Benzenamine, 4,4'-oxybis-: Human health tier II assessment

18 September 2014

CAS Number: 101-80-4

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.

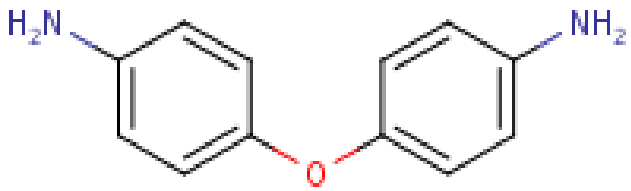
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	4,4-oxydianiline (ODA) aniline, 4,4'-oxydi- 4,4'-diaminodiphenyl ether p-aminophenyl ether 4,4'diaminobiphenyl oxide
Structural Formula	
Molecular Formula	C12H12N2O
Molecular Weight (g/mol)	200.2
Appearance and Odour (where available)	Light pink to white solid.
SMILES	c1(Oc2ccc(N)cc2)ccc(N)cc1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; Galleria Chemica and various international assessments (NCI, 1980; IARC, 1983; US EPA, 2009; NTP, 2011).

The chemical is used as an intermediate in manufacturing synthetic rubber, polyimide and poly(ester) imide resins. These resins are used in manufacturing temperature resistant products such as wire-enamels, coatings, film, and adhesives. The chemical could also be used as an intermediate in manufacturing epoxy resins and adhesives.

The chemical was detected in hair dye products (Lizier & Zanoni, 2012) and in one item of clothing under the European Union (EU) rapid alert system (RAPEX), either as an impurity or breakdown product of an azo-dye or pigment. There are no reports of the chemical being detected in tattoo inks (Danish EPA, 2012; RAPEX).

Restrictions

Australian

This chemical is not individually listed in the *Poisons Standard*—the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). However, the chemical falls under the scope of the following group entry in Schedule 5:

'AMINES for use as curing agents for epoxy resins except when separately specified in these Schedules' (SUSMP, 2013).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.' (SUSMP). Schedule 5 chemicals are labelled with 'Caution'.

International

Cosmetic

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

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- China List of banned substances for use in cosmetics; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

Other

The chemical is restricted under Annex XVII to REACH Regulations. 'The chemical cannot be used in substances and preparations placed on the market for sale to the general public in individual concentrations ≥ 0.1 %' (European Parliament and

Council 1999; European Parliament and Council 2006; European Parliament and Council 2008).

The chemical is on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2013). In the EU, companies could have legal obligations if the chemical that they produce, supply, or use is included on the candidate list whether on its own, in mixtures, or present in articles.

The New Zealand Environmental Protection Agency recommends that tattoo and permanent make up substances should not contain or release the chemical (NZ EPA, 2012).

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):

- Carc. Cat. 2; R45 (carcinogenicity);
- Muta. Cat. 2; R46 (mutagenicity);
- Repr. Cat. 3; R62 (reproductive toxicity); and
- T; 23/24/25 (acute toxicity).

Exposure Standards

Australian

No specific exposure standards are available. The *Workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

International

An occupational exposure limit (OEL) of 4 mg/m^3 (0.5 ppm) time weighted average (TWA) and 16 mg/m^3 (2 ppm) short-term exposure limit (STEL) in Canada (Northwest Territories).

Health Hazard Information

Toxicokinetics

The chemical can enter the body through oral, dermal and inhalation exposure. Elimination of the chemical is via urinary and faecal excretion.

The toxicokinetics of the chemical was investigated in a single dose radiolabelling study in male Crl:CD®BR rats. The chemical was administered to rats using two routes: oral gavage of 0.5 or 200 mg ^{14}C-ODA suspended in polyethylene glycol (PEG) and dermal application of 1 mg ^{14}C-ODA formulated in a mixture of methanol, PEG and water. The results showed distribution of the the chemical in the liver (highest concentration identified), kidneys, plasma and in whole blood. Trace amounts of ^{14}C-ODA were

also found in the brain and in fat tissues (REACH). The chemical is considered to have low bioaccumulation potential based on its partition coefficient value (log Kow) of 1.36 (US EPA, 2007).

