was decreased at higher dose levels. In female mice, the rate of elimination was not linear at all dose levels (REACH).

In a study conducted in rabbits (strain and sex not specified; n=6 animals), a single dose of the chemical (0.7 g) in water was administered via gavage and the animals were observed for 24 hours after treatment. The chemical was excreted mainly as conjugated metabolites, with a portion of the dose being the demethylated form, hydroquinone. Three of the conjugated metabolites, including ether sulphate (13%), ether glucuronide (69%) and free phenol (1%), accounted for approximately 83% of the dose (Bray et al., 1955; REACH).

Hepatocytes (106 cells/mL) were isolated from rats with or without treatment (i.p.) with pyrazole (inducing agent for CYP450; CYP2E1; and CYP1A2) for three consecutive days. Glutathione-depleted hepatocytes were prepared by pre-incubating hepatocytes with 1-bromoheptane (300 µM) for 20 mins. Hepatotoxicity was observed to be concentration-dependent with a concentration of 13 mM inducing 50% cytotoxicity in 2 hours at 37 °C. Glutathione-depleted hepatocytes and enzyme induced hepatocytes were more susceptible to toxic effects of the chemical. However, the addition of cytochrome inhibitors to the hepatocytes only partially prevented toxicity (Moridani et al., 2002).

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 data (median lethal dose (LD50) of 1000–2000 mg/kg bw) support this classification (CIR, 1985; EFSA, 2006; REACH).

In a study conducted in female rats (strain not specified; n=2 animals/dose), the chemical in corn oil was administered at a single dose of 1000 or 2000 mg/kg bw. No deaths were reported at 1000 mg/kg bw; however, both animals died at 2000 mg/kg bw after 2 hours of treatment. At the highest dose, convulsions were observed 10 minutes after dosing and kidney damage was reported. The LD50 was determined to be between 1000–2000 mg/kg bw (CIR, 1985; EFSA, 2006; REACH).

In another study conducted in rats (strain and sex not specified; n=1–10 animals/dose), the chemical was administered once via gavage at doses 150, 200, 250, 300 and 350 mg/rat (equivalent to 1162, 1550, 1786, 2143 and 2187 mg/kg bw) and observed for 14 days. Mortality was reported at doses of 1150 mg/kg bw (4/10), 1786 mg/kg bw (6/7), 2143 mg/kg bw (5/6) and 2187 mg/kg bw (1/1). The LD50 was determined to be 1630 mg/kg bw (CIR, 1985; US EPA, 2010; REACH).

The oral LD50 in mice (number; strain; and sex not specified) was reported to be 621 mg/kg bw (EFSA, 2006).

Dermal

The chemical has low acute dermal toxicity based on results from animal tests following dermal exposure. The LD50 value in rats and rabbits was >2000 mg/kg bw.

In a study conducted in Wistar rats (n=5/sex/dose), the chemical in water was applied to the skin at 2000 mg/kg bw, and covered with semi-occlusive dressing for 24 hours. The animals were observed during the first 30 minutes, after 1, 2, 3 and 5 hours and then twice daily for 15 days. No mortality was reported throughout the study. The LD50 was determined to be >2000 mg/kg bw (REACH).

The LD50 in New Zealand White rabbits was reported to be >2000 mg/kg bw. Animals were exposed to the chemical at 2000 mg/kg bw under occlusive conditions for 24 hours (US EPA, 2010; REACH).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on a weight of evidence (WoE) approach from the available animal studies, the chemical is considered to cause slight to moderate skin irritation. The effects were not sufficient to warrant hazard classification.

In a study conducted according to OECD TG 404, the neat chemical (0.5 g; moistened with water) was applied to the skin of New Zealand White rabbits (n=3; sex not specified) under semi-occlusive patch for 4 hours and observed for 14 days. The mean erythema and oedema scores were reported to be 1.78 and 1.44, respectively. Effects reversed within 8–15 days. The chemical was determined to be slightly irritating (REACH).

