2,5-Furandione: Human health tier II assessment

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Preface

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

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

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

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

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

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

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

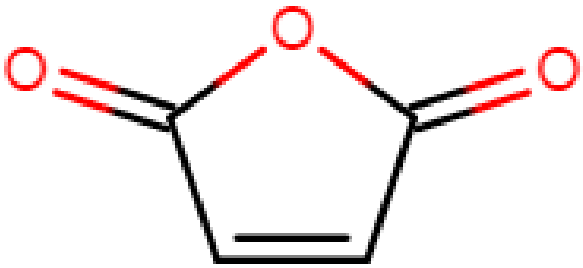
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	butenedioic anhydride, cis- dihydro-2,5-dioxofuran maleic acid, anhydride toxilic anhydride
Structural Formula	
Molecular Formula	C4H2O3
Molecular Weight (g/mol)	98.0568
Appearance and Odour (where available)	Colourless needles with a pungent odour
SMILES	C1(=O)C=CC(=O)O1

Import, Manufacture and Use

Australian

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of 1000–9999 tonnes.

The following Australian industrial uses are reported under previous mandatory and/or voluntary calls for information.

The chemical has reported domestic use in adhesives and binding agents and in surface coatings.

The chemical has reported site-limited uses including:

- as an intermediate for manufacturing other chemicals; and
- as a stabiliser.

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation Authorisation and Restrictions of Chemicals (REACH) dossiers; the Organisation for Economic Cooperation and Development (OECD) Screening Information Dataset Initial Assessment Report (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 Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and the US Houshold Products Database.

The chemical has reported cosmetic uses including in:

- artificial nail builders; and
- film forming agents.

The chemical has reported domestic uses including:

- in adhesives or binding agents;
- in paints, lacquers and varnishes;
- in cleaning or washing agents;
- in colouring agents;
- as a corrosion inhibitor; and
- in flame retardants and fire extinguishing agents.

The chemical has reported domestic use in the SPIN database. However, it should be noted that SPIN does not distinguish between direct use of the chemical, or use of the materials that are produced from chemical reactions involving the chemical.

The chemical has reported commercial uses including:

- as a textile finishing agent;
- as a lube oil additive;
- for manufacturing plywood and construction materials;

- in impregnation materials;
- as a process regulator; and
- as a reprographic agent.

The chemical has reported site-limited uses including:

- in personal care products (as copolymers);
- for manufacturing polyester and coating resins; and
- as an intermediate in producing other chemicals (fumaric and tartaric acid, tetrahydrofuran, rosin adducts, surfactants and reactive plasticisers).

The chemical has reported non-industrial uses in:

- pesticides and herbicides; and
- preservatives for oils and fats.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

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)
- C; R34 (corrosivity)
- Xi; R42/43 (sensitisation)

Exposure Standards

Australian

The chemical has an exposure standard of 1 mg/m^3 (0.25 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

TWA:

- 0.2–1.2 mg/m^3 (0.05–0.30 ppm) in Canada (Alberta, British Columbia, Quebec, Saskatchewan, Yukon), Estonia, Germany, Japan, Poland, Spain, Sweden, Taiwan and the United States of America (USA).

Short-term exposure limits (STEL)

- 0.4-1.0 mg/m^3 (0.10-0.25 ppm) in Canada (Yukon), France, Hungary, Switzerland and Poland;
- 2-3 mg/m^3 in China, Estonia and the United Kingdom; and
- 0.75 ppm in the USA (Washington).

Health Hazard Information

Toxicokinetics

Animal studies indicate that the chemical can be absorbed via all routes of exposure: oral, dermal and inhalation. Following oral administration in dogs at 60 mg/kg bw/day for 90 days, the plasma levels were measured and the uptake and elimination rate constants of the chemical were calculated to be 0.00349/day and 0.0832/day, respectively, assuming a one-compartment model. The model indicated that 99 % of the steady state concentration was reached by day 55 of exposure (HSDB; REACH).

The chemical has the potential to form haptens via amino acid acylation causing sensitisation (OECD, 2004). However, the chemical is rapidly hydrolysed to maleic acid under aqueous conditions, and this either contributes to the Krebs cycle, or is excreted from the body unchanged or in its conjugated form (HSDB). Oral uptake is expected to be in the form of maleic acid, and maleic acid will be present systemically.

