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

04 July 2014

CAS Number: 90-04-0

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.

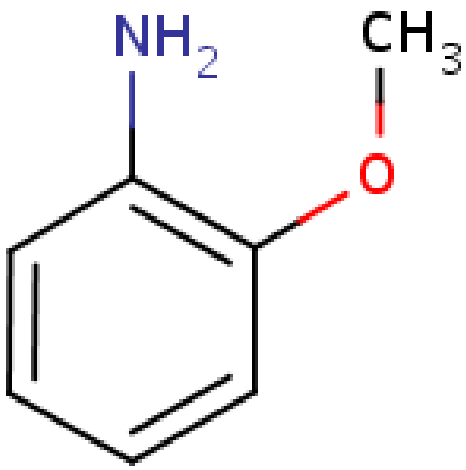
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	ortho-anisidine 1-amino-2-methoxybenzene 2-methoxyaniline 2-methoxybenzenamine 2-aminoanisole
Structural Formula	
Molecular Formula	C7H9NO
Molecular Weight (g/mol)	123.15
Appearance and Odour (where available)	Colourless to yellowish, pink, or reddish with an amine-like odour.
SMILES	c1(OC)c(N)cccc1

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 (IARC, 1999; EU RAR 2002; NTP, 2011; SCOEL, 2011).

The chemical has site-limited uses as an intermediate in the production of azo, naphthol and acid dyes and pigments including:

- direct yellow (DY) 44, DY117, DY118, DY120, DY132;
- pigment yellow (PY) 74, PY65, PY17, and PY73;
- pigment red (PR) 15, PR119, PR188, PR261, and PR9;
- direct red (DR) 24, DR26, DR72; and
- acid dyes such as Acid Yellow 219, Acid Red 4 and Acid Violet 12.

These pigments are used in paints, printing inks, alkyd lacquers, crayons and coloured pencils, while the dyes are used in textiles, papers and leathers (EU RAR, 2002).

The chemical has been detected in tattoo inks, either as an impurity or breakdown product of an azo-pigment (ECHA, 2011, Danish EPA, 2012, RAPEX).

The chemical has reported commercial use including as:

- a corrosion inhibitor for steel storage,
- an antioxidant for some polymercaptan resins; and
- a bactericide in metal working fluids.

Restrictions

Australian

No known restrictions have been identified.

International

Cosmetic

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

- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;

- Egypt Unified Lists—List (A) List of banned chemicals; and
- United Arab Emirates Restricted Chemicals.

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. 3; R68 (mutagenicity); and

T; R23/24/25 (acute toxicity).

Exposure Standards

Australian

The chemical has an exposure standard of 0.5 mg/m^3 (0.1 ppm) time weighted average (TWA). Notices: Sk (absorption through the skin may be a significant source of exposure) (Safe Work Australia).

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).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (OEL), time weighted average (TWA), threshold limit value (TLV), permitted exposure limit (PEL) or short-term value (STV) of:

- 0.5 mg/m^3 (0.1 ppm) in different countries such as Argentina, Norway, Canada, Denmark, Indonesia, Japan, Switzerland, South Africa, France, Mexico, Malaysia, Germany, Finland, Spain, Ireland, Austria, Belgium, the United Arab Emirates, Iceland, Croatia, India, Poland, Italy, China, Nicaragua, South Korea, Bulgaria, the Philippines, and Portugal.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommended a threshold limit value (TLV) of 0.5 mg/m^3 TWA with a skin notation. 'This value is intended to minimize the potential for methemoglobinemia and the resulting anoxia in exposed workers' (ACGIH, 2011). Similarly, the Occupational Safety and Health Administration (OSHA) has listed an exposure limit of 0.5 mg/m^3 with a skin notation (NIOSH, 1992).

Health Hazard Information

Toxicokinetics

There is limited information on the toxicokinetics and mode of action of the chemical. However, based on the available toxicological profile, it is assumed that the chemical can enter the body through oral, dermal and inhalation routes (SCOEL, 2011). It is considered that skin absorption could be a significant source of exposure (NIOSH, 1992; ACGIH, 2011).