In another study conducted in New Zealand White rabbits (n=6; sex not specified), the chemical (5% in almond oil) was applied under an occlusive patch to the clipped skin for 24 hours. The irritation index was calculated to be 0.3 out of a maximum score of 8.0, indicating minimal skin irritation (CIR, 1985).

In four separate studies conducted in rabbits (number of animals, strain and sex not specified), the following results were reported at the specified concentrations (CIR, 1985):

- Neat chemical was applied to the intact skin for 3 or 7 hours. Very slight hyperaemia (excess blood in the vessels) was observed after exposure for 7 hours.
- Neat chemical was applied under an occlusive patch for 24 hours to abraded and intact skin of the abdomen. Extensive oedema and necrosis were observed, and moderate eschar formation was reported 21 days post-treatment;
- the chemical at 50% in dipropylene glycol monomethyl ether (DPGME) was applied to the clipped skin of 2 rabbits and covered with an impervious plastic sleeve for 24 hours. Slight hyperaemia was observed.
- The chemical at 10% in DPGME was applied three times to intact skin of the ear, and intact and abraded skin of the abdomen. The test sites were covered with a cotton pad. Slight hyperaemia was observed on the intact skin of the abdomen, and slight to moderate hyperaemia on the abraded skin. Irritation was not observed on the intact skin of the ear.

In a study conducted in guinea pigs (n=1 animal/dose; strain not specified), the chemical (40% in 23:2 acetone/olive oil) was applied as a single dose of either 10 or 20 mL/kg bw to clipped skin. Observation was for 24 hours. Slight to moderate skin irritation was observed (CIR, 1985).

Eye Irritation

According to the harmonised classification and labelling approved by the European Union, the chemical causes severe eye irritation (REACH). In Australia, the chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). Available data suggest corneal and iris effects are more severe than expected; however, data are insufficient to amend this classification. Alternatively, the available data show that at low concentrations the chemical is a non-irritant.

New Zealand White rabbits (n=3/sex) were treated with 0.1 mL of neat chemical into the right eye which was rinsed after 24 hours. Slight to moderate conjunctival irritation (6/6 animals), corneal opacity (1/6 animal), corneal ulceration (5/6 animals) and iridial changes (2/6 animals) were reported after 24 hours. These reversed within 7 days (US EPA, 2010).

Neat chemical and the chemical at 1% in aqueous solution were instilled into the eyes of New Zealand White rabbits (n=3–6 animals; exact numbers were not specified). Minimal conjunctival irritation, which reversed after 24 hours was observed after instillation of the chemical at 1% . The undiluted chemical produced corneal, iridial and conjunctival irritation one hour after instillation. Maximum corneal and iridial scores under the system used were reached after seven days of instillation. The chemical was determined to be a severe eye irritant (CIR, 1985).

In a study conducted on rabbits (number, strain, and sex were not specified), neat chemical or the chemical at 10% in propylene glycol was instilled into one eye. In some of the animals, eyes were rinsed for 2 minutes after exposure. The chemical at 10% produced slight conjunctivitis and iritis

(inflammation of the iris) in both the rinsed and unrinsed eye, which reversed one hour after instillation. Neat chemical produced corneal injury, moderate conjunctivitis and slight iritis in both the rinsed and unrinsed eyes. These effects 'completely subsided' in the animals with rinsed eyes or 'essentially subsided' in the animals with unrinsed eyes, one week after treatment (CIR, 1985).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). The positive results reported in guinea pig maximisation test (GMPT) and Freund's complete adjuvant test support this classification.

In a GMPT conducted according to OECD TG 406, the chemical at 6.2% in peanut oil was used for intradermal induction in female Dunkin-Hartley guinea pigs (n=10 treated; 6 control). The animals were topically treated with 10% sodium lauryl sulphate (SLS) in petrolatum prior to topical induction with the chemical at 20% in ethanol. In the first (day 21) and second challenge (day 35), both closed and open patches were applied to the shaved skin at different sites for 24 hours, respectively. Positive reactions were reported in 50% of animals during challenge (CIR, 1985; REACH).

