Benzenamine, N,N-dimethyl-: Human health tier II assessment

21 April 2016

CAS Number: 121-69-7

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.

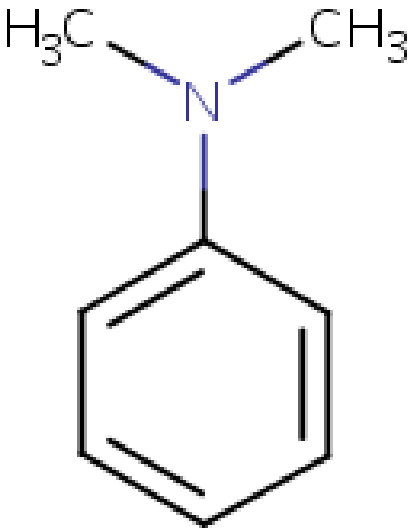
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	N,N-dimethylaniline (dimethylamino)benzene N,N-dimethylphenylamine
Structural Formula	
Molecular Formula	C8H11N
Molecular Weight (g/mol)	121.18
Appearance and Odour (where available)	Yellow to brown oily liquid with an amine-like odour
SMILES	c1(N(C)C)ccccc1

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: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments including from the International Agency for Research on Cancer (IARC) and National Toxicology Program (NTP).

The chemical has reported domestic uses in the SPIN database including in:

- binding agents;
- corrosion inhibitors;

- fillers (including insulating materials); and
- paints, lacquers and varnishes.

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

The chemical has reported commercial uses including:

- in catalysts and accelerators;
- in construction materials; and
- in lubricants.

The chemical has reported site-limited uses, including:

- as an intermediate in the manufacture of various chemicals, including dyes and vanillin;
- in stabilisers;
- in the plastics industry;
- in process regulators;
- in textile treatment products; and
- in rubber vulcanising agents.

Restrictions

Australian

No known restrictions have been identified for the chemical, specifically. However, there is a general group entry in Schedule 5 of the Poisons Standard —the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for: 'AMINES for use as curing agents for epoxy resins except when separately specified in these Schedules.' This general entry may cover the use of the chemical as a curing agent for epoxy resins.

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.' Schedule 5 chemicals are labelled with 'Caution' (SUSMP, 2016).

International

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

- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1—List of substances which must not form part of the composition of cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

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):

- T; R23/24/25 (acute toxicity)
- R40 Carc. Cat 3 (carcinogenicity)

Exposure Standards

Australian

The chemical has exposure standards of 25 mg/m^3 (5 ppm) time weighted average (TWA) and 50 mg/m^3 (10 ppm) short-term exposure limit (STEL) (Safe Work Australia).

In the HSIS, the notice 'Sk' applies to the chemical: 'Absorption through the skin may be a significant source of exposure' (Safe Work Australia).

International

The following exposure standards are reported for the chemical (Galleria Chemica):

- TWA of 25 mg/m^3 (5 ppm) and STEL of 50 mg/m^3 (10 ppm) in different countries including the United States of America (USA), Canada, Malaysia, Indonesia, Japan and many countries in the EU such as France, Spain, Germany and the United Kingdom; and
- TWA of 5 mg/m^3 (1 ppm) and STEL of 10 mg/m^3 (2 ppm) in different countries including China, Estonia and Sweden.

Health Hazard Information

The chemical is reported to cause methaemoglobinaemia, although it is considered to be quantitatively less toxic than aniline (IARC, 1993; MAK, 2012; HSDB). The major target organs for toxicity of the chemical are reported to be the haematopoietic system and the spleen, similar to other anilines (NTP, 1989).

Toxicokinetics

The chemical is absorbed via the oral, dermal and inhalation routes. It is reported to be highly bioavailable following skin absorption (see **Repeat Dose Toxicity: Dermal** section) (MAK, 2012; REACH).