The chemical was quickly absorbed into the blood plasma and distributed to various tissues following intraperitoneal (i.p.) administration using a radiotracer (^3H) in IMP:WIST (Rattus) rats. The highest concentrations were found in the liver, kidney and muscle 12 hours after exposure. Approximately 72 % of the chemical was excreted in the urine 72 hours following exposure. Prolonged retention was observed in tissues, which could indicate a potential to accumulate with repeated exposures (Sapota et al., 2003).

Whilst information on the metabolism of the chemical is limited, N-, O-acetylation, N-hydroxylation and O-demethylation pathways have been suggested (EU RAR, 2002; SCOEL, 2011).

N-acetylated metabolites of the chemical, N-acetyl-2-methoxyaniline (97 %) and N-acetyl-4-hydroxy-2-methoxyaniline (1.5 %), were detected in the urine of rats exposed to the chemical by i.p. injection (Sapota et al., 2003). O-demethylation, forming o-aminophenol, has been observed from in vitro studies with hepatic microsomes of rats and rabbits (EU RAR, 2002; REACH).

The metabolite, N-(2-methoxyphenyl)hydroxylamine, resulting from N-hydroxylation, has been observed in in vitro studies with human, rat and rabbit hepatic microsomes (Stiborova et al., 2005; REACH). This process is catalysed by cytochrome P450 enzymes, including subunits CYP1A1, 1A2, 2B2, 2B4 and 3A6 (Stiborova et al., 2005). The chemical also induced significant increase in 7-ethoxyresorufin O-deethylation, which is a marker of activity for both CYP1A1 and 1A2 (Rydlova et al., 2005).

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. Oxidation by prostaglandin H synthase, or horseradish peroxidase via a radical mechanism, formed reactive intermediates including electrophilic diimine and quinonimine metabolites. These intermediates have been shown to bind to DNA and protein (in vitro). A dimeric metabolite with an azo bond was also observed (IARC, 1999; EU RAR 2002; Stiborova et al., 2002).

DNA adducts derived from the N-hydroxylated metabolite have been detected in both in vitro and in vivo (i.p. route of administration) studies. In the in vivo study (Wistar rats), the majority of the adducts were identified in the urinary bladder with low levels found in the liver, kidney and spleen (Stiborova et al., 2005). DNA binding was not observed in the liver and bladder of mice (in vivo) following oral exposure (Ashby et al., 1994).

Elevated methaemoglobin levels observed in acute toxicity studies in animals (see **Acute toxicity: oral**) are considered a result from the interaction of the N-hydroxylated metabolite with the haem group of haemoglobin (SCOEL, 2011). Haemoglobin adducts of the chemical have been detected in the blood of children (NTP, 2011).

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 (1505–1890 mg/kg bw) do not support this classification. However,

methaemoglobinaemia was observed following a single exposure to relatively low doses. An amendment of the classification based on these non-lethal effects is recommended (refer **Recommendation** section).

Results from a key study, which is compliant with OECD Test Guideline (TG) 401, with male and female Wistar rats exposed to 1250–4000 mg/kg bodyweight (bw) of the chemical, via gavage, produced pathological changes. These include haemorrhages in the urinary bladder, intestine and stomach; congestion of blood vessels in the gastrointestinal tract and lungs; and yellow-red foamy liquid in the intestine. Mortalities occurred between 20 minutes to about 60 hours in animals from 1800-4000 mg/kg dose groups. Other treatment-related changes were also observed in animals in low dose groups (1250, 1600, 1800, 2000 mg/kg bw) such as staggering gait, squatting, reduced spontaneous activity, dizziness and respiratory depression. In high dose groups (2500, 3150, 4000 mg/kg bw), animals displayed the abdominal position, a negative righting reflex, orange urine, and pale skin. In some cases, respiratory sounds were noted at doses more than 2500 mg/kg bw (EU RAR, 2002).

