Benzenamine, 2-methyl-: Human health tier II assessment

18 September 2014

CAS Number: 95-53-4

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.

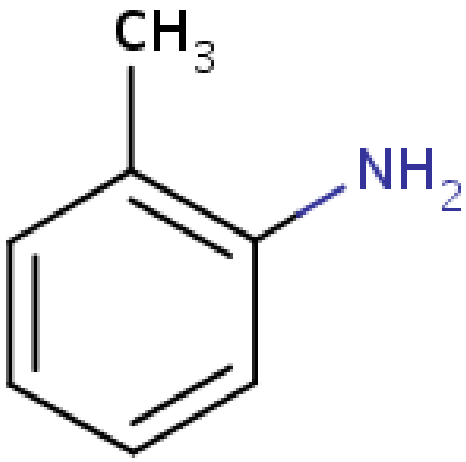
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	2-Aminotoluene o-Toluidine 2-Methylbenzenamine 1-Amino-2-methylbenzene C.I. 37077
Structural Formula	
Molecular Formula	C7H9N
Molecular Weight (g/mol)	107.15
Appearance and Odour (where available)	Light yellow liquid (room temperature) that darkens to reddish brown upon exposure to air with an aniline-like odour.
SMILES	c1(N)c(C)cccc1

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified. The chemical is a restricted carcinogen in Australia under the Work Health Safety (WHS) Regulations 2011 (see **Restrictions: Australia**).

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 (OECD, 2004; NTP, 2011; IARC, 2012).

The chemical has the following site-limited uses as a curing agent in epoxy resins and an intermediate in producing:

- azo dyes and pigments, acid-fast dyestuffs, triarylmethane dyes, sulphur dyes, indigo compounds, photographic dyes; and
- synthetic rubber and rubber vulcanising chemicals.

The chemical is also used in manufacturing non-industrial chemicals (pesticides and pharmaceuticals) including the anaesthetic prilocaine.

The chemical has been detected in tattoo inks (Danish EPA, 2012; RAPEX) and permanent hair dyes and commercial henna samples (colours not specified) (Akyuz & Ata, 2008; Johansson et al., 2014), either as an impurity or breakdown product of an azo-colourant.

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'.

Work health and safety regulations

The chemical is listed in Table 10.2 under Schedule 10 in the *Model Work Health and Safety Regulations* as a restricted carcinogen that cannot be used at a concentration greater than 0.1 % without authorisation from the appropriate state or territory regulator (SWA, 2011).

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;

- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist") under the entry 'Toluidines, their isomers, salts and halogenated and sulfonated derivatives'.

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

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 chemical is also listed in Chile List of Dangerous Substances to Health (Galleria Chemica).

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);
- T; R23/25 (acute toxicity); and
- Xi; R36 (eye irritation).

Exposure Standards

Australian

The chemical has an exposure standard of 8.8 mg/m^3 (2 ppm) time weighted average (TWA) with skin notation. This indicates that absorption through the skin could be a significant source of exposure (Safe Work Australia).

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).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit (occupational exposure limit (OEL)), technical exposure limit (TRK), permitted exposure limit (PEL) of 0.5–22 mg/m^3 (0.1–5 ppm) TWA and 22–44 mg/m^3 (5–10 ppm) short-term exposure limit (STEL) in different countries such as Austria, Argentina, Canada (Yukon), Egypt, Germany, Malaysia, Mexico, New Zealand, Norway, Singapore, and the United Kingdom.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 2 ppm as an 8-hour TWA with skin notation. This TLV is recommended 'primarily to protect against potential methaemoglobinaemia, but should also provide protection against skin, eye, kidney and bladder irritation' (ACGIH, 2011).

Health Hazard Information

Toxicokinetics

The chemical is rapidly absorbed through dermal contact, inhalation of vapour and oral ingestion (OECD, 2004; IARC 2010; IARC, 2012).

The peak level of the chemical in the blood was observed 24 hours after oral gavage with radiolabelled o-toluidine in Crl:CD®BR rats (REACH). After 72 hours, the chemical was widely distributed throughout various organs in the body including the blood, spleen, kidneys, liver, subcutaneous abdominal fat, lungs, heart, abdominal skin, bladder, gastrointestinal tract, bone marrow, brain, thigh muscle and testes (REACH).

The main route of excretion is via urine with smaller amounts excreted in the faeces. Whilst the metabolism of the chemical is not fully defined, N-acetylation and hydroxylation of the 4-position of the aromatic ring are considered to be major metabolic pathways. Other pathways include hydroxylation at the sixth position and oxidation of the methyl and amino groups (occurring to a lesser extent). Sulfate conjugates predominate over glucuronides. (IARC, 2010; IARC, 2012).