Acute Toxicity

Oral

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

The median lethal dose (LD50) was 400–1050 mg/kg bw in rats, 465 mg/kg bw in mice, 875 mg/kg bw in rabbits and 390 mg/kg bw in guinea pigs. In rats, sublethal signs of toxicity included depressed appetite and activity, sedation and ataxia, ruffled fur, staggering gait, breathing difficulties, tremors, convulsions and glassy eyes. Necropsy revealed gastrointestinal inflammation and haemorrhagic areas in the lungs and liver (HSDB; REACH).

In an acute exposure study, dogs (n = two/sex/dose) were administered the chemical in capsules at doses of 60, 120 or 180 mg/kg bw. Two days after dosing, deaths occurred in the two high-dose groups (numbers not available). Toxicity effects included decreased body weights and vomiting (including blood) in all treated animals, and diarrhoea and bloody stools in amimals at ≥120 mg/kg bw (HSDB). An LD50 value in dogs was not reported. The effects might be due to the chemical's corrosive nature.

Dermal

The chemical has moderate acute dermal toxicity in rats, warranting hazard classification.

The reported dermal LD50s were 610 mg/kg bw in rats, 1600–2620 mg/kg bw in rabbits, and >20000 mg/kg bw in guinea pigs. Toxicity effects observed in rabbits included decreased appetite and activity; and increased weakness and collapse. Lung and liver hyperaemia, enlarged gallbladder, gastrointestinal inflammation and discolouration of the spleen and kidney were also observed upon necropsy (OECD, 2004; HSDB).

Inhalation

Only limited data are available.

In an acute inhalation toxicity study (with limited documentation), one cat, one rabbit, one guinea pig, four rats and 10 mice were exposed to the saturated vapour of the chemical at 4.35 mg/L for one hour. Respiratory (and eye) irritation was observed in all animals. After six days, the guinea pig and 2/10 mice died due to broncho-pneumonia. No other toxicity effects were reported. The median lethal concentration (LC50) was reported as >4.35 mg/L for one hour of exposure (OECD, 2004; REACH).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase ‘Causes burns’ (C; R34) in the HSIS (Safe Work Australia). The available data support this classification.

In a skin irritation study (non-guideline), the chemical (0.5 g) was applied (occlusively) on the shaved skin of New Zealand White rabbits (n = 6) for four hours, with observation up to seven days. Severe skin irritation including eschar formation with epidermal regeneration was present throughout the observation period. The mean erythema and oedema scores over 24, 48 and 72 hours were 4.0 and 3.6, respectively. The chemical was therefore considered to be corrosive to the skin (REACH).

In another skin irritation study, White Vienna rabbits (n = 2/dose) were exposed (occlusively) to the liquid chemical at concentrations of 0.1, 0.5, 1.0, 10, 20, 50 % in oil. The animals were treated for 20 hours and observed for up to 24 days. Skin irritation increased in severity with increased concentrations, resulting in leather-like necrosis with bleeding, crust and scar formation, and poorly healing lesions at the highest concentration. These effects were not fully reversible within 24 days (REACH).

Several studies showed that the chemical, when applied as fine ground, was non-irritating. However, corrosive effects were observed when it was moistened with water, resulting in hydrolysis to maleic acid via an exothermic reaction (OECD, 2004).

In an eye irritation study (according to the Draize and OECD criteria), the chemical (0.1 g) was instilled into the eyes of New Zealand White rabbits (n = 3). Observations were made at one, 24 and 48 hours following administration, whereupon the study had to be terminated due to the severe ocular effects. No mortalities occurred. A maximum eye irritation score of 106.7 (out of 110) was obtained. The mean scores for the timepoints (24, 48 hours) were 2.0 for iritis, 4.0 for chemosis, and 3.8 for corneal opacity. Corneal bulging was observed in one animal, a lesion not addressed by the study criteria. Based on the effects observed, the chemical was considered a severe eye irritant (OECD, 2004; REACH).

Several other studies in rabbits have also indicated severe eye irritation effects following administration of the chemical as a powder (0.045–0.1 g) or in solution (1–5 %) for a duration of two minutes to 24 hours. Effects of the chemical in a solution at 5 % were intense and non-reversible, developing into corneal ulceration after three days. Other effects reported in these studies were oedema, inflammation, profuse whitish discharge in the conjunctival sac, cloudiness of the cornea and necrosis (OECD, 2004).