In a Freund’s complete adjuvant test, intradermal injections of the chemical (0.5 M; 3.9% in water) were administered to female albino Dunkin-Hartley guinea pigs (n=8) for induction on days 0, 2, 4, 7 and 9. Challenge patches were applied to shaved skin for 24 hours on days 21 and 35, respectively. The challenge dose used was the maximum non-irritating concentration in petrolatum, peanut oil or Aramek for challenges (no further details provided). Positive reactions were reported in 4/8 animals (CIR, 1985; REACH).

Observation in humans

Several human repeated insult patch tests (HRIPT) were conducted using nail products containing the chemical.The chemical in nail product(s) was applied to the nail of human subjects for 10 minutes, 3 times/week for 9 applications (induction period). After a two week rest period, the product was then applied to the same finger nail (challenge period). No positive reactions were reported (CIR, 2015)

Repeated Dose Toxicity

Oral

Considering the no observed adverse effect level (NOAEL) of 125 mg/kg bw/d in a one year repeat oral toxicity studies in rats, repeated oral exposure to the chemical is not considered to cause serious damage to health.

In a study conducted in rats (strain not specified; n=10/sex/dose), the chemical was administered via the diet at concentrations of 0, 0.02, 0.1, 0.5, 2.0 or 5.0% (equivalent to approximately 0, 10, 50, 250, 1000 or 2500 mg/kg bw/d) for 5–7 weeks. No deaths occurred in any dose groups. A dose-dependent decrease in body weight was observed at ≥250 mg/kg bw/d in males; and ≥1000 mg/kg bw/d in females. Dose-dependent increases in urine glucose levels were also reported in males. The lowest observed adverse effect level (LOAEL) was determined to be 250 mg/kg bw/d based on dose-dependent decrease in body weight in males. A NOAEL of 50 mg/kg bw/d was determined (US EPA, 2010).

Male Fischer 344 (F344) rats (n=10–11/group) were administered the chemical in the diet at doses of 0, 125, 250, 500 or 1000 mg/kg bw/d for 51 weeks. Dose-dependent body weight reduction, and increases in liver and kidney weights were observed in all the treated groups. Animals at the highest dose developed forestomach ulcers. At doses 250 mg/kg bw/d and above, mild to severe induced hyperplasia was reported in the forestomach of the animals. A NOAEL was determined to be 125 mg/kg bw/d based on the observed hyperplasia at higher doses (EFSA, 2006; US FDA, 2008).

In a study conducted in Wistar rats (n=10/sex/dose), the chemical in water was administered via gavage at doses of 0, 50, 150 or 300 mg/kg bw/d for 28 days in males; and for 14 days prior to mating until the F1 generation reached day 4 post-partum in females (see **Reproductive and Developmental toxicity)**. At the highest dose, reduced activity was seen in all animals. Food consumption and reductions in body weight were reported. At 150 mg/kg bw/d, two females had ruffled fur and difficulty in delivery. A NOAEL was determined to be 50 mg/kg bw/d (REACH).

In a study conducted in rabbits (strain and sex not specified; n=6/dose), the chemical was administered in the diet at doses of 0, 300, 1500 or 3000 mg/kg bw/d for 5–9 weeks. At the completion of the study, red blood cell counts were low in the 1500 and 3000 mg/kg bw groups. Based on the decreased red blood cell counts, the LOAEL and NOAEL were determined to be 1500 mg/kg bw/d and 300 mg/kg bw/d, respectively (US EPA, 2010).