The major urinary metabolites identified in rats 24–72 hours after subcutaneous injection or oral administration of the radiolabelled chemical were conjugated or unconjugated o-toluidine, 4-amino-m-cresol and N-acetyl-4-amino-m-cresol. Minor metabolites detected included azoxytoluene, o-nitrosotoluene, N-acetyl-o-toluidine, N-acetyl-o-aminobenzyl alcohol, 4-amino-3-methylphenol, anthralinic acid, and N-anthralinic acid (ACGIH, 2011).

The chemical has been shown to cause an increase in hepatic cytochrome P450 and the activity of several additional enzymes, including ethoxyresorufin-O-deethylase, ethoxycoumarin-O-deethylase, and aldrin epoxidase. The chemically-induced increases in the microsomal aryl hydrocarbon hydroxylase (catalysed by CYPA1 isoenzyme activity) and nicotinamide adenine dinucleotide phosphate (NADPH)-cytochrome c reductase were also detected (IARC, 2000). Furthermore, a dose-dependent induction of CYP1A2 was also observed following oral exposure to the chemical (IARC, 2010). 'By comparison to most other aromatic amines, the chemical is metabolised in rats and humans by CYPs other than 1A2. Candidates for the responsible CYPs are CYP2A6 and 2E1' (IARC, 2010).

Peroxidation enzymes such as prostaglandin H synthase (which is found in the urinary bladder) could also play a role in the metabolism of the chemical (IARC, 2012). Oxidation by prostaglandin H synthase to form reactive intermediates that can bind to DNA has been observed with the structurally similar chemical o-anisidine (NICNAS).

The chemical binds to haemoglobin and other macromolecules including the DNA. Haemoglobin adduct formation was detected both in laboratory animals and in humans. In Germany, these adducts were present in the blood of children exposed to the chemical (NTP, 2011). These molecules were also found in the urinary bladder of patients treated with local anaesthetic, prilocaine, which metabolises to o-toluidine (IARC, 2012). Haemoglobin adducts were also detected in hairdressers with chronic exposure to hair dyes containing the chemical (Johansson et al., 2014). DNA binding and/or DNA damage has been observed in both in vivo and in vitro tests. Metal-mediated DNA damage by the metabolite 4-amino-m-cresol, involving formation of H_2O_2 has also been observed (IARC, 2010).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia). The available median lethal dose (LD50) values in rats do not support this classification. However, methaemoglobinaemia was observed following single exposures in cats to relatively low doses. Methaemoglobin forming capacity is similar in humans and

cats (and more sensitive than in rats). An amendment of the classification based on these non-lethal effects is recommended (refer **Recommendation** section).

In a well-documented study in Wistar rats, the median lethal dose (LD50) was 750 mg/kg bodyweight (bw). Observed sub-lethal effects include increased urination, cyanosis, lethargy and bloody eyes (OECD, 2004; REACH). A similar range of LD50 values (515–900 mg/kg bw/day) has been reported for mice, rats and rabbits (ACGIH, 2011; REACH). No study details were available.

High levels of methaemoglobin formation (59.6–71.7 %) were observed in cats following oral exposure to 50 mg/kg bw of the chemical (OECD, 2004; REACH). Similar levels of methaemoglobin formation were observed in cats following a single intravenous injection of 27 mg/kg bw of the chemical (ACGIH, 2011).

Dermal

The chemical showed low acute toxicity in a study in New Zealand White rabbits with a reported LD50 of 3250 mg/kg bw (REACH). No further details were reported.

However, dermal exposure of Wistar rats to solution containing 0.75–1.25% of the chemical produced a dose-related increase in the formation of methaemoglobin in the blood (methaemoglobinaemia). These effects were reversible after 48 hours (REACH).

Methaemoglobinaemia has been observed following a single exposure (oral and intravenous) to relatively low doses of the chemical (see **Acute toxicity: Oral**). As skin absorption is considered to be a significant source of exposure and there is similarity in methaemoglobin forming capacity between humans and cats (and more sensitive than in rats), classification based on these non-lethal effects is recommended (refer **Recommendation** section).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in HSIS (Safe Work Australia). The median lethal concentration (LC50) value (3.8 mg/L) does not support this classification; however, non-lethal effects have been observed in humans at relatively low doses (refer **Acute toxicity: observation in humans)**. An amendment of the classification based on these non-lethal effects is recommended (refer **Recommendation** section).