Two main metabolic pathways of the chemical have been determined by using in vitro liver microsomes studies in rats, rabbits, hamsters, guinea pigs and humans. In microsomes from animals, the chemical is converted mostly by demethylation to aniline (CAS No. 62-53-3), which is then oxidised into 4-aminophenol and phenylhydroxylamine. In microsomes from humans, it is predominantly metabolised into N,N-dimethylaniline-N-oxide (two to four times more than aniline) by a flavin monooxygenase (MAK, 2012).

In multiple toxicokinetic studies, dogs and cats were intravenously (i.v.) injected with the chemical at doses of 40–92 mg/kg bw and 24–25 mg/kg bw, respectively. Chemical metabolites were detected almost immediately in the blood (after two to ten minutes) and highest peak levels were measured within 30 minutes to two hours. The metabolites were detected in the urine within 48 hours. The major metabolites 4-methylaminophenol and 2-aminophenol were found in the blood and urine, whereas aniline was found in the blood but not in the urine (MAK, 2012; REACH).

Methaemoglobin formation was identified as part of the metabolism of the chemical (see also **Repeat Dose Toxicity** sections). In dogs, methaemoglobin formation was investigated after a single oral dose of the chemical at 50 mg/kg bw. Methaemoglobin represented 20 % of the total blood haemoglobin four hours after administration, reaching a peak of 40 %, eight hours after administration (MAK, 2012). In female Wistar rats administered the chemical by gavage, the haemoglobin binding index (HBI) indicated that conversion to phenylhydroxylamine giving rise to haemoglobin binding was half of that for aniline (MAK, 2012).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in the HSIS (Safe Work Australia). Although the available animal data do not support this classification, a lowest lethal concentration (LCLo) of 50 mg/kg bw has been reported in humans (see **Observation in humans** section). Humans have been reported to be more sensitive than rats to formation of methaemoglobin following exposure to aniline. Following oral administration (and possibly inhalation exposure), the dose that produced increased levels of methaemoglobin was stated to be much lower for humans than for rats (US EPA, 1994; NICNAS). Therefore, the existing hazard classification is appropriate.

The following median lethal dose (LD50) values are reported for the chemical (Krasavage, 1979; NTP, 1989; IARC, 1993; MAK, 2012; ChemID Plus; HSDB; REACH; RTECS):

- 951, 1120, 1300 and 1410 mg/kg bw in male rats;
- between 700 and 1410 mg /kg bw in female Fischer 344/N (F344/N) rats;
- 1336 mg/kg bw in male F344/N rats;

- 1350 mg/kg bw in male Carworth-Wistar rats; and
- 1376 and 1480 mg/kg bw in male and female B6C3F1 mice, respectively.

Observed sublethal effects included somnolence (depressed activity), cyanosis (skin discolouration due to poor blood oxygenation) and nasal discharge (NTP, 1989; ChemID Plus; RTECS).

Dermal

The chemical is classified as hazardous with the risk phrase 'Toxic in contact with skin' (T; R24) in the HSIS (Safe Work Australia). The available animal data do not support this classification. However, considering that humans are more sensitive than animals to formation of methaemoglobin following exposure to aniline and absorption of the chemical through skin could be a significant source of exposure (HSIS, SWA), the existing hazard classification is appropriate.

The following dermal LD50 values are reported for the chemical (IARC, 1993; MAK, 2012; HSDB; REACH; RTECS):

- 1690 mg/kg bw in male New Zealand White rabbits; and
- 1770 mg/kg bw in rabbits (no further details).

Inhalation

The chemical is classified as hazardous with the risk phrase 'Toxic by inhalation' (T; R23) in the HSIS (Safe Work Australia). While the available rat data do not support this classification, humans have been reported to be more sensitive than rats to formation of methaemoglobin following exposure to aniline. Following oral (and possibly inhalation) exposure, the dose that produced increased levels of methaemoglobin was stated to be much lower for humans than for rats (US EPA, 1994; NICNAS). Cases of inhalation toxicity have been reported in humans (see **Observation in humans** section). Therefore, the existing hazard classification is appropriate.

