Benzenesulfonic acid, 5-[(2,4-dinitrophenyl)amino]-2-(phenylamino)-,monosodium salt: Human health tier III assessment

25 November 2016

CAS Number: 6373-74-6.

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 III because the Tier II assessment indicated that it needed further investigation. The report should be read in conjunction with the Tier II assessment.

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

Disclaimer

Acronyms & Abbreviations

Synopsis

Under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework, it was determined that further work is required to assess the extent of use and determine appropriate risk management for some hair dye chemicals with limited hazard data. These chemicals were listed as being used in hair dyes in Australia in 2007 (NICNAS, 2007). The Tier II assessment report for these hair dye chemicals is available at:https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1702
This Tier III assessment focuses on the chemical Acid Orange 3 (CAS No. 6373-74-6), which was identified as being used in hair dyes in Australia following stakeholder consultations in 2015.

Rationale for Tier III Assessment

The chemical is listed on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007). Following consultation with industry representatives in 2015, the chemical Acid Orange 3 has been confirmed to be used in hair dyes in Australia.

The chemical was reported to be used overseas in soaps and semi-permanent hair dyes at concentrations up to 0.2 % (International Agency for Research on Cancer (IARC), 1993), and in commercial dyes for wool, nylon, silk, acetate fibres and leather and for wood staining (Cosmetic Ingredient Review (CIR), Galleria Chemica, HSDB).

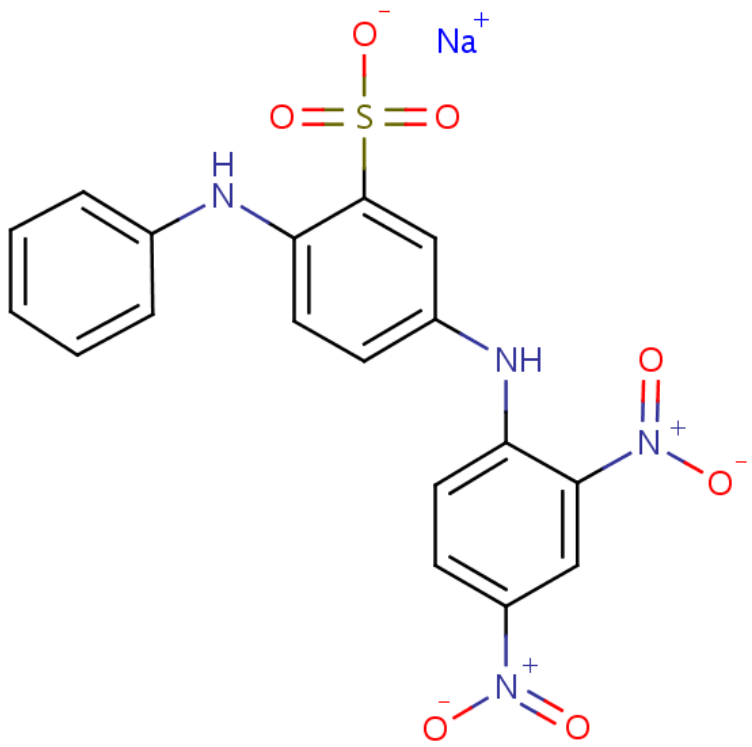
Although there are no restrictions in Australia for using this chemical in hair dyes or cosmetics, the use of the chemical in hair dyes has been prohibited in the European Union (EU) under the EU Cosmetics Regulation 1223/2009 Annex II (List of substances prohibited in cosmetic products). The chemical is also prohibited for cosmetic use in New Zealand (Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain) and under the Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1 (List of substances which must not form part of the composition of cosmetic products) (Galleria Chemica).

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

This Tier III assessment was conducted in order to evaluate all available hazard data to determine if a risk management recommendation for public health is required for prohibition or restriction of use of this chemical in hair dyes in Australia.