Dose-related signs of intoxication were noted in male Sprague Dawley (SD) rats following a ‘head only’ inhalation exposure to the chemical at concentrations of 492–1000 ppm for four hours. Tremors, slight to moderate cyanosis, muscle spasm, breathing difficulty, slight to moderate corneal opacity, extreme exhaustion (prostration) and reddish-brown nasal discharge were observed in the exposed animals. The reported medial lethal concentration (LC50) for this study is 862 ppm (3.8 mg/L) (OECD, 2004; REACH).

Observation in humans

The chemical is highly toxic to humans and can be absorbed via inhalation and through dermal contact. Exposed individuals have been reported to exhibit clinical signs of toxicity including methaemoglobinaemia, haematuria, renal and bladder irritation, physiological and psychological deficits. Severe intoxication was also observed in individuals exposed to 40 ppm of the chemical for 60 minutes (OECD, 2004; ACGIH, 2011).

Corrosion / Irritation

Skin Irritation

The chemical caused slight to moderate erythema and oedema when applied to the skin of Vienna white rabbits (concentration not reported) with observations at 24, 48 and 72 hours post application. In addition to erythema and oedema, the animals displayed scaling. The effects were reversible after eight days, except in 1/6 tested (REACH). The available data were not sufficient to warrant a hazard classification.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available data support this classification.

In an eye irritation study in six Vienna white rabbits, the chemical was found to be irritating. The average scores were 1 for corneal opacity, 0.6 for iris swelling, 2 for conjunctivae (redness), and 1.7 for conjunctivae (chemosis). Effects were not reversible within the observation period of eight days (REACH).

In another study, corneal opacity, swollen iris, red conjunctiva and lacrimation were reported within 24 hours of an application of 0.1 mL o-toluidine in the conjunctival sac of one eye of the New Zealand White rabbits. However, these were reversible except for the observed effects in the cornea, which was partly recovered by the end of the seven-day recovery period (OECD, 2004; REACH).

Sensitisation

Skin Sensitisation

The limited data available for the chemical indicate that the chemical could have some potential to cause skin sensitisation. However, these data do not provide sufficient information for the chemical to be classified as a skin sensitiser.

Although the chemical does not contain a structural alert for skin sensitisation, a potential metabolite (skin metabolism stimulator), o-nitrosotoluene (CAS No. 611-23-4), can react with proteins through nucleophilic addition reaction (OECD Toolbox).

The chemical and its para substituted analogue, p-toluidine (CAS No. 106-49-0), have been demonstrated to bind to protein in vivo (IARC, 2010). Whilst the level of binding is lower for o-toluidine than for p-toluidine, the difference was not as large as that observed for DNA binding. The chemical p-toluidine was positive for skin sensitisation in a Hartley guinea pig patch test with positive reactions observed at challenge concentrations of 2, 1 and 0.5 % (REACH).

A major urinary metabolite in rats, 4-amino-3-methyl phenol (CAS No. 2835-99-6), is considered to be a skin sensitiser based on the positive results seen in a local lymph node assay. The estimated concentration three (EC3) values of 1.45 % and 2.15 % were calculated for dimethyl sulfoxide (DMSO) and the solution of aqua, acetone, and olive oil, respectively (SCCP, 2005).

Observation in humans

Results from a patch test study in 40 dermatitis patients, known to be hypersensitive to p-phenylenediamine, indicated positive reactions in 25 % of participants following exposure to the chemical in yellow paraffin (OECD, 2006; REACH).

Repeated Dose Toxicity

Oral

The toxic effects of the chemical have been investigated in several sub-chronic and chronic repeated dose oral toxicity studies. The results demonstrated not only chemically-induced development of tumours (see **Carcinogenicity** section), but also non-cancer effects.

The sub-chronic studies, whilst limited by poor documentation or a single dose test concentration, demonstrated consistent effects with the targets for toxicity being the blood, liver, kidney, spleen and urinary bladder. A no observed adverse effect level (NOAEL) value could not be established. Observed effects included:

- reduced body weight (lowest observed effect level (LOEL)) approximately 24 mg/kg bw/day in a 14-day study);

- blood-related disorders, including methaemoglobinaemia, deficiency of red blood cells (erythropaenia) and an increase in the number of reticulocytes (lowest LOEL approximately 24 mg/kg bw/day in a 14-day study);
- partially reversible haemosiderin deposition in the kidneys and liver (LOEL approximately 300 mg/kg bw/day in 13- and 26-week studies);
- changes in the mucous membrane in the bladder (LOEL 7.5–12 mg/kg bw/day in a 90-day study) although hyperplasia in the bladder was found to be reversible (LOEL approximately 300 mg/kg bw/day in 13- and 26-week studies); and
- splenic fibrosis, splenic mesothelial hyperplasia, spleen congestion with haemosiderosis, extramedullar haematopoiesis, and the presence of an abnormal excess of cells (hypercellularity) of bone marrow (LOEL approximately 225 mg/kg bw/day in a 20-day study) (OECD, 2004; ACGIH, 2011; REACH).