Dermal

The available data for this chemical has identified that repeated dermal exposure to the chemical has long term effects on the skin of animals and humans (see **Observation in humans)**. Repeated application of the chemical to the skin of animals at concentrations ≥0.25 % may cause local irritation and skin depigmentation. No systemic toxicity was reported. Skin depigmentation is not regarded as severe organ toxicity or a systemic effect; therefore, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a study conducted on black guinea pigs (strain and sex not specified; n=6/dose), the chemical in an unspecified cream vehicle was applied to the epilated skin of the back at 0, 0.1, 0.25, 0.5 or 1.0% daily for 42 days. Hypopigmentation or depigmentation of the skin were observed at concentrations ≥0.25%. In a similar study, the chemical in an unspecified vehicle at 0, 0.5 or 1% was applied daily for 6 months to the ear and epilated backs of black guinea pigs (strain and sex not specified; n=3/dose). The skin in both doses appeared hypomelanotic (lacking melanin) and amelanotic (without melanin) after 4 months. Moderate to severe skin and hair depigmentation were observed at the highest dose (CIR, 1985).

Two separate studies were conducted on black guinea pigs (strain and sex not specified). In the first study, the chemical at 20 % in lanolin was administered to the back of the ears of the animals once per day for 1–8 weeks. Depigmentation of the skin occurred within 5–10 days of treatment. After 5–6 weeks, large areas of the skin were completely depigmented and this persisted for up to 6 months. The depigmentation did not extend beyond the area of application (CIR, 1985; US EPA, 2010). In the second study, the chemical at 20 % in dimethyl sulfoxide was administered to the back of guinea pig ears (n=10) once per day for 13 days. Depigmentation of the skin was observed in 4/10 animals after 5 days of treatment. All animals had varying degrees of skin depigmentation, 25 days after the initial exposure. The effects were reversed 1 month after dosing. Microscopic changes in the skin include: acanthosis (characterised by darkening (hyperpigmentation) and thickening (hyperkeratosis) of the skin); and a decrease in the number of 4-dihydroxyphenylalanine (DOPA) active melanocytes and a transposition of melanin granules from the epidermis into the dermis (CIR, 1985).

The chemical at 10 or 20 % in petroleum jelly was applied to the ear of guinea pigs (sex and strain not specified; 5/dose) daily for 4 weeks and the necks of mice (sex and strain not specified; n=10/dose) daily for 8 weeks. Skin irritation (acanthosis) and depigmentation were observed in both species at the highest dose. The chemical at 10% did not produce observable skin effects (CIR, 1985).

The chemical at 5 % in 50:50 propylene glycol/ethanol was applied to the skin of female Yucatan miniature pigs (n=2), twice daily, 7 days per week for 90 days. Depigmentation of the skin occurred after 70 days of exposure (US EPA, 2010).

Inhalation

No data are available.

Observation in humans

In 2002, IFRA banned the use of this chemical in fragrances due to skin depigmentation (IFRA, 2009).

It was reported by CIR (1985) that localised depigmentation (leukoderma) induced by the chemical in animals resembles that in man (vitiligo) with respect to:

- depigmentation after long term exposure;
- tendency for hair follicles to depigment last;
- initial repigmentation—or depigmentation—occurs perifollicular;
- DOPA-positive epidermal melanocytes are reduced;
- depigmentation is inversely proportional to the amount of melanin in the epidermis; and
- supra-basal cells (keratinocytes found in the epidermal layer of the skin) are damaged in the depigmented zone.

Cases of depigmentation of the skin following chemical exposure have been reported (CIR, 1985):

- A 33-year-old female developed leukoderma of the face after 2 months of applying the chemical (unknown concentration) as a component of an ointment to a chloasma (a tan or dark skin discoloration) on the face. Repigmentation did not occur 6 months after ointment usage.
- A 56-year-old man developed leukoderma of the hands after occupational exposure to the chemical at concentrations of 5–10 %.
- Skin depigmentation of the forearm and forehead were observed in 2/8 workers exposed to the chemical for 3 years. When exposed to sunlight, skin erythema developed in the areas of depigmentation in one worker.

Genotoxicity

The WoE from both *in vitro* and *in vivo* studies, does not indicate that the chemical is genotoxic.