For the dermally applied dose, 7.3 % was absorbed and about 3 % of this amount was excreted in the urine after 24 hours. Retention of 87 % of the absorbed dose was observed at the site of application. This suggests a likelihood of a continuous release of the chemical and/or its metabolites into the systemic circulation (REACH).

The proportion of the total ^{14}C-ODA excreted in the urine within 48 hours was similar for the 0.5 and 200 mg/kg doses (approximately 35% and 28%, respectively). Faecal excretion was greater in the low dose group (28.7%) compared with the high dose group (13.4%) (REACH).

As with other aromatic amines, it is expected that the chemical can be metabolised through N-acetylation, N-hydroxylation, and ring hydroxylation. The metabolites identified include N-acetyl ODA and N,N'-di-acetyl ODA (major component) (REACH; Wiley, VCH). The urinary data suggest that conjugation by glucuronide or sulfate is not a major process in excreting the chemical (REACH).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia). Although the reported median lethal dose (LD50) of 725 mg/kg bw in rats is not consistent with the classification, there is insufficient evidence to support a recommendation to amend the existing classification.

Several clinical signs of chemically-induced toxicity were observed following the exposure of Crl-CD rats to the chemical from 40–5000 mg/kg bw (in peanut oil) via gavage. These include: discomfort; inactivity; glassy and pale eyes; prostration; slow respiration; salivation; lacrimation; tremors; convulsive movement of the head; loss of coordination; loss of hair; bulging eyes; and ruffled fur. The group exposed to 60 mg/kg bw/day and above displayed weight loss. Discomfort, weight loss (for three days) and loss of hair were noted in animals dosed with 200 mg/kg of the chemical. This dose also produced liver injury and extramedullary blood formation. Death occurred within 12 days following exposure at doses $\geq$1500 mg/kg bw/day (US EPA, 2007; REACH).

Hepatitis and enlarged liver were observed in Fischer 344 (F344) rats exposed to 300–30000 mg/kg bw/day of the chemical. Exposure to 3000, 10000 and 30000 mgkg/bw/day produced haemorrhage in the digestive tract and in the renal medulla at 30000 mg/kg bw/day (NCI, 1980).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in HSIS (Safe Work Australia). Limited data are available to evaluate this classification. In the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend this classification.

The potential for acute dermal toxicity was investigated in rabbits (strain not specified). The animals were exposed to 450, 670 and 1000 mg/kg of the chemical, in dimethylacetamide (DMAC) solution (vehicle), for 24 hours under occlusive conditions. The animals were placed under observation for 14 or 17 days. Mortality occurred at day one in a rabbit treated with 1000 mg/kg of the chemical. At this dose, pathological changes such as focal necrosis in the liver and enteritis in the small intestine were also noted (REACH). Temporary weight loss and appetite loss were among the clinical signs displayed by animals dosed with 450 and 670 mg/kg of the chemical. No pathological alterations were observed in the 450 mg/kg group. By contrast, the liver of animals from the 670 mg/kg group displayed a slight focal necrosis (REACH). However, the potential contribution of the vehicle, DMAC, to the observed toxicity cannot be ruled out.

In another study, loss of appetite and weight were reported in albino rabbits that were exposed (single exposure) to 5000 mg/kg of the chemical for 24 hours under an occlusive condition. No mortality was recorded in this study (US EPA, 2007).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in HSIS (Safe Work Australia). No data are available to evaluate this classification.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is not considered to be a skin irritant.

The chemical did not produce skin irritation in albino rabbits dermally exposed to 0.5 g of the chemical under semi-occlusive conditions for four hours. No erythema or oedema were identified during the study (US EPA, 2007; REACH).

In another study, strong erythema was observed in guinea pigs following exposure of the shaved intact skin to the chemical as a 10% solution in DMAC. However, similar effects were observed in control animals exposed to the solvent DMAC only (US EPA, 2009; REACH).

Eye Irritation

The chemical causes slight eye irritation in animal studies. Effects were not sufficient to warrant a hazard classification.

Slight clouding of the cornea and mild conjunctivitis were observed in male albino rabbits from the exposure of the conjunctiva (right eye) to 10 mg of the chemical for four hours. These effects were reversible one day after the treatment (US EPA, 2009).