A median lethal concentration (LC50) of >5.1 mg/L in rats is reported for the chemical (Galleria Chemica; HSDB; RTECS).

The following lowest lethal concentration (LCLo) values are reported for the chemical (REACH; RTECS):

- 250 mg/m^3/four hours in rats; and
- 980 mg/m^3/30 minutes in rats and guinea pigs.

Observation in humans

An oral lowest lethal concentration (LCLo) of 50 mg/kg bw is reported for humans (ACGIH, 2001; HSDB; RTECS). The chemical is also reported to present a risk of aspiration into the lungs after oral exposure, leading to pneumonia. Symptoms of toxicity after short-term exposure to the chemical (route not stated) include anoxia (total depletion in the level of oxygen reaching the tissues), cyanosis, weakness, dizziness and ataxia (HSDB).

A worker exposed to hot vapours of the chemical (and phenol) for a few minutes collapsed and was unconscious for eight hours. He then presented with 'visual disturbances, noise in the ears, and intense abdominal pain'. Another worker was 'less severely poisoned' following seven hours of exposure to the chemical when moving it between containers (HSDB).

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is not irritating to the skin.

The chemical was tested using the Draize method, in three female New Zealand White rabbits (OECD Test Guideline (TG) 404). The chemical (or distilled water as control) was applied (0.5 mL) under occlusive patches to the dorsal skin of animals for four hours and skin reactions were recorded over 72 hours. Two rabbits showed very slight erythema (mean individual scores of 0.33) and recovered at the 48 hours observation. None of the animals showed oedema (mean score of 0). No mortalities or systemic toxicity effects were observed in this study (REACH).

In an open irritation test, rabbits were administered 10 mg of the chemical for 24 hours and in a standard Draize test, rabbits were administered 500 mg of the chemical for 24 hours. Only 'mild' irritation was reported (REACH; RTECS). No further details were available.

Eye Irritation

Based on the results of the study below, the chemical is considered to be slightly irritating to the eyes.

The chemical was tested using the Draize method in three female New Zealand White rabbits (OECD TG 405). The chemical (0.1 mL) was instilled into the right eye of each rabbit (left eye used as control) for 24 hours before the eyes were rinsed with normal saline. Mean conjunctivae scores from 24, 48 and 72 hour observations were 1, 2 and 1.67 in each of the three rabbits, respectively. The eyes were normal after seven days. Mean chemosis scores from 24, 48 and 72 hour observations were 0.33 in each of the three rabbits and zero after seven days. No corneal opacity or iris lesions were observed. However, examination of corneal epithelium cell damage using sodium fluorescein strips at the 24 hours observation showed that all three animals had corneal damage (individual rates: 30, 30 and 35 % damage, in each of the three rabbits respectively) (REACH).

In two separate standard Draize tests, rabbits were administered 20 mg of the chemical into the eye for up to 24 hours. Moderate eye irritation was reported (REACH; RTECS). No irritation scores or further details were available.

Observation in humans

Only limited information is available. In human subjects (n = 5 males), application of 0.1 g petrolatum containing 0.6 % of the chemical, for 24 hours, was not irritating to the skin with observation up to 72 hours (HSDB; REACH).

Sensitisation

Skin Sensitisation

No human or animal data are available. The chemical has no structural alerts for skin sensitisation (QSAR Toolbox 3.3).

A quantitative structure-activity relationship (QSAR) prediction based on a local lymph node assay (LLNA) gave 24 % concentration of the chemical as that required to produce a three-fold increase in lymphocyte proliferation (EC3). Based on this prediction, the chemical could be a weak skin sensitiser in mice (REACH).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is considered to cause harmful effects in the spleen and blood following repeated oral exposure, warranting hazard classification (refer to **Recommendation** section).