In vitro

The following *in vitro* genotoxicity test results:

- Ames assay with *Salmonella typhimurium* strains TA98, 100, 102, 1530, 1535, 1537 at concentrations up to 5000 µg/plate gave negative results, with and without metabolic activation (CIR, 1985; US EPA, 2010; the Health Council of the Netherlands, 2011; REACH);
- A gene mutation assay in mammalian cells (MLTK assay) gave positive results only in the absence of metabolic activation (EFSA, 2011);

- Chromosomal aberrations were induced in Chinese hamster ovary (CHO) cells at concentrations ≥1269 µg/mL and ≥954 µg/mL with and without metabolic activation, respectively (US EPA, 2010; EFSA, 2011);
- The chemical did not induce sister chromatid exchanges (SCE) in human lymphocytes (EFSA, 2011);
- A mammalian chromosome aberration test in human lymphocytes gave negative results, with and without metabolic activation, at concentrations up to 5000 µg/mL (REACH);
- DNA denaturation was observed in T4 bacteriophage which were exposed to the chemical at a concentration of 0.09 M (CIR, 1985);
- A mammalian cell gene mutation assay in L5178Y mouse lymphoma cells showed positive results at concentrations ranging from 8–1500 µg/mL, without metabolic activation. Gene mutations did not occur in the presence of metabolic activation at concentrations of up to 56 µg/mL (US EPA, 2010).

In vivo

Sprague-Dawley (SD) rats (number and sex not specified) were administered a single dose of the chemical via gavage at 100, 333 or 1000 mg/kg bw. Bone marrow cells were analysed. Increases in the number of chromosomal aberrations were not observed (EFSA, 2011; REACH).

SD rats (number and sex not specified) were dermally administered the chemical in ethanol at doses of 4, 12 or 40 mg/kg (equivalent to 0.2, 0.6 or 2 mg/kg bw/d) as a component in a depigmentation cream for 6 months. No genotoxic effects were reported. No further study details were provided. (CIR, 2015).

CD-1 mice (n=5/sex/dose) were injected (i.p.) with the chemical at doses of 175, 875 or 1750 mg/kg (equivalent to 8.75, 43.75 or 87.5 mg/kg bw/d). Bone marrow was harvested 24, 48 and 72 h after treatment. Mortality was reported at the highest dose and an increase in micronucleated polychromatic erythrocytes was observed at the lowest dose only (US EPA, 2010).

Carcinogenicity

The chemical caused hyperplasia and squamous cell carcinoma specifically in the forestomach of experimental rodents following oral exposure. Given that there is no human equivalent to the rodent forestomach, the carcinomas seen in the rodents are not relevant in predicting cancer risk to humans (Proctor et al., 2007). The chemical is not expected to be carcinogenic to humans.

In a study conducted in male F344 rats (n=26/group), the chemical was administered in the diet at 0 or 0.4 % (equivalent to 0 or 100 mg/kg bw/d) for 104 weeks. Histopathological findings in the forestomach revealed papillary and modular hyperplasia in 8/26 treated animals and one animal in the control group; and papilloma in 3/26 treated animals and none in the control group. No increases in carcinomas or treatment-related tumour growth were found in any dose groups. There was a significant decrease in the body weight of the treated group compared with the control (EFSA, 2006; EFSA, 2011; the Health Council of the Netherlands, 2011; US FDA, 2008; CIR, 2015; REACH).

Male F344 rats (n=15/group) were administered the chemical at 0 or 1.5 % (equivalent to 0 or 375 mg/kg bw/d) in the diet for 51 weeks. Hyperplasia (15/15 animals; 0/10 controls) and atypical hyperplasia (1/15 treated; 0/10 controls) were observed in the forestomach. Kidney and liver weights were significantly increased relative to the control (EFSA, 2006; EFSA, 2011; the Health Council of the Netherlands, 2011; REACH).