Respiratory Irritation

The chemical is considered to be a respiratory irritant, warranting hazard classification under the Globally Harmonised System (GHS). A separate hazard classification for respiratory irritation (R37) is not recommended as R34 classification includes respiratory irritation.

In an acute inhalation toxicity study that exposed different animals (a cat, a rabbit, a guinea pig, four rats and 10 mice) to the saturated vapour of the chemical at 4.35 mg/L for one hour, all animals showed eye and respiratory irritation (OECD, 2004; REACH).

The chemical was a respiratory irritant in humans at concentrations of 1–1.6 mg/m^3 (0.25–0.38 ppm) (CalEPA, 2001).

Observation in humans

The chemical has been reported to cause skin, eye and respiratory irritation in humans. Eye and respiratory irritation was reported to occur at concentrations of 1–1.6 mg/m^3 (0.25–0.38 ppm) (CalEPA, 2001).

Exposure to the vapours from contaminated clothes or direct dermal contact caused lesions of the eye (conjunctivitis, keratitis, transient photophobia and double vision), and effects on the respiratory tract (coughing, wheezing, rhinitis and asthma), and vesicular dermatitis. Eye and respiratory effects were often immediate. Recovery periods were reported to be nine days for conjunctivitis, 25 days for dermatitis, and 40 days for a combination of both effects (HSDB).

In a case study, drum-filling workers were continuously exposed to the vapours of the chemical in a small room. One worker who was exposed to the chemical vapour for eight hours during his shift (wearing a gas mask with a canister recommended for one-hour exposure, but no vapour-proof goggles) suffered burning eyes, wheezing and coughing. These symptoms became more severe a few hours post-exposure and included chest constriction, reddened conjunctivae, blepharitis of the eyelids, nasal discharge and mildly reddened mucous membranes of the nose and throat. Further examination revealed typical asthmatic symptoms in his lower respiratory tract. After an eight-day treatment, the worker still displayed occasional mild coughing attacks. Another worker who did not use appropriate respiratory or eye protection reported wheezing and occasional coughing fits. Comparable but less severe symptoms were observed in five other workers following excessive vapour exposure (REACH).

In another case study, a 25-year-old man who had worked in a polymer-producing factory for eight months was accidentally exposed to concentrated vapours of the chemical. Immediate effects reported were burning eyes and throat, a serious cough, dyspnoea and vomiting. The next morning he was diagnosed with bronchitis and, upon resuming work, had a new incidence of acute bronchitis. A 27-year-old colleague displayed the same symptoms following comparable exposure (OECD, 2004).

Two men occupationally exposed (dermally) to the chemical for one hour developed erythema on their thighs in three to four hours. The men complained of itching and burning of the affected area, and this worsened after showering. The burns healed in nine days (REACH).

Sensitisation

Respiratory Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by inhalation’ (R42) in the HSIS (Safe Work Australia). Only limited animal data are available. However, human case reports indicated that the chemical had respiratory sensitisation properties (see **Sensitisation: Observations in Humans**), supporting this classification.

In a non-guideline study, groups of Sprague Dawley (SD) rats (n = 10/sex) were exposed to the chemical (aerosol) at a concentration of 0 or 500 µg/m^3, six hours/day for five days. The animals were challenged after a three-week rest period with the chemical at 500 µg/m^3 for six hours. One group was not challenged. Small but statistically significant increases in chemical-specific serum IgG antibody levels were observed in the exposed animals (higher incidences in females). Two rats in the non-challenged group developed lung foci. However, the mean values for respiratory sensitisation effects (lung foci, weight and volume) were not significantly different from the controls in this group. The chemical was reported to be a possible respiratory sensitiser (OECD, 2004; REACH).

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (R43) in the HSIS (Safe Work Australia). The available data support this classification.

Several skin sensitisation studies in guinea pigs have reported skin sensitisation at a range of concentrations (1–5 %) (OECD, 2004; REACH).