The severity of effects in the spleen increased with exposure duration (OECD, 2004).

Based on the available data, classification for serious damage to health from repeated oral exposure, is considered warranted (refer **Recommendation** section).

Dermal

The available data for chronic dermal toxicity for the chemical are limited. However, massive bladder haemorrhage and vacuolisation of bladder epithelial cells in rats (species not known) were seen following dermal exposure to 0.5 % of the chemical in a chloroform solution (REACH). No further details were provided in this study.

Inhalation

No data are available.

Observation in humans

Workers with chronic exposure to the chemical have been reported to display anaemia, weight loss, anorexia, cyanosis, methaemoglobinaemia, skin lesions, and disturbance in the central nervous system such as headache, dizziness and confusion (HSDB). Additionally, haemoglobin adducts were found in the urine of workers exposed to the chemical, where higher levels were identified in those with existing impaired skin condition (Korinth et al., 2006). These adducts were also present in the blood of children with exposure to the chemical (NTP, 2011) and in hairdressers with chronic exposure to hair dyes containing the chemical (Johansson et al., 2014).

Genotoxicity

The chemical is considered mutagenic based on the weight of evidence from available, well-documented in vitro and in vivo studies. The available data support the classification (refer to the **Recommendation** section).

Most bacterial tests (*Salmonella typhimurium* and *Escherichia coli*) conducted on the chemical showed non-mutagenic or inconsistent results. However, metabolites formed by N-hydroxylation, N-hydroxy-ortho-toluidine and ortho-nitrotoluene, were mutagenic in *S. typhimurium* strain TA100 in the presence of metabolic activation (WHO, 1998; IARC, 2012). The chemical induced intrachromosomal recombination in *Saccharomyces cerevisiae* (in an assay that detects DNA deletions). The frequency of recombination was reduced by the presence of an antioxidant indicating that the genotoxicity of the chemical was at least in part due to the formation of free radicals.

The chemical gave positive results in the following in vivo tests:

- induction of micronuclei in peripheral blood in rats;
- single-strand DNA breaks in the liver and kidney cells of mice (100 mg/kg bw);

- sister chromatid exchange (SCE) in bone marrow cells of male B6C3F1 mice (150–600 mg/kg bw);
- host-mediated bacterial assay; and
- somatic mutation in *Drosophila melanogaster* (IARC, 2010; IARC, 2012).

The chemical showed negative results in a number of in vitro tests and, in some cases, conflicting data were reported. However, the chemical or the hydrochloride form of the chemical (not listed in the Australian Inventory of Chemical Substances) gave positive results in the following:

- induction of SCE and chromosomal aberrations in Chinese hamster ovary (CHO) cells;
- *Escherichia coli* DNA repair test (pol A) in the absence of metabolic activation;
- unscheduled DNA synthesis in HeLa cells and primary hepatocytes from hamsters and rats;
- DNA strand breakage in human mammary cell line (MCL-5) and in primary cultures of cells isolated from human breast milk;
- gene mutations in L5178Y cells in the presence of metabolic activation; and
- transformations in baby hamster kidney (BHK) 21C13 cells (WHO, 1998; IARC, 2010; ACGIH, 2011).

The chemical was reported to induce DNA lesions in different organs of exposed rats (liver, bladder) and mice (liver, bladder and brain) (IARC, 2012). Furthermore, inhibited testicular DNA synthesis was reported in male mice following oral intubation. Renal DNA synthesis was also inhibited after a single intraperitoneal injection of the lethal doses of the chemical in the suckling mice (ACGIH, 2011).

Carcinogenicity

The chemical is currently classified as hazardous (Category 2 carcinogen) with the risk phrase ‘May cause cancer’ (T; R45) in HSIS (Safe Work Australia). The available epidemiological data support an amendment to this classification (refer **Recommendation** section).