The chemical was concluded to not be an ocular corrosive or severe irritant in an in vitro bovine corneal opacity and permeability assay. Values for opacity and permeability were similar to the negative control (REACH).

Sensitisation

Skin Sensitisation

The chemical is a moderate to severe skin sensitiser as reported in a dermal sensitisation study (modified Maguire method) in Duncan Hartley guinea pigs. In this study, 0.1 mL of the chemical was topically applied to the clipped and depilated backs of the animals four times a day for 10 days. Freund's adjuvant at a concentration of 0.2 mL was admininistered intradermally at the time of the third application (injected at a point adjacent to the site of induction). Two weeks after induction, the animals were challenged by applying the chemical to one clipped flank. The treated site was assessed for erythema and oedema at 24 and 48 hours post application. Of the 10 guinea pigs tested, six animals showed skin sensitisation (REACH).

Overall, the available data support the recommendation for classification (see **Recommendation** section).

Repeated Dose Toxicity

Oral

The repeated dose oral toxicity of the chemical was investigated in a number of studies in rats and mice. The results demonstrated not only the development of tumours (see **Carcinogenicity** section), but also non-cancerous effects. The targets for toxicity include the pituitary, thyroid and liver. At higher doses, the kidneys and male reproductive organs are also affected.

As the effects observed are associated with the modes of toxicity for which the chemical is classified (see **Carcinogenicity** and **Reproductive and developmental toxicity** sections), classification for repeated dose toxicity is not recommended.

In 90-day oral studies (Weisburger et al., 1984; Wiley VCH) F344 rats and B6C3F1 mice were exposed to the chemical at concentrations of 300, 600, 1000 and 2000 mg/kg in the diet. Using approximate diet conversion factors (Derelanko & Auletta, 2014), this is equivalent to an exposure of 30–200 mg/kg bw/day in rats and 60–400 mg/kg bw/day in mice. The following effects were observed:

- delayed body weight gain (all groups of rats and mice except the lowest dose);
- increase in mortality in rats (≥100 mg/kg bw);
- loss of hair, internal bleeding, laboured breathing, cyanosis and lethargy in rats (≥100 mg/kg bw);
- abnormalities in the pituitary (hyperplasia) and thyroid (hyperplasia of the follicles) in animals exposed to ≥60 mg/kg bw (rats) and ≥200 mg/kg bw (mice);
- pathologies in the liver (accentuated lobular pattern) and in the pancreas (200 mg/kg bw in rats); and
- histopathological changes in the testes (degeneration of the seminiferous tubules) and prostate (atrophy) in animals exposed to 200 mg/kg bw/day (rats) and 400 mg/kg bw/day (mice).

Although a no observed adverse effect level (NOAEL) value was not reported, no adverse treatment related effects were reported at the lowest doses tested (30 mg/kg bw/day (rats) and 60 mg/kg bw/day (mice)).

No mortality and no histopathological changes in male reproductive organs were observed in a 90-day study in CD and F344 rats exposed to a maximum of 20 mg/kg bw/day of the chemical (see **Reproductive and developmental toxicity** section).

In a limited documented study, adverse effects for the liver and kidney were observed in rats and mice. In this study, rats were exposed orally five days a week for a period of more than two months to 25 mg/animal (rats) and 5 mg/animal (mice). Based on a bodyweight of 0.15 kg (rats) and 0.02 kg (mice), this is approximately exposure to 167 mg/kg bw/day (rats) and 250 mg/kg bw/day (mice). Observed effects included degeneration of the liver lipids, proliferation of bile duct epithelia, enlarged and degenerative changes in kidneys. In some cases, there was a complete loss of the renal tubular epithelium, and deposition of homogeneous eosinophilic protein masses in the glomeruli was observed (Wiley VCH). The animals also exhibited enlargement of the kidneys (with pale yellow colour) and nephrosis (Wiley VCH).