Chemical Identity

Synonyms	Acid Orange 3 C.I. 10385

Structural Formula	
Molecular Formula	C18H14N4O7S.Na
Molecular Weight (g/mol)	452.378
Appearance and Odour (where available)	Dark orange-brown solid
SMILES	c1(Nc2cc(S(=O)(=O)O)c(Nc3ccccc3)cc2)c(N(=O)=O)cc(N(=O)=O)cc1

Health Hazard Information

There are no data available on acute oral, dermal and inhalation toxicity and irritation potential of the chemical. Although no toxicokinetic data are available, toxicity studies in animals indicate that the chemical can be absorbed orally. High molecular weight dyes such as this chemical are expected to be poorly absorbed resulting in likely low systemic toxicity. The chemical has a sulfonic acid substituent that can also contribute to the low bioavailability (Government of Canada, 2016).

Data available for the chemical on specific hazard end points such as skin sensitisation, repeat dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity are provided below.

Sensitisation

Skin Sensitisation

Based on the available guinea pig study, the chemical gave positive results for skin sensitisation at 10 % but results were negative at 1 %. Therefore, hazard classification is warranted.

The chemical was tested for inducing contact dermatitis in guinea pigs, using a modified Buehler and Klecak method for open epicutaneous testing (OET). During the induction phase, the chemical at 10 % concentration in propylene glycol (0.1 mL) was applied, three times/week for three consecutive weeks on the shaved left flanks of albino guinea pigs (n = 10). After a 14-day non-treatment period, the animals were challenged topically at three concentrations 2.5 %, 5 % and 10 % (in propylene glycol) on the shaved right flank for 24 hours. Observations were made at 24 and 48 hours post-application. The chemical was observed to elicit positive reactions in 30, 60 and 80 % of animals with 2.5, 5 and 10 % challenge concentrations, respectively. However, negative results were observed in guinea pigs when the induction concentration used was 1 % (in propylene glycol) and challenged with 0.25, 0.50 and 1 % concentrations (in propylene glycol) (Dinardo & Draelos, 2007).

There are no case reports of skin sensitisation to the chemical in humans.

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause severe effects from repeated oral exposure.

The target organ for oral toxicity was observed to be the kidneys, but only at high doses. Nephropathy was observed at 1500 mg/kg bw/day in rats, and at 1000 mg/kg bw/day in mice.

In repeat dose oral studies conducted by the National Toxicology Program (NTP) according to the OECD Test Guideline (TG) 408, groups of Fischer 344 (F344) rats and B6C3F1 mice (n = 10/sex/dose) were administered (gavage) the chemical in corn oil for 13 weeks. Rats were administered doses of 0, 94, 187, 375, 750 or 1500 mg/kg bw/day, and mice received doses of 0, 250, 500, 1000 or 2000 mg/kg bw/day. In rats at the highest dose, observations included mortality in five females from week 1, slightly decreased final mean body weights in both sexes (5–8 % compared with controls), and renal toxicity (nephrosis in both sexes and suppurative inflammation papillary necrosis in females). Five females that survived at the highest dose, developed acidophilic cytoplasmic inclusion bodies or granules in the transitional epithelium of the urinary bladder, and two also had hyperplasia in the same region. Discoloured yellow fur coats were observed in males at ≤750 mg/kg bw/day and in all treated females (NTP, 1988; CIR, 2000; REACH).

In mice, no mortality occurred. Decreased final mean body weights (11–12 % compared with controls) were observed at the highest dose and orange urine at ≥1000 mg/kg bw/day. Renal toxicity at ≥1000 mg/kg bw/day consisted of mild to severe nephropathy (increased basophilia of the tubular epithelium, tubule dilatation and cast formation) (NTP, 1988; CIR, 2000; REACH). No adverse effects were reported in rats at ≤750 mg/kg bw/day and in mice at ≤500 mg/kg bw/day and therefore, the no observed adverse effect levels (NOAELs) for rats and mice were 750 mg/kg bw/day and 500 mg/kg bw/day, respectively.

In short term oral toxicity studies, F344 rats and B6C3F1 mice (n = 5/sex/dose) were administered (gavage) the chemical in corn oil for 14 days (at 0, 94, 187, 375, 750 or 1500 mg/kg bw/day in rats, and at 0, 62, 125, 250, 500 or 1000 mg/kg bw/day in mice). Both species did not show any treatment-related effects at necropsy. In rats, one female died at the highest dose on day 16, and orange urine or extremities were observed in increased incidences from the lowest administered dose. The final mean body weights were not affected by the treatment. In mice, no mortalities occurred. At the two highest doses, decreased body weight gains in males were attributed to decreased water availability due to malfunction of the water system in week one. Orange urine was observed in all treated mice, and all but two mice in the 1000 mg/kg bw/day group were inactive (NTP, 1988; CIR, 2000). The NOAEL for mice was 1000 mg/kg bw/day.