In a subacute gavage study, groups of F344/N rats (n = 5/sex/dose) were administered the chemical at 0, 94, 188, 375, 750 or 1500 mg/kg bw/day, for 14 days. The highest dose used approximates the LD50 values determined in rats. All rats that received 1500 mg/kg bw/day and 9/10 rats that received 750 mg/kg bw/day died before the end of the study. At the two highest doses, signs of toxicity included cyanosis, lethargy, fine body tremors, diarrhoea and red ocular or nasal discharge. Splenomegaly (abnormal enlargement of the spleen) was observed in rats exposed to the chemical at all doses at study termination. Extramedullary haematopoiesis and increased haemosiderin were observed in the spleen of three males and three females at 375 mg/kg bw/day. Final mean body weights of male rats treated with 750 or 1500 mg/kg bw/day were 15 and 47 % lower than those of controls, respectively (NTP, 1989). Based on the data, the lowest observed adverse effect level (LOAEL) in this study was determined to be 94 mg/kg bw/day.

In a subchronic gavage study, groups of F344/N rats (n = 10/sex/dose) were administered the chemical at 0, 31, 62, 125, 250 or 500 mg/kg bw/day, five days per week for 13 weeks. Final mean body weights of male rats treated at 250 or 500 mg/kg bw/day were 15 and 27 % lower than those of controls, respectively. Symptoms of toxicity included cyanosis, lethargy and hypersalivation in all treated groups. Extramedullary haematopoiesis (non-bone marrow red blood cell production) and haemosiderosis (increased iron storage complex) in the spleen were observed in both sexes at all doses at very high incidences (20/20 in the lowest dose group compared with 0/20 in the control groups). The increased number of haematopoietic cells led to spleen enlargement in some rats (number not specified). Other histopathological changes included kidney pigmentation (starting at 31 mg/kg bw/day in females (6/10) and present in the control females (1/10)), liver pigmentation and bone marrow hyperplasia (starting at 62 mg/kg bw/day in both sexes). Minimal pigmentation in the testes was recorded in all treated males at 250 and 500 mg/kg bw/day. For most of the lesions observed, the severity increased with the dose. Based on the results, a no-observed adverse effect level (NOAEL) could not be determined in this study (NTP, 1989) and the LOAEL was determined to be 31 mg/kg bw/day.

Dermal

Only limited information is available on the chemical. However, as the chemical is reported to be readily absorbed through the skin, the toxic effects following repeated dermal exposure are expected to be similar to those observed following repeated oral exposure. Therefore, hazard classification is recommended.

In a ten-day study, rats (n = 8) were exposed to the chemical (dose not stated) on the tail. Treatment was lethal for most animals and signs of toxicity included body weight loss, marked methaemoglobinaemia, erythropenia (deficiency in the number of erythrocytes) and reticulocytosis (increased number of reticulocytes) (MAK, 2012).

In another study, five guinea pigs were exposed to repeated dermal applications of the chemical (dose not stated) for ten days. Treatment caused a slight to moderate erythema initially, dry skin and scattered eschars at one week, and heavy eschars for three animals at the end of the study (Krasavage, 1979). Systemic toxicity effects were not reported.

Inhalation

Based on the limited available data, the chemical may cause toxic effects in the blood after repeated inhalation exposure, similar to those observed following repeated oral exposure. However, the data are insufficient to warrant classification.

In an inhalation study, male rats (n = 15) were exposed to the chemical at concentrations of 0.21 or 2.03 mL/m^3 five hours per day, six days per week for four months. At the high dose, there was a significant increase in methaemoglobin (to 12 %); a significant decrease in total haemoglobin level (by 8.8 %); significantly decreased erythrocyte numbers; decreased blood catalase activity (by approximately half); increased blood peroxidase activity (by approximately 33 %); also, during the first month only, the coproporphyrin level in urine increased slightly. The same effects were observed at the low dose but the animals were less affected. Biochemical analyses also suggested liver function disorders, dysproteinaemia (abnormality in protein content of the blood) and hyperplasia of the lymphatic tissue in the spleen at the high dose only (MAK, 2012).