The carcinogenicity of the hydrochloride form of the chemical (not listed on the AICS) was investigated in a number of well-conducted OECD Test Guideline (TG) 452-compliant oral studies (feeding) in male and female Fischer 344 (F344) and CD-1 rats and mice (B6C3F1 and CD-1). In addition to reduced bodyweight and survival, significant increases in the incidence of multi-organ benign and/or malignant tumours were reported in animals exposed to 3000–16000 ppm of the chemical over three months to two years. The equivalent intake doses were calculated at 130–800 mg/kg bw/day. Compared with controls, tumours were found in the spleen, scrotum, urinary bladder, mammary glands, liver, skin, abdominal cavity and blood vessels of the chemically-exposed animals. Sarcomas, angiosarcomas, fibrosarcomas and osteosarcomas in the spleen and in other organs were observed in male and female F344 rats. A significant increase in the incidence of urinary bladder transitional cell carcinoma and mammary gland fibroadenomas was detected in the exposed females. Malignant mesothelioma of the serous covering of the testes, splenic and skin fibromas were also noted in the exposed males. These types of tumours and target organs were consistent with the findings reported from another feeding study in F344 rats dosed with 130 or 470 mg/kg of the chemical for 72 weeks. In CD-1 rats, subcutaneous fibroma and fibrosarcoma were identified following long-term exposure (approximately 18 months) to 400 or 800 mg/kg of the chemical (WHO, 1998; IARC, 2010; NTP, 2011; IARC, 2012; REACH).

Furthermore, chronic oral exposure of B6C3F1 mice to 1000 or 3000 ppm of the chemical resulted in hepatocellular carcinomas, adenomas and haemangiosarcomas. In CD-1 mice, doses of 8000 and 16000 ppm caused increased incidence in abdominal haemangiosarcomas and haemangiomas (WHO, 1998; IARC, 2010; REACH).

In humans, findings derived from several cohort studies of workers provide strong evidence for an increased risk of urinary bladder cancer associated with long-term occupational exposure to the chemical (Ward et al., 1991; Carreon et al., 2010; NTP, 2011). For three of the cohort studies, other bladder carcinogens were reported to be present only at trace levels (IARC, 2010). 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 reviewed epidemiological data and subsequently concluded that it is 'carcinogenic to humans' (Group 1) (IARC, 2010; IARC, 2012).

The mechanism of action underlying the carcinogenicity of the chemical is not fully understood, although it is considered to involve metabolic activation, DNA adduct formation and induction of DNA-damaging effects (see **Toxicokinetics**). A genotoxic mechanism cannot be ruled out (WHO, 1998; IARC, 2012).

Reproductive and Developmental Toxicity

Limited data are available. In one poorly-documented study, the chemical has been shown to produce transplacental toxicity in mice. Development of tumours was identified in the offspring of Balb/c mice after 4–5 subcutaneous injections of 2 mg of the chemical to their pregnant mothers in the final week of gestation. The effects include lung adenomas and mammary gland tumours (REACH).

Risk Characterisation

Critical Health Effects

The chemical is carcinogenic following long-term repeated exposure. A genotoxic mode of action cannot be excluded. The critical health effects for risk characterisation also include systemic acute and chronic toxicity by all routes of exposure (refer to **Acute toxicity** and **Repeated dose toxicity** sections). The chemical might produce eye irritation and skin sensitisation reactions (particularly in individuals with sensitive skin).

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 the release of, the chemical from dyes and pigments manufactured using the chemical by:

- dermal contact with the chemical from prolonged exposure to articles of clothing and leathergoods containing the dye;
- oral exposure by young children sucking the materials containing the dye;
- applying or removing tattoos; 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 can 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. Use of skin barrier creams could enhance percutaneous uptake of the chemical (Korinth et al., 2006) and should be avoided.

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).

The data available support an amendment to the hazard classification in HSIS (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.

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.

This chemical is a restricted carcinogen in Australia under the Work Health Safety Regulations 2011. Suppliers of this chemical and persons conducting a business or undertaking (PCBU) using this chemical, have specific obligations to protect the safety of workers using, handling, and/or storing the chemical (Work Health and Safety Regulations 2011). The information about the status of the chemical as a restricted carcinogen under the Work Health Safety Regulations 2011 will be included in the Australian Inventory of Chemical Substances (AICS) according to section 13(1)(b) of the *Industrial Chemicals (Notification and Assessment) Act 1989*.

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: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed (T; R39/23/24/25)	Causes damage to organs - Specific target organ tox, single exp Cat. 1 (H370)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed (Xn; R48/20/21/22)	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 1 - May cause cancer (T; R45)*	May cause cancer - Cat. 1A (H350)

[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.

Using skin barrier creams could enhance percutaneous uptake of the chemical and should be avoided.

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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