In another study, oral exposure to the chemical (1250–3200 mg/kg bw) via gavage resulted in deaths occurring within 30–48 hours in Wistar rats (REACH). During the observation period, exposed animals displayed disturbed equilibrium and a deteriorating condition. The LD50 value for this study was 1505 mg/kg bw (REACH).

Furthermore, other investigations reported significant increases in the methaemoglobin levels in Alpk:APfSD rats and CBA mice following a single oral administration of 1380 mg/kg bw and 690 mg/kg bw of the chemical respectively. In addition to methaemoglobin formation, other severe adverse effects included blood-related disorders and nephrotoxicity (EU RAR, 2002; REACH).

Compared with controls (1.1 %), a significant increase in methaemoglobin levels (11.5 %) was observed in cats after a single intravenous injection of 7.7 mg/kg bw of the chemical. Methaemoglobin-forming capacity is similar in humans and cats (EU RAR 2002; SCOEL, 2011; REACH).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in HSIS (Safe Work Australia). The available LD50 values (>2000 mg/kg bw) do not support this classification. An amendment to the classification is recommended (refer **Recommendation** section) based on the following:

- observed methaemoglobinaemia following single exposure (oral and intravenous) to relatively low doses of the chemical (see **Acute toxicity:oral**); and
- skin absorption is significant source of exposure (ACGIH, 2011).

The chemically-induced changes in Wistar rats were observed following exposure to 2000 mg/kg of chemical for 24 hours under an occlusive condition (OECD TG 402 standards). These include reversible ataxia, lacrimation, constriction of the eyelid and orange urine. The tested dose and exposure did not produce mortality in the animals (SCOEL, 2011; REACH).

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 (>3.87 mg/L) does not support this classification. An amendment to the classification (refer **Recommendation** section) is recommended, based on the following:

- observed methaemoglobinaemia following a single exposure (oral and intravenous) to relatively low doses of the chemical (see **Acute toxicity:oral**); and
- the chemical is absorbed by all routes of exposure.

In an acute inhalation study in male and female Wistar rats, exposure of the animals to 2.17 and 3.87 mg/L of the chemical as an aerosol (nose only) for four hours resulted in movement impairment, changes in respiration and reflexes, cyanosis, and bloody nasal discharge. These changes were reversible after eight days. No mortalities were observed. The potential for methaemoglobin formation was not investigated (SCOEL, 2011; REACH).

Corrosion / Irritation

Skin Irritation

Based on the limited data available, the chemical is reported to slightly irritate skin in animal studies. However, the effects were not sufficient to warrant hazard classification.

Acute dermal exposure to the chemical produced very mild erythema and slight oedema reactions in New Zealand White (NZW) rabbits. These animals were exposed to 0.5 mL solution containing the chemical, under an occlusive condition, for four hours (OECD TG 404). The effects were reversible within 24–72 hours (EU RAR, 2002; REACH). In a similar study in yellow-silver rabbits, the chemical did not cause dermal irritation (REACH).

Eye Irritation

Based on the limited data available, the chemical is reported to slightly irritate the eyes in animal studies. However, the effects were not sufficient to warrant a hazard classification.

In an OECD TG 405-compliant acute eye irritation study, only minor effects were observed in the NZW rabbit eyes after exposure to 0.1 mL of solution containing the chemical for 24 hours. These effects include chemosis, reddened conjunctiva, and inflamed cornea and iris, of which all were reversed within 24–72 hours of exposure (EU RAR, 2002; REACH).

Sensitisation

Skin Sensitisation

Based on the limited data available, the chemical showed potential for dermal sensitisation reactions in a guinea pig test and in a mouse local lymph node assay (LLNA). However, these studies were either poorly documented or the results were insufficient to warrant classification.

A weak dermal sensitisation reaction was observed after intra- and epicutaneous administration of 0.5 or 2.5 mg/kg bw of the chemical to guinea pigs. No other information was provided for this study (EU RAR 2002; REACH).