In a study conducted in F344 rats (n=20 females, 26 males), the chemical was administered in the diet at 0 or 2 % (equivalent to 0 or 500 mg/kg bw/d) for 104 weeks. Histopathological findings in the forestomach revealed atypical hyperplasia (67 % male and 37 % female); papilloma (50% male, 23% female); and squamous-cell carcinomas (77 % males, 20 % females). Relative kidney and liver weights were significantly increased; and body weights were decreased compared with the control. No abnormalities were found in the control group (Asakawa, 1994; EFSA, 2006; EFSA, 2011; the Health Council of the Netherlands, 2011; US FDA, 2008; CIR, 2015; REACH).

In another study conducted in male F344 rats (n=10–11/group), the chemical was administered in the diet at concentrations of 0.25, 0.5, 1 or 2 % (equivalent to 100, 200, 400 or 800 mg/kg bw/d) for 51 weeks. Mild forestomach hyperplasia was reported at all doses. Moderate hyperplasia in the forestomach was observed in the 400 and 800 mg/kg bw/d groups. Increased incidences of papillomas and carcinomas were not found in any dose groups. Organ investigations revealed erosion and ulceration in the glandular stomach in the 400 and 800 mg/kg bw/d groups (EFSA, 2006; EFSA, 2011; the Health Council of the Netherlands, 2011; REACH).

Male F344 rats (n=10/group) were administered the chemical at 0 or 2 % (equivalent to 0 or 800 mg/kg bw/d) in the diet for up to 48 weeks. Group 1 received daily treatment for 24 weeks; group 2 received daily treatment for 24 weeks followed by the basal diet for a further 24 weeks; and group 3 received daily treatment for 48 weeks. Controls received the basal diet only. In group 1: severe simple or papillary hyperplasia were observed in all animals; and mild and moderate basal cell hyperplasia were observed in 7/10 and 1/10 animals, respectively. In group 2: mild simple or papillary hyperplasia was observed in 7/10 animals and mild basal cell hyperplasia in 7/10 animals. In group 3: mild to moderate simple or papillary hyperplasia were observed in all animals with one animal suffering severe simple or papillary hyperplasia. Mild to moderate basal cell hyperplasia in all animals was also observed. Final body weights were significantly lower than the control (EFSA, 2006; EFSA, 2011; the Health Council of the Netherlands, 2011).

In a study conducted in male hamsters (strain not specified; n=15/dose), the chemical was administered in the diet at concentrations of 0 or 1.5 % (equivalent to 0 or 600 mg/kg bw/d) for 20 weeks. Induction of hyperplasia in the forestomach was observed in all dosed animals. No further study details were provided (EFSA, 2006; EFSA, 2011).

The chemical inhibited the carcinogenic effects of beta-propiolactone and benzo(a)pyrene in the forestomach of female HCR/Ha mice (number not specified) when administered in the diet or via oral intubation prior to carcinogen exposure (Wattenberg et al., 1983; CIR, 1985).

In a study conducted in albino mice (strain and sex not provided; n=30), an area of clipped skin was initiated with a drop of 12-dimethylbenz(a)anthracene (DMBA; 75 µg). One week later, a single drop of the chemical at 13.1% in benzene solution was applied to the same site, twice weekly for 20 weeks. One mouse developed a benign tumour (site not reported). The chemical was concluded to be inactive as a tumour promoter (CIR, 1985).

Female Swiss albino mice (n=50/dose) and New Zealand White rabbits (n=5/sex/dose) were applied with 0.02 mL of the chemical in acetone at concentrations of 5 or 10 % on the dorsal skin of the back (mice) or to the inner surface of the left ear (rabbits), twice per week throughout the lifetime of the animals. No local toxicological changes or tumours were reported (CIR, 1985).

The International Agency for Research on Cancer (IARC) identified the chemical as an antioxidant that induces forestomach tumours in rats (IARC, 1998). No classification was provided. The Health Council of the Netherlands (2011) came to the decision that the chemical does not pose a risk and the data was insufficient for carcinogenicity classification.

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not expected to cause reproductive or developmental toxicity. The chemical does not cause any specific reproductive toxicity. Any reproductive and developmental effects were secondary to maternal toxicity.