In another inhalation study, albino rats (numbers not available) were exposed to the chemical at concentrations of 0.0011 or 0.059 mL/m^3, 24 hours per day for 100 days. No adverse effects were reported at the low dose. At the high dose, increased methaemoglobin, reduced erythrocyte number and haemoglobin level, reticulocytosis, leukopenia (decreased number of white blood cells), chromatolysis (dissolution of the Nissl bodies in the cell body of a neuron) in brain cells, hypoproteinaemia, accumulation of pyruvic acid in the liver, increased excretion of coproporpyrin in urine and reduced level of ascorbic acid in the adrenals were reported (MAK, 2012; REACH).

Observation in humans

Workers exposed to the chemical (route of exposure not stated) on a long-term basis exhibited significant increases in methaemoglobin levels (up to 5.2 %) compared to a control group of 18 people (2 % in only one person) (MAK, 2012).

Genotoxicity

Based on the available data, the chemical is not mutagenic in bacterial systems but may cause clastogenic effects in mammalian cells, in vitro. An vivo study in rats and mice showed increased DNA elution rates with intraperitoneal (i.p.) administration of the chemical, but not with oral gavage dosing. The available data are not sufficient to warrant hazard classification.

The following in vitro genotoxicity results are available for the chemical:

- negative in a bacterial gene mutation test (preincubation method) in *Salmonella typhimurium* strains TA98, TA100 and TA1537 at doses up to 1000 µg/plate, with or without metabolic activation (NTP, 1989; REACH);
- negative in a bacterial gene mutation test (preincubation method) in *S. typhimurium* strains TA98, TA100, TA102, TA104, TA1535, TA1537 and *Escherichia coli* at doses up to 625 µg/plate, with or without metabolic activation (CCRIS);
- positive in a mouse lymphoma cell assay in L5178Y cells with doses of 200–800 nL/mL without metabolic activation and 10–80 nL/mL with metabolic activation (CCRIS; NTP, 1989);
- statistically significant increases in micronuclei in a micronucleus test in Chinese hamster lung (CHL) cells, with doses of 0.9 and 1.2 mM (DECOS, 2002);
- positive in a sister chromatid exchange (SCE) assay on Chinese hamster ovary (CHO) cells only with metabolic activation (NTP, 1989);
- positive in a chromosomal aberration test on CHO cells at doses up to 830 µg/mL with or without metabolic activation (NTP, 1989; REACH);
- induced structural changes in a chromosomal aberration test on CHL cells at doses from 0.02 to 0.06 µg/mL with metabolic activation and at doses from 0.2 to 0.8 µg/mL without metabolic activation (CCRIS);
- negative in an unscheduled DNA synthesis (UDS) assay in rat primary hepatocytes at doses up to 1000 µM (IARC, 1993; REACH).

One in vivo genotoxicity study was available for the chemical—an in vivo alkaline DNA elution test, performed in Sprague Dawley (SD) rats and BALB/c mice. Rats were administered a single dose of the chemical at 970 mg/kg bw by oral gavage or 485 or 970 mg/kg bw by i.p. injection. Mice were administered a single dose of the chemical at 242 or 485 mg/kg bw by i.p. injection. The chemical caused small but statistically significant increases in the DNA elution rate in both species, by the i.p. route only (DECOS, 2002).

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of a carcinogenic effect’ (Xn; R40) in the HSIS (Safe Work Australia). The available data (increased incidence of sarcomas in male F344/N rats) support this classification.

In a carcinogenicity study, groups of F344/N rats (n = 50/sex/dose) were administered the chemical by oral gavage at 0, 3 or 30 mg/kg bw/day, five days per week for two years. Survival was not affected by the treatment. Spleen sarcomas in 3/50 male rats and one osteosarcoma in a male rat were observed at 30 mg/kg bw/day. Although not statistically significant compared to control males (0/50), the sarcomas in this study exceeded the greatest incidence in historical control males (1/45). One sarcoma was also observed in the spleen of a control female rat.