Dermal

Only limited data are available. The chemical at 0.2 % concentration is not expected to cause severe systemic effects from repeated dermal exposure.

In a repeat dose dermal toxicity study, groups of New Zealand White (NZW) rabbits (n = 6/sex/dose) were exposed to a semi-permanent hair dye formulation containing 0.2 % of the chemical for 13 weeks. The formulation was applied (undiluted) at 1 mL/kg (approximately 2 mg/kg chemical) twice a week to abraded sites on the dorsolateral aspect of the thoracic and lumbar regions. No treatment-related effects were observed and no gross abnormalities or microscopic lesions were reported. No discolouration of the urine following treatment was observed (CIR, 2000).

Inhalation

No data are available.

Genotoxicity

Based on limited in vitro genotoxicity data, the chemical may have some genotoxic potential. No in vivo genotoxicity data are available. The Quantitative Structure-Activity Relationship (QSAR) predictions did not give clear results for in vitro and in vivo predictions. However, all predictions were out of the applicability domain.

An in vitro assay indicated positive results for point mutations in *Salmonella typhimurium* strains TA100, TA1535, TA97 and TA98, at concentrations from 10–2000 µg/plate, with or without metabolic activation (CIR, 2000). The chemical was reported to be cytotoxic in an in vitro transformation assay which used A-31-1-13 BALB/c-3T3 cells at concentrations of 0.0278–0.2220 mM and 0.0445–0.1780 mM, without metabolic activation (CIR, 2000).

QSAR modelling using OASIS–TIMES predicted the following:

- negative for Ames and positive for chromosomal aberrations, in vitro;
- positive for micronucleus and liver clastogenicity, in vivo; and
- negative for comet and liver transgenic rodent (TGR), in vivo.

The positive predictions were based on the nitroaniline derivative structure of the chemical. However, the chemical structure was out of the applicability domain in all of these models, indicating uncertainty about the reliability of the results.

Reactive nitrenium ions are formed after the metabolic activation of nitroaniline. The stability of these ions correlates with mutagenic activity (Benigni & Bossa, 2011). Additionally, the position of the substituents on the aromatic ring is indicative of mutagenic potential of a substance (Assmann et al., 1997).

Carcinogenicity

The chemical is a nitroaniline derivative, containing a structural alert for genotoxic carcinogenicity. The available studies do not provide sufficient evidence for the chemical to be considered as carcinogenic.

Following oral administration of the chemical, female rats developed renal neoplasms at 750 mg/kg bw/day, but none were observed in male rats. The survival of male rats was reported to be reduced at this dose level, which reduces the likelihood of observations of neoplasms. Dose-dependent non-neoplastic renal lesions were observed in mice at all doses (up to 250 mg/kg bw/day in females and 500 mg/kg bw/day in males), these were not statistically significant, compared to controls. Significantly increased incidences of pituitary adenomas and mammary tumours were observed in female rats when a hair dye formulation containing the chemical at 0.2 % concentration was applied dermally for 12 months. These were not considered to be biologically relevant. Dermal carcinogenicity studies using hair dye formulations containing the chemical at 0.2 % did not cause neoplasms in mice (CIR, 2000).

Two-year oral carcinogenicity studies were conducted in F344 rats and B6C3F1 mice by the National Toxicology Program (NTP, 1988). Rats (n = 50/sex/dose) were administered the chemical at doses of 0, 375 or 750 mg/kg bw/day, five days/week. At the high dose, a significant reduction in the survival rate was observed in both sexes, which was primarily caused by kidney lesions or renal failure. All males at the high dose died by week 97. No kidney neoplasms were observed in treated males. The high dose group was considered inadequate for assessment for male rats due to the high mortality rate. A statistically significant increased incidence of transitional cell carcinomas, which originated from the transitional epithelium of the renal pelvis, was observed in female rats at the high dose. These carcinomas were uncommon in historical controls. The authors concluded that there was no evidence of carcinogenic activity in male rats at 375 mg/kg bw/day (due to clear reduction in survival and no observed carcinogenicity), and clear evidence of carcinogenicity of the chemical in female rats in this study (NTP, 1988; CIR, 2000; REACH).