Reproductive toxicity

In a study conducted in female rats (strain not specified; n=16/group), the chemical was administered once via gavage at 0, 333, 667 or 1000 mg/kg bw on day 11 of gestation. Significant changes (not specified) in body weight of dams were observed. The NOAEL for maternal toxicity was determined to be <333 mg/kg bw/d while the NOAEL for foetal toxicity was determined to be 1000 mg/kg bw/d (EFSA, 2006; EFSA, 2011).

The chemical was administered via gavage to Wistar rats (n=10/sex/dose) at a dose of 0, 50, 150 or 300 mg/kg bw/d for 28 days (in males), or from 14 days prior to pairing, throughout mating and gestation periods, until the F1 generation reached day 4 post-partum (in females). At the highest dose, reduced activity and signs of discomfort in all the dose groups were observed. Ruffled fur and difficulty in pup delivery was reported in three females. At 150 mg/kg bw/d, two females had ruffled fur and difficulties in delivery—one showed higher post-implantation loss, while the other showed higher post-natal loss at the first litter check. Post-natal and post-implantation loss were not dose-dependent. The NOAEL for reproductive toxicity was considered to be >300 mg/kg bw/d (REACH).

In a study conducted in female rats (strain not specified; n=3/group), 1 mg of the chemical in PMSG was subcutaneously injected into the animals. The animals were sacrificed after 72 hours. The treated group had lower average ovarian weights (114 mg) compared to controls (127 mg) (CIR, 1985)

Developmental toxicity

In a study conducted according to OECD TG 414, mated female SD rats (n=24/dose) were administered the chemical via gavage, once daily from days 6 to 20 post-mating, at doses of 100, 200 or 400 mg/kg bw/d. Animals were monitored daily for mortality and clinical toxicity. Maternal toxicity was reported as follows:

- At 100 mg/kg bw/d: hypoactivity (14/24); hypersalivation (1/24); half closed eyes (12/24) were observed.
- At 200 mg/kg bw/d dose: piloerection (9/24), hypoactivity (24/24); locomotory difficulties (9/24); sedation (11/24); hypersalivation (3/24); and half closed eyes (24/24) were observed.
- At the highest dose: piloerection (10/24); round back (1/24); tonic contraction (13/24); hypoactivity (23/24); locomotory difficulties (17/24); sedation (19/24); hypersalivation (3/24); and half closed eyes (24/24) were observed.

Statistically significant increases in the mean number of early resorptions and post-implantation loss were reported at the highest dose. Developmental delays including reduced foetal body weight and ossification; and malformations of the brain, skull, head and axial skeleton were reported. The NOAEL for developmental toxicity was determined to be 200 mg/kg bw/d (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects including acute toxicity from oral exposure and local effects (skin sensitisation). The chemical can also cause eye irritation.

Public Risk Characterisation

Use of the chemical in cosmetic products in Australia is restricted in the Poisons Standard to 0.02 % (200 ppm) for use in cosmetic nail preparations (SUSMP, 2016), although the chemical is reported to be used in cosmetic products overseas at concentrations up to 1% (CIR, 1985). International uses also indicate that the chemical is used in fragrances, in artificial nail gels and in skin depigmentation creams.

The chemical could also have specific domestic uses such as cleaning and washing agents; components in paints, lacquers and varnishes; and adhesive and sealants, with potential risks associated through dermal exposure. The concentration of the chemical in these products is unknown. However, dermal exposure of the chemical from these products are likely to be restricted to only occasional splashes and spills.

Provided that normal precautions are taken to avoid prolonged skin contact and ocular exposure, the risk to the public from exposure to cosmetic products containing the chemical is not considered to be unreasonable at concentrations below 0.1%. The existing scheduling requirements are considered adequate to mitigate any risk to public health from the industrial uses identified.

Occupational Risk Characterisation

During product formulation, oral, dermal and ocular exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical (acute oral toxicity, skin sensitisation and eye irritation) health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal and ocular exposure to the chemical 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.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2016).

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)*	Causes serious eye irritation - Cat. 2A (H319)
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 that 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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