In a skin sensitisation study with limited documentation (Buehler test, OECD Test Guideline (TG) 406), guinea pigs (n = 20) were administered the chemical (5 % w/v in mineral oil) during the induction phase. The challenge concentration was not reported. Erythema reactions (scores of 0.5 in eight animals and 1.0–2.0 in 12 animals) were observed. Pinpoint areas of subcutaneous haemorrhaging were observed in two animals. No reactions were observed with the vehicle control. The chemical was reported to be a skin sensitiser (OECD, 2004; REACH).

In a local lymph node assay (LLNA) (OECD TG 429), the chemical was applied at concentrations of 0, 0.10, 0.25, 0.50, 1.0 or 2.5 % in acetone/olive oil (4:1 v/v) on female mice (n = 4/dose). Increasing stimulation index (SI) values were reported to be dose related (1, 1.91, 4.86, 6.32, 14 and 15.98, respectively). The chemical was reported to be a skin sensitiser, with an EC3 (effective concentration needed to produce a three-fold increase in lymphocyte proliferation) of 0.16 % (REACH).

Observation in humans

Increased incidences of bronchitis and dermatitis have been reported among workers repeatedly exposed to the chemical. In a patch test with 190 workers (enamellers and decorators) from five ceramic factories, only two gave positive results for skin sensitisation with the chemical (HSDB; REACH).

In a cohort study, workers (n = 401) from four factories were occupationally exposed to three acid anhydrides (including the chemical), the workers completed questionnaires and underwent skin-prick testing. The tests were conducted with acid anhydride human serum albumin (AA-HSA) conjugates and common inhalant allergens. Among these workers, 34/401 reported respiratory symptoms and 12 showed an immediate reaction to AA-HSA conjugates (REACH).

In a few case reports, respiratory sensitisation was reported among factory workers exposed to the chemical. Effects were reversible following complete avoidance of exposure, but re-exposure caused a more severe response. A 34-year-old man developed respiratory symptoms (cough, rhinitis, breathlessness and wheezing) one month after working in the alkyd-polyester section of a factory. The symptoms were acute and occurred while loading the chemicals into a reactor. The man recovered when he was removed from that section but new exposure caused another incidence of acute asthma. Airborne dust concentrations of the chemical were estimated to be 0.8 mg/m^3 (inhalable) and 0.2 mg/m^3 (respirable) in the work area. Bronchial challenge tests with the chemical at 0.83 mg/m^3 (inhalable) and 0.09 mg/m^3 (respirable) showed an immediate asthmatic response, accompanied by rhinitis and lacrimation. Rales developed in the lungs within 30 minutes (CalEPA, 2001; OECD, 2004).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not considered to cause serious damage to health from repeated oral exposure. Although kidney effects were reported in rats at doses ≥100 mg/kg bw/day in the 90-day study, no such effects were reported in a two-year study in rats. Severe kidney effects were also reported in rats at 150 mg/kg bw/day in a reproductive toxicity study.

In a repeated dose oral toxicity study (non-guideline), SD rats (n = 15/sex/dose) were administered the chemical in the diet at doses of 0, 20, 40, 100, 250 or 600 mg/kg bw/day, seven days/week for 90 days. At doses ≥100 mg/kg bw/day, kidney effects (increased size, pale discolouration and dilated tubules in the cortex, and microscopically visible changes such as diffuse tubular dilatation, hypertrophy, and degeneration and regeneration of the tubular epithelial cells in the nephron) were observed. These effects were more severe in males than in females. A no observed adverse effect level (NOAEL) of 40 mg/kg bw/day was determined (OECD, 2004; REACH).

In a two-year study (OECD TG 452), no kidney effects were observed in rats (n = 30/sex/dose) administered the chemical up to 100 mg/kg bw/day. The NOAEL was reported as 10 mg/kg bw/day, based on marginal toxicity effects (decreased body weights and reduced food consumption) observed at doses ≥32 mg/kg bw/day. These effects were more pronounced in males than in females. Although high incidences of eye lesions (cataracts or inflammation of the iris) were reported, those were not considered relevant to the treatment (REACH).

In a two-generation reproductive toxicity study (OECD TG 416) in rats, histopathological examination revealed chemical-related changes in the kidneys and bladder (all doses), and renal cortical necrosis at 150 mg/kg bw/day in F0 adults (OECD, 2004) (see **Reproductive and developmental toxicity**).