The data from an LLNA study in female CBA mice (OECD TG 429) indicated a chemically-induced sensitisation reaction. In this assay, stimulation index (SI) values of 2.26, 3.43, and 1.27 were obtained in animals exposed daily to 25 %, 50 % or 100 % for five consecutive days (EC3 value of 40.8 % weight/volume). One animal died after the second application (within 24 hours) in the 100 % group. However, the results of this study were deemed equivocal or inconclusive due to the lack of the dose-response relationship between the concentrations tested and the associated SI values (REACH).

A structurally related chemical, 2-ethoxyaniline (CAS No. 94-74-2), was negative in a well-conducted guinea pig maximisation test (EU RAR, 2002). A potential metabolite, o-aminophenol (CAS No. 95-55-6) has some potential to cause skin sensitisation. However, the data available do not provide sufficient information for o-aminophenol to be classified as a skin sensitiser (NICNAS).

Repeated Dose Toxicity

Oral

The toxic effects of the chemical from repeated oral exposure were investigated in a number of well-conducted studies (OECD TG 407) in Fischer 344 and Wistar rats, and B6C3F1 mice. The results demonstrated not only chemically-induced development of tumours (see **Carcinogenicity** section), but also non-cancerous effects.

Given the lowest observed adverse effect level (LOAEL) available from the 28-day study in rats (80 mg/kg bw/day), classification for danger to health from repeated oral exposure is considered warranted (refer **Recommendation** section). The targets for toxicity are the bone marrow and spleen.

Wistar rats treated with 80 or 400 mg/kg of the chemical daily for 28 days displayed the following abnormalities (EU RAR, 2002):

- slight haemolytic anaemia and elevated levels of bilirubin in the blood;
- increased relative liver weights;
- yellow urine;
- changes in the spleen including weight increase, haemosiderosis, hyperaemia, and increased haematopoiesis;
- increased levels of liver enzyme, alanine aminotransferase (400 mg/kg bw only); and
- elevated levels of urea-nitrogen in the blood.

The no observed adverse effect level (NOAEL) for this study was 16 mg/kg bw/day.

In a seven-week range finding study in rats and mice with the chemical in its hydrochloride form, CAS No.134-29-2 (not listed on the Australian Inventory of Chemical Substances), enlarged spleens that were black and granular were observed at approximately 750 mg/kg bw/day in rats and 1500 mg/kg bw/day in mice (EU RAR, 2002).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Complaints of headache and vertigo, increased sulfhaemoglobin and methaemoglobin, and frequent occurrence of Heinz bodies were reported in workers exposed to 0.4 ppm (2 mg/m³) (ACGIH, 2011).

Genotoxicity

The chemical is classified as hazardous (Category 3 mutagenic substance) with the risk phrase ‘Possible risk of irreversible effects’ (Xn; R68) in HSIS (Safe Work Australia). The available data support this classification.

The genotoxic and mutagenic potentials of the chemicals were evaluated in several well-conducted in vitro and in vivo studies.

The chemical showed negative results in a number of in vitro tests and, in some cases, conflicting data were reported. In particular, some studies found that the chemical tested positive in *Salmonella typhimurium* strains TA98, TA100, TA1537, and TA1538 in the presence of metabolic activation (EU RAR, 2002). By contrast, earlier reports indicated that these strains, along with TA1535 and *Escherichia coli* strain WP2 uvrA, tested negative with or without metabolic activation (IARC, 1999; REACH). The chemical gave positive results in *S. typhimurium* strain YG1029 but negative results in strain YG1012. Both these strains have elevated levels of N-acetyltransferase activity (Thompson et al., 1992; REACH).

However, the chemical produced unequivocally positive results in the following in vitro assays (IARC, 1999):

- DNA strand breaks/cross links in mouse lymphoma cells L5178Y cells with metabolic activation;

- gene mutation in the thymidine kinase (tk) locus in L5178Y mouse lymphoma cells with and without metabolic activation;
- cell transformation in Syrian hamster embryo cells (clonal assay) without metabolic activation; and
- sister chromatid exchange and chromosomal aberration in Chinese hamster ovary (CHO) cells with or without metabolic activation.

The chemical also induced inhibition of gap junctional intercellular communication in mouse hepatocytes and intrachromosomal recombinations in *Saccharomyces cerevisiae* (Brennan & Schiestl, 1999; IARC, 1999).