Degenerative changes in the liver were also observed in two-year oral studies in rats (see **Carcinogenicity** section for study details). A dose-related increase in focal angiectasis and/or focal hepatocyte alteration was observed in ChR-CD rats exposed to 10 or 20 mg/kg bw/day of the chemical (US EPA, 2007; US EPA, 2009). Cystic degeneration of the liver was observed in F344 rats exposed to 20–25 mg/kg bw/day (NCI, 1980). In both of these studies, effects in the eyes (diffused retinopathy or cloudy/swollen eyes) were observed (US EPA, 2007; US EPA, 2009). Thyroid follicular cell hyperplasia was observed in a two-year study in F344 rats (25 mg/kg bw/day) and B6C3F1 mice (120 mg/kg bw/day).

Dermal

No data are available.

Inhalation

Limited information is available. One study reported that exposure of rats to the chemical at a concentration of 5.5 mg/m^3 in air, four hours daily for four months resulted in a significant increase in the threshold of nerve-muscle stimulus and a slight reduction of blood haemoglobin level (Wiley VCH).

Genotoxicity

The chemical is classified as hazardous (Category 2 mutagenic substance) with the risk phrase ‘May cause heritable genetic damage’ (T; R46) in HSIS (Safe Work Australia). Whilst there is a lack of in vivo studies on the effects of the chemical on germ cells, repeated dose findings show that the chemical reaches the testes, with the potential to affect germ cells.

The chemical tested positive in the following in vitro tests (US EPA, 2009; Wiley VCH):

- Ames test in *Salmonella typhimurium* strains TA97, TA98, TA1537 (with metabolic activation), TA1535 and TA100 (with or without metabolic activation);
- L5178Y mouse lymphoma cell assay with or without metabolic activation;
- unscheduled DNA synthesis in rat hepatocytes pretreated with Aroclor-1254 or phenobarbital;
- chromosomal aberration (CA) and sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells with and without metabolic activation; and
- cell transformation tests in primary Syrian hamster embryo (SHE) cells, in adenovirus SA7-infected SHE cells, retrovirus infected rat cells and in mouse Balb/c-3T3 cells.

The metabolite N-acetyl-4,4'-ODA was also mutagenic in TA98 and TA100 strains with metabolic activation.

In an in vivo assay, the chemical induced a dose-dependent formation of micronucleated polychromatic erythrocytes (MNPCE) in B6C3F1 male mice. These animals were exposed via a single intraperitoneal injection of the chemical at 37.5–150 mg/kg bw for three consecutive days (US EPA, 2009). The chemical did not produce unscheduled DNA synthesis in rat hepatocytes following treatment in vivo (REACH; Wiley VCH).

Carcinogenicity

The chemical is classified as hazardous (Category 2 carcinogenic substance) with the risk phrase ‘May cause cancer (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

In a two-year carcinogenicity study in F344 rats and B6C3F1 mice, the animals were exposed to the chemical at doses ranging from 150–800 ppm (22.5–120 mg/kg bw/day) in B6C3F1 mice and 200–500 ppm (10–25 mg/kg bw/day) in F344 rats.

Dose-dependent benign and malignant tumours developed in various tissues in both sexes. These included hepatocellular carcinoma or neoplastic nodules in the liver (rats and mice), follicular cell adenomas or carcinomas in the thyroid (rats and female mice), and adenomas in the Harderian glands (mice). In some of the exposed animals, pituitary adenomas and haemangiomas in the circulatory system (male mice) were also reported (NCI, 1980). In addition, adenocarcinoma or carcinomas in the uterus of females and testicular interstitial cell tumours were also reported in male Sprague Dawley (SD) and ChR-CD rats with two years of exposure to approximately 10–20 mg/kg bw of the chemical in the diet (USA EPA, 2009; Wiley VCH).

Earlier studies in Rappolovo rats also reported findings of leukosis, liver fibrosarcomas, mammary fibroadenomas, reticulosarcomas and renal carcinomas in a small number of animals subcutaneously injected with 25 mg of the chemical (Wiley VCH).

The chemical is listed in the National Toxicology Program (NTP) *Report on Carcinogens* (Twelfth Edition) as 'reasonably anticipated to be a human carcinogen' (NTP, 2011). The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Possibly carcinogenic to humans’ (Group 2B), based on sufficient evidence for carcinogenicity based on animal testing. There are no epidemiological data available on the carcinogenicity of the chemical in humans.