In a 90-day dietary study (OECD TG 409) in beagle dogs (n = 4/sex/dose), the highest dose of 60 mg/kg bw/day was determined to be the NOAEL as there were no toxicity effects related to treatment up to the highest dose tested (OECD, 2004; REACH).

Dermal

No data are available.

Inhalation

The repeated dose inhalation toxicity studies in animals have shown adverse effects due to the corrosive nature of the chemical. The chemical is already classified for causing burns (C; R34) (see **Recommendation**).

In a repeated dose inhalation toxicity study (OECD TG 412), SD rats exposed to the chemical vapour at 86 mg/m^3 (highest dose) exhibited ocular and nasal discharge, along with periodic nasal bleeding and respiratory distress. These symptoms were less severe at lower concentrations, and were reversible when exposure ceased. A lowest observed adverse effect concentration (LOAEC) of 12 mg/m^3 was determined, based on concentration-dependent lesions observed at all exposure levels in the nasal turbinates and trachea (epithelial hyperplasia and inflammatory exudate), and in the lungs (epithelial hyperplasia, squamous metaplasia and intra-alveolar haemorrhage (OECD, 2004; REACH).

In six-month inhalation studies, CD rats (n = 15/sex/dose), Engle hamsters (n = 15/sex/dose) and rhesus monkeys (n = 3/sex/dose) showed respiratory and eye irritation when exposed to the chemical vapour at 3.3, 9.8 and 9.8 mg/m^3, respectively. Both rats and hamsters displayed reversible hyperplastic and metaplastic changes in the nasal tissues at all exposure levels (1.1, 3.3 and 9.8 mg/m^3 or 0.3, 0.8 and 2.4 ppm), indicating irritation. The NOAEC was 3.3 mg/m^3 for rats, based on systemic effects (decreased body weights) and localised irritation effects. A NOAEC of 9.8 mg/m^3 was determined for hamsters and monkeys, based on the localised nasal irritation effects (OECD, 2004; REACH).

Genotoxicity

Based on the weight of evidence from the available data, the chemical is not considered to be genotoxic.

The chemical gave negative results in the following in vitro assays (OECD, 2004; HSDB):

- both the chemical and maleic acid were negative in several bacterial reverse mutation assays with strains of *Salmonella typhimurium* at concentrations up to 5000 µg/plate, with or without metabolic activation; and
- in a recombination assay in *Bacillus subtilis*, with or without metabolic activation.

In one in vitro assay, increased chromosomal aberrations were observed in Chinese hamster lung (CHL) cells, with or without metabolic activation. This result was reported as unclear as it could be due to the chemical hydrolysing to maleic acid, or a pH change to an acidic environment causing a non-specific effect (OECD, 2004).

In a chromosomal aberration assay (OECD TG 475), there was no chromosomal damage in the bone marrow cells of SD rats (n = 15/sex/dose) exposed to the chemical vapour at 1 or 100 mg/m^3 (0.25 or 25 ppm) for six hours (OECD, 2004; REACH).

Carcinogenicity

Only limited data are available.

In a carcinogenicity study (OECD TG 451), Fischer 344 rats were administered the chemical in the diet at doses of 0, 10, 32 or 100 mg/kg bw/day, seven days/week for two years. The chemical caused marginal toxicity (small, but dose-related decreases in body weights and slightly reduced food consumption) at doses ≥32 mg/kg bw/day. No treatment-related increase in tumour incidence was reported. An unusually high incidence of uterine adenocarcinomas was observed in the control and treated animals (23/86 and 20/82, respectively; dose not stated). The authors stated that 'uterine adenocarcinoma is not a common spontaneous lesion in the strain of rat', but no historical data were available and, therefore, it was unclear whether this was caused by the chemical. It was speculated that continuous exposure to light during the study might have altered the hormonal status in the rats. Therefore, the relevance of this effect to carcinogenicity of the chemical was not clear (OECD, 2004; REACH).

A two-year oral carcinogenicity study on rats administered with maleic acid up to doses of 750 mg/kg did not show any carcinogenicity (OECD, 2004).