Whilst results from a number of in vivo studies were negative, the chemical tested positive for DNA repair in a host-mediated assay in male mice and produced weak gene mutation in the *lacI* transgene in the mouse urinary bladder (Ashby et al., 1994; EU RAR, 2002). DNA breaks were also observed in the bladder and colon of exposed CD-1 mice (IARC, 1999; EU RAR, 2002).

The mechanism of action for the genotoxicity or mutagenicity of the chemical is still not completely understood. However, the role of peroxidation or N-acetyltransferase enzymes and production of radical species (see **Toxicokinetics** section) have been implicated (Ashby et al., 1994; Brennan & Schiestl, 1999; EU RAR, 2002; Stiborova et al., 2002; Stiborova et al., 2005).

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 data support this classification.

Data from long-term carcinogenicity studies indicated that chronic exposure to the chemical in its hydrochloride form, CAS No.134-29-2 (not listed on the Australian Inventory of Chemical Substances) produced malignant and benign tumours, particularly in the urinary bladder of rats and mice.

Chronic oral exposure of Fischer 344 rats and B6C3F1 mice to the chemical and its hydrochloride (free base) for two years resulted in transitional-cell papillomas and carcinomas of the urinary bladder in both species. The doses tested were 5000 or 10000 ppm (average of 333 or 666 mg/kg bw/day) for rats and 2500 or 5000 ppm for mice (average of 214 or 428 mg/kg bw/day). A very rare form of tumour in the rat, leiomyosarcoma, was also observed in the urinary bladder of high dose animals. Kidney and thyroid gland cancer, including transitional cell carcinoma of the renal pelvis, follicular-cell adenoma and carcinoma, papillary cystadenoma, and cystadenocarcinoma, were also identified in rats (NCI, 1978). Cancer-related deaths occurred within 83–88 weeks in animals treated with 5000 or 10000 ppm of the chemical (NCI, 1978; NTP, 2011). Another study has indicated the tumour-promoting activity of the chemical (SCOEL, 2011).

No human case reports or epidemiological studies are available. The International Agency for Research on Cancer (IARC) overall evaluation is that the chemical is ‘possibly carcinogenic to humans’ (Group 2B) (IARC, 1999).

The mechanism of action for carcinogenicity of the animal is not completely understood; although, both genotoxic and non-genotoxic modes of action considered plausible (EU RAR, 2002; SCOEL, 2011). The formation of reactive species that are capable of binding to DNA has been observed (see **Toxicokinetics** section). Results from a two-year carcinogenicity study suggested that the observed increased incidence of follicular-cell tumours in male Fischer 344 rats is a potential consequence of the inhibition of thyroid hormone formation, which is catalysed by the thyroid peroxidase (EU RAR, 2002).

Reproductive and Developmental Toxicity

Limited data are available. Both chronic and subacute studies in rodents did not produce pathologies in the reproductive organs of the animals (NCI, 1978; EU RAR, 2002).

Risk Characterisation

Critical Health Effects

The chemical could be 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 toxicity by all routes of exposure and chronic effects from oral exposure (refer to **Acute toxicity** and **Repeated dose toxicity** sections). The chemical could 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 with the pigments from printed cardboards, papers or foils;
- 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 (packaging, paper) and crayons containing pigments and the textiles containing the dye; and
- applying or removing tattoos.

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. Workers can be exposed to the chemical in the form of a liquid emulsion, solid pellets with dust, or solid pellets without dust. Dermal exposure due to contact with contaminated surfaces is considered the most significant route of exposure, although oral and inhalation exposure might occur.

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. The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation** section).

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. In addition, formulators and importers of tattoo inks should consider substituting products containing the chemical.

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 if swallowed - Specific target organ tox, single exp Cat. 1 (H370)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure if swallowed (Xn; R48/22)	May cause damage to organs through prolonged or repeated exposure through the oral route - Cat. 2 (H373)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)	May cause cancer - Cat. 1B (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.

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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