In mice (n = 50/sex/dose), the chemical was administered at doses of 0, 125 or 250 mg/kg bw/day for males, and at 0, 250 or 500 mg/kg bw/day for females. A number of dose-dependent non-neoplastic renal lesions were observed at all doses in both sexes.Observed neoplasms included squamous cell urinary bladder carcinoma in one low dose female, squamous cell papillomas of the forestomach in four control females, and hemangiosarcanomas in males (six controls, one low-dose and two

high-dose). There was no significant increase in the incidence of neoplasms. It was concluded that there was no evidence of carcinogenic activity in male and female mice (NTP, 1988; CIR, 2000). The single squamous cell carcinoma in the low dose female was not considered to be related to administration of the chemical (NTP, 1988).

Dermal carcinogenicity data were obtained from reproductive studies in rats. A semi-permanent hair dye formulation containing the chemical at 0.2 % was applied topically (0.5 mL) to the shaved backs of Sprague-Dawley (SD) rats (n = 60/sex), twice a week for 12 months. There were three negative control groups (n = 120). Observed signs of toxicity included an increased incidence of skin lesions at various locations, colouration of the hair and skin at the applied site, and consistently dark straw-coloured urine after 3, 12 and 24 months. Dark brown urine was observed in 3 animals at 12 months and in 9 animals at 18 months. In females, significantly increased incidences of pituitary adenomas (number not stated, compared with two out of three control groups), and significantly increased mammary adenocarcinomas/carcinomas (number not stated,compared with one out of three control groups) were observed in treated groups. None were reported in males. The study authors considered these effects as not biologically significant. Life table (survival) analysis did not indicate significant variations in tumour-bearing indices in treated animals compared with the controls (CIR, 2000).

In a skin painting study, Eppley Swiss Webster mice (n = 50/sex) were exposed to a semi-permanent hair dye formulation containing the chemical at 0.2 % for 23 months. The formulation was applied undiluted (0.05 mL) to the clipped interscapular site of the animal. No treatment-related skin tumours developed. Other observed tumours (primarily liver haemangioma, lung adenoma, and malignant lymphoma) were characteristic of the breed and were not statistically significantly different among treated and control groups. The authors concluded that there was no evidence of carcinogenic activity in this study (Burnett et al., 1980; CIR, 2000).

Based on QSAR predictions, the chemical, as a nitroaniline derivative, contains a structural alert for genotoxic carcinogenicity (OECD QSAR Toolbox ver.3.4). Nitroaniline derivatives are metabolically activated into electrophile species. This usually involves N-hydroxylation and eventual formation of the pro-carcinogenic nitrenium ions. The highly reactive nitrenium ions bind covalently to DNA, provided that they are sufficiently stabilised so as not to undergo further reactions. The stability of the nitrenium ion is correlated with mutagenicity, for example in an Ames test with metabolic activation (Benigni & Bossa, 2011). However, the stability of the nitrenium ion depends on the type of substituents and the isomeric position of the nitro group. The combination of one nitro and one amino group attached to the same benzene ring is a structural alert for mutagenic activity, except for 2-nitroaniline derivatives (OECD QSAR Toolbox). Genotoxicity results for Ames tests showed positive results for the chemical (see **Genotoxicity**), indicating mutagenic potential.

The chemical has the nitro group attached in an *ortho*- position to the amine, which could disrupt the activation of the N-hydroxylamine metabolites. However, another nitro group attached in the *para*- position indicates mutagenic potential (Assmann et al., 1997). Additionally, the chemical has a sulfonic acid substituent and, hence, can cause increased solubility and increased detoxification, reducing the ability to be metabolised to nitrenium ions (Marchisio et al., 1976; Lin & Solodar, 1988; OECD QSAR Toolbox). The potential metabolites released may be sulfonated aromatic amines and available information indicates that sulfonated aromatic amines have minimal genotoxic effects (Government of Canada, 2016).

The International Agency for Research on Cancer (IARC) has classified the chemical as '*not classifiable as to its carcinogenicity to humans (Group 3)*', based on inadequate evidence for carcinogenicity in humans and limited evidence in experimental animals (IARC, 1993).