Non-neoplastic lesions of the spleen included haematopoiesis and haemosiderosis in males and females, and fibrosis and fatty metamorphosis in males at all treated groups. The incidences of haematopoiesis and haemosiderosis were not statistically significantly different compared to controls but the severity of the lesions was significantly higher in the high dose groups. In males of the high dose group, the incidences of splenic fibrosis (22/50) and fatty metamorphosis (10/50) were significantly higher than those in controls (5/49 and 0/49, respectively).

At the highest dose, the incidence of mononuclear cell leukaemia in males (4/50) and females (0/50) was significantly lower than those in controls (13/50 and 11/50 in males and females, respectively). This decrease 'may be a direct effect of the chemical on the mechanism responsible for the induction of leukaemia in the aging rat' (NTP, 1989). Non-statistically significant effects included forestomach papillomas in 2/50 males at the highest dose and neurilemmomas (benign encapsulated tumours of the nerve sheath) (7/50, 7/50, 2/50) in low and high dose males, and control male rats, respectively (NTP, 1989).

In another carcinogenicity study, B6C3F1 mice (n = 50/sex/dose) were administered the chemical at 0, 15 or 30 mg/kg bw/day, five days per week for two years. Although there were no clinical signs observed related to the treatment, the incidence of squamous cell papillomas was significantly higher in the high dose females (8/50) compared with the control group (2/50). In the pituitary gland, the incidence of adenomas and/or carcinomas was significantly lower in the high dose female group (8/44) than in the control group (18/45). However this result was not considered to be treatment-related because of the variable incidence of those neoplasms in historical controls. The NTP concluded there was 'equivocal evidence of carcinogenic activity for female B6C3F1 mice' based on the incidence of forestomach lesions (squamous cell papillomas) (NTP, 1989).

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 for carcinogenicity in animal testing (IARC, 1993).

The mechanism of carcinogenicity of the chemical in animals is not clear. A non-genotoxic mechanism of carcinogenicity was suggested for aniline (Bomhard and Herbold, 2005), stating that the damage to the blood caused by chronic exposure could lead to a massive overload of the spleen with iron, leading eventually to oxidative stress (Bomhard and Herbold, 2005; NICNAS). Given the metabolism of the chemical, that includes release of aniline and methaemoglobin formation, a similar mechanism could be relevant in terms of carcinogenicity.

Reproductive and Developmental Toxicity

No data are available on the reproductive toxicity of the chemical. Based on the limited information available, the chemical does not show specific developmental toxicity.

In a prenatal development toxicity study, pregnant CD1 mice (n = 50) were administered the chemical by oral gavage at 365 mg/kg bw/day on gestation days (GD) 7 to 14. Three animals died before the end of the treatment. Clinical signs of toxicity included exhaustion and lethargy and were seen in two animals. Dam weights were not affected by the treatment. The time of birth, number of pups, birth weight and pup viability were also not affected by the treatment (MAK, 2012; REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute effects from oral, dermal and inhalation exposure; and
- systemic long-term effects (carcinogenicity and harmful effects from repeated oral exposure).

Public Risk Characterisation

Given the uses identified for the chemical (commercial and site-limited), it is unlikely that the public will be exposed. Although the public could come into contact with articles/coated surfaces derived from the chemical (such as textiles and fabrics), it is expected that the chemical will be bound within the article/coated surface and hence will not be bioavailable. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, oral, dermal and inhalation 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 critical health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, 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 the appropriate controls.

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

NICNAS Recommendation

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

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 (HCIS)[b]
Acute Toxicity	Toxic if swallowed (T; R25)* Toxic in contact with skin (T; R24)* Toxic by inhalation (T; R23)*	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Toxic if inhaled - Cat. 3 (H331)
Repeat Dose Toxicity	Harmful: danger of serious damage to health by prolonged exposure in contact with skin (Xn; R48/21) 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 dermal route - Cat. 2 (H373) May cause damage to organs through prolonged or repeated exposure through the oral route - Cat. 2 (H373)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

[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 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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and

- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

References

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Last update 21 April 2016