The mechanism of action for its carcinogenicity is not completely understood. Based on the results of carcinogenicity and genotoxicity studies in animals, a genotoxic mechanism cannot be excluded. There is a lack of evidence to support the theory that the chronic tissue damage (liver) or tissue-stimulation (thyroid) effects cause thyroid and liver tumours in rats and mice. The tumours observed in animals are considered to have potential relevance for humans.

Reproductive and Developmental Toxicity

The chemical is classified as hazardous (Category 3 substance toxic to reproduction) with the risk phrase 'Possible risk of impaired fertility' (Xn; R62) in HSIS (Safe Work Australia).

Data from rat studies demonstrated the potential for the chemical to cause reproductive toxicity. A low observed adverse effect level (LOAEL) of 20 mg/kg bw/day was reported from a 90-day study in CD and F344 rats. For the first 29 days of this study, the animals were fed with a diet containing the chemical, ad libitum, at doses of 0.5, 5 or 20 mg/kg bw/day. The feeding regimen was then changed from ad libitum to two hours daily until the end of the 90-day study (US EPA, 2009). Subsequent matings were carried out for CD rats only. The reproductive organs of the male F344 and CD rats underwent histopathological examination. A reduction in the mean body weight, weight gain and food efficiency in female CD rats in the 20 mg/kg dose group were observed. Significant decreases in the mean number of pups per litter and mean weanling body weight were observed following mating female rats in the 20 mg/kg dose group with untreated male rats. Conversely, no change was noted in the reproductive function of male rats. Reduced testes weight was observed in the high dose F344 rats only, but this was not accompanied by treatment-related histopathological changes. No deaths were reported throughout the duration of the study (US EPA, 2009; REACH). Exposure to the chemical also caused changes in the male reproductive system. Degeneration of the seminiferous tubules (testes) and prostate (atrophy) in animals exposed to the chemical at doses of 200 mg/kg bw/day (rats) and 400 mg/kg bw/day (mice) were observed.

Additionally, maternal and developmental changes were observed in pregnant Crl:CD rats after exposure to the chemical (from 30 mg/kg bw/day), via gavage, during gestation days 6–20. These include:

- hair loss (alopecia) and stained fur in dams;
- reduction in body weights and/or weight changes and food consumption in dams;
- decrease in mean foetal weight;
- increased incidence in foetal variations (supernumerary ribs); and
- pale liver in several foetuses.

Overall, the available data support the existing classification.

Risk Characterisation

Critical Health Effects

The chemical is carcinogenic in animals following long-term repeated exposure. A genotoxic mode of action cannot be excluded. The critical health effects for risk characterisation also include reproductive toxicity and systemic acute toxicity by all routes of exposure. The chemical can also produce skin sensitisation reactions.

Public Risk Characterisation

Based on the current information available, the intentional inclusion of the chemical in consumer products is not expected. Hence, the public risk from this chemical is not considered to be unreasonable.

However, the public could be exposed to the chemical as an impurity in, or through release of the chemical from dyes and pigments manufactured using the chemical, including by:

- dermal contact from prolonged exposure to consumer articles containing the chemical;
- oral exposure by young children sucking the materials containing the chemical; and
- hair dye application.

The risk to the public from these routes of exposure will be considered in subsequent IMAP assessments of the relevant dye and pigment chemicals.

Occupational Risk Characterisation

Occupational exposure to the chemical is likely to occur during chemical manufacture or its use in producing polyimide-type resins (NTP, 2011). Dermal, ocular and inhalation exposure of workers to the chemical 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. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation 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 appropriate controls. Based on the available data, the hazard classification in HSIS is considered appropriate.

The *Guidance on the interpretation of workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia).

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.

Recommendations for additional regulatory controls might be required to limit exposure to the chemical due to its presence as an impurity in, or release due to breakdown from, dyes and pigments. This will be considered in subsequent IMAP assessments of the relevant dye and pigment chemicals.

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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Toxic in contact with skin (T; R24)* Toxic by inhalation (T; R23)*	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Toxic if inhaled - Cat. 3 (H331)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)*	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	Suspected of damaging fertility - Cat. 2 (H361f)

[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 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 can 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 assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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