Reproductive and Developmental Toxicity

Only limited data are available. The chemical at 0.20–0.24 % concentration is not considered to have reproductive and developmental effects in rats and rabbits following oral and dermal exposure to the chemical.

In oral studies, two strains of female rats administered a hair dye composite containing the chemical at 0.24 % in the diet at 1950 ppm or 7800 ppm (CFE-S rats (n = 20/group) on gestation days (GD) 6–15 and SD rats (n = 20) at 8 weeks prior to mating, during gestation, and until day 21 of lactation) showed no reproductive and developmental effects. Female NZW rabbits (n = 12) administered the chemical or composite on GD 6–18 by gavage at 0.24 % concentration, at doses of 19.5 or 97.5 mg/kg bw/day, showed no reproductive, developmental or teratogenic effects (CIR, 2000).

Dermal effects from the chemical were reported in a multigeneration reproductive study in SD rats. A 0.5 mL of a semi-permanent hair dyeformulation containing the chemical at 0.2 % was applied topically twice a week (duration not stated) to the shaved backs of the parental generation (F0) (n = 40/sex). Twenty rats per group were chosen to produce the next generation, and this procedure was repeated up to the third (F3) generation. Observed dermal effects included mild scabbing, fissuring,

atonia and leathery texture intermittently throughout the duration of treatment. Sialoadenitis (salivary gland inflammation) was observed at week 61 in some animals (in both treated and control groups) and regressed two weeks later. This was followed by an increased incidence of respiratory congestion in both treated and control groups which persisted in the F2 parental generation during the reproductive stages. A significant reduction in fertility indices was observed in F2 parents, but the difference was not prominent between the treated and control groups. It was not stated by the authors that respiratory congestion played a significant role in decreased fertility. A subsequent study showed that decreased fertility was due to reproductive tract changes in the treated and control rats. Reproductive and developmental parameters including gestation, survival and live birth indices were not affected (CIR, 2000).

In a teratology dermal study, no embryotoxic or teratogenic effects were observed in gravid CD rats exposed to a semi-permanent hair dye formulation containing 0.2 % of the chemical. The formulation was applied at 2 mL/kg to shaved skin on GD 1, 4, 7, 10, 13, 16, and 19. The skin and hair at the application site were reported to show a change in colour. No other adverse effects were reported (CIR, 2000).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include skin sensitisation. Although the chemical at a 10 % concentration was sensitising, concentrations up to 1 % gave negative results for sensitisation in guinea pigs.

The chemical may have some genotoxic potential as it contains a stuctural alert for genotoxic carcinogenicity. The oral carcinogenicity studies showed clear evidence of carcinogenicity in female rats, but not in male rats (reported reduced survival rates in males) and mice. A dermal carcinogenicity study in rats also produced tumours in female rats at 0.2 % concentration (no information on tumour numbers in treated female rats, although CIR (2000) stated these effects as not biologically relevant).

Only limited data are available on some other health end points such as reproductive and developmental toxicity and repeated dose dermal toxicity, showing no adverse effects at 0.2 % concentration.

Public Risk Characterisation

The chemical is used in hair dyes in Australia, but use concentrations in hair dyes are not available. Based on the reported overseas chemical uses, it is possible that the chemical is used in soaps, commercial dyes (for wool, nylon, silk, acetate fibres and leather) and for wood staining. Considering these uses, the main route of public exposure is expected to be through the skin.

Based on the available toxicity data, the CIR (2000) reported the chemical at 0.2 % concentration in hair dyes as safe to use. However, the use of the chemical in hair dyes is prohibited in the EU under the Cosmetics Regulation 1223/2009 Annex II.

Currently there are no restrictions in Australia on using this chemical in hair dyes. In the absence of regulatory controls, the anticipated critical health effects (skin sensitisation and genotoxic carcinogenicity based on structural alerts) have the potential to pose an unreasonable risk under the identified uses. However, the available toxicity studies indicate no adverse systemic effects following dermal exposure to 0.2 % concentration. Therefore, the chemical is not considered to pose an unreasonable risk to public health at 0.2 % in hair dyes.

Occupational Risk Characterisation

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

Given the local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person

conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support classification of the chemical as a hazardous substance (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

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 and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from dermalexposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- 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;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

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

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

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

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

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