Experimental genotoxicity data show that the chemical is not genotoxic (see **Genotoxicity**). Quantitative Structure Activity Relationship (QSAR) modelling using OASIS–TIMES gave negative predictions for Ames tests and positive predictions for chromosomal aberrations in vitro. These predictions were considered reliable as the chemical structure was in the applicability domain for these tests. The chemical structure was out of the applicability domain for all in vivo models and, therefore, not used.

Compounds with an a,β-unsaturated carbonyl, similar to the chemical, are particularly reactive and might interact with nucleophilic groups on biological macromolecules (peptides, proteins, or DNA), causing a wide range of adverse effects. These compounds can exhibit different interactions with DNA, which could lead to different genotoxic and mutagenic responses. Conjugation of the carbonyl group causes the β-carbon to be positively polarised, resulting in a site of action for nucleophilic attack similar to the Michael type addition mechanism (Koleva, Madden & Cronin, 2008). Although the known metabolic pathway of this chemical indicates this possibility (see **Toxicokinetics**), current information is inadequate to sufficiently determine the carcinogenic potential of the chemical.

Reproductive and Developmental Toxicity

The available information indicates that the chemical does not cause reproductive and developmental toxicity.

In a two-generation reproductive toxicity study (OECD TG 416), rats (10 males and 20 females/dose) were administered (gavage) the chemical at doses of 0, 20, 55 or 150 mg/kg bw/day, seven days/week, for a minimum of 80 days (F0 and F1 generation). The chemical was toxic to the parental animals at 150 mg/kg bw/day (with mortalities in the F1 and F0 generations). Histopathological examination of the F0 adults revealed chemical-related changes in the kidneys and bladder (all doses), and renal cortical necrosis in the high dose group. Significantly increased absolute kidney weights of the F1 adult females were observed at 20 or 55 mg/kg bw/day, but there were no microscopic changes in the kidneys. No adverse effects on pup survival and litter size were observed up to 150 mg/kg bw/day for F1 and up to 55 mg/kg bw/day for F2. A reproductive NOAEL of 55 mg/kg bw/day was determined based on maternal mortality at the highest dose (OECD, 2004; REACH).

In a developmental toxicity study (OECD TG 414), female rats were administered (gavage) the chemical in corn oil at 0, 30, 90 or 140 mg/kg bw/day on gestational days (GD) 6–15. No treatment-related developmental effects in foetuses (external, soft tissue and skeletal abnormalities) were observed. However, a few malformations were observed in foetuses (in two foetuses at 30 mg/kg bw/day in 2/23 litters; three foetuses at 140 mg/kg bw/day in 3/21 litters; and in one foetus in the control group in 1/23 litters). These were considered to be random occurrences. A maternal and developmental NOAEL of 140 mg/kg bw/day was reported (OECD, 2004; REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute effects (acute toxicity from oral and dermal exposure);
- local effects (corrosivity, skin sensitisation and respiratory sensitisation); and
- harmful effects following repeated exposure through inhalation.

Public Risk Characterisation

Although use in cosmetic products in Australia is not known, the chemical is reported to be used overseas in film forming agents (co-polymers in cosmetics, hair care, or skin care products) (concentrations not specified). Considering the range of cosmetic and personal care products that could contain the chemical, the main route of public exposure is expected to be through the skin.

The SPIN database indicates domestic uses. Nevertheless, SPIN does not distinguish between direct use of the chemical or use of the materials that are produced from chemical reactions involving the chemical. Nevertheless, the chemical is likely to be hydrolysed or reacted in product formulations to maleic acid (see **Toxicokinetics**) and, therefore, exposure to the chemical is not expected to cause any unreasonable risks from potential cosmetic or domestic product formulations.

Occupational Risk Characterisation

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

Given the critical health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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.

If any information becomes available to indicate significant consumer exposure to the chemical in Australia (i.e. higher concentrations or quantities in cosmetics or domestic products), risks to public health and safety may have to be managed by changes to poisons scheduling.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2014).

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 if swallowed - Cat. 4 (H302) Toxic in contact with skin - Cat. 3 (H311)
Irritation / Corrosivity	Causes burns (C; R34)*	May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335) Causes severe skin burns and eye damage - Cat. 1B (H314)
Sensitisation	May cause sensitisation by inhalation (Xn, R42)* May cause sensitisation by skin contact (Xi; R43)*	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) 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, ocular and inhalation 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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