Benzenamine, N,N,4-trimethyl-: Human health tier II assessment

27 October 2017

CAS Number: 99-97-8

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.

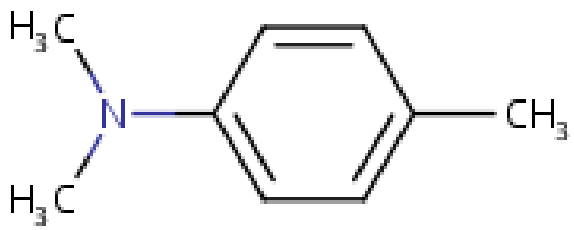
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	N,N-dimethyl-p-toluidine dimethyl-4-toluidine N,N-dimethyl-p-tolylamine p,N,N-trimethylaniline dimethyltolylamine
Structural Formula	
Molecular Formula	C9H13N
Molecular Weight (g/mol)	135.209
Appearance and Odour (where available)	Light yellow liquid
SMILES	c1(N(C)C)ccc(C)cc1

Import, Manufacture and Use

Australian

Based on available safety data sheets (SDSs) in Australia, the chemical may have cosmetic and domestic uses in acrylic nail preparations (at concentrations <1 %) and plastic and toy glue (at concentrations <1 %), respectively.

The chemical has reported use as an industrial adhesive.

International

The following international uses were identified through Galleria Chemica, European Union Registration, Evaluation, Authorisation and Restriction of Chemicals dossier (REACH), Substances and Preparations in the Nordic countries (SPIN) database, United States (US) Department of Health National Toxicology Program (NTP), US Environmental Protection Agency Chemical and Product Categories (CPCat) and Hazardous Substances Data Bank (HSDB).

The chemical may have cosmetic use as a component of artificial nail preparations (CosIng) and is listed in the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011), indicating its use in 5 cosmetic products.

The chemical may have domestic uses as a component in

- cleaning and washing agents; and
- paints, lacquers and varnishes.

The chemical is not listed in the US household product data base (HPD).

The chemical has reported commercial uses including:

- in leather tanning;
- as a component of industrial glues; and
- as a component of photo chemicals.

The chemical has reported site-limited uses:

- as a component of textile dyes;
- as a component of industrial glues;
- in the manufacture of rubber and plastic products; and
- as a solvent.

The chemical has reported non-industrial use as a polymerisation accelerator for the manufacture of bone cements and dental materials and as an intermediate in pesticide synthesis.

Restrictions

Australian

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

'AMINES for use as curing agents for epoxy resins except when separately specified in these Schedules' (SUSMP, 2017).

Schedule 5 chemicals are described as 'Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label (SUSMP, 2017). Schedule 5 chemicals are labelled with 'Caution'.

International

The chemical is listed on the Hennes & Mauritz (H&M) Chemical Restrictions Cosmetic Products as a banned product. The substance must not be used in the production of or added to any cosmetic products sold by H&M (Galleria; H&M, 2016).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity – category 3; H331 (Toxic if inhaled)
- Acute toxicity – category 3; H311 (Toxic in contact with skin)
- Acute toxicity – category 3; H301 (Toxic if swallowed)
- Specific target organ toxicity (repeated exposure) – category 2; H373 (May cause damage to organs through prolonged or repeated exposure)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards were identified through Galleria Chemica:

- Time weighted average (TWA) is 5 mg/m^3 in Czech Republic and 0.5 ppm (2.5 mg/m^3) in USA.
- Short-term exposure limit (STEL) range is 10 mg/m^3 in Czech Republic.

Health Hazard Information

Toxicokinetics

In a toxicokinetic study conducted for the US National Toxicology Program (NTP), toxicokinetics and metabolism of ^{14}C-labelled N,N-dimethyl-p-toluidine (^{14}C-DMT) was assessed in male Fischer 344 (F344) rats (4/dose) and male B6C3F1 mice (4/dose) following oral exposure (gavage) at single doses of 2.5, 25, or 250 mg/kg bw (in 10 % aqueous PEG 30 castor oil) or 2.5 mg/kg bw by intravenous (i.v.) injection. Female rats and mice (4/dose) received an oral dose of 25 mg/kg bw.

In rats receiving 2.5 and 25 mg/kg bw of ^{14}C-DMT, the chemical was rapidly eliminated via excretion in urine (approximately 90 % of the total radioactivity dose recovered) and in faeces (4 %) within 24 h of dosing. Approximately 4 % of the total dose remained in tissues and the gastrointestinal tract at the 24-hour terminal time point. In the 250 mg/kg bw group, 70 % of the total dose was recovered in urine, 2 % in faeces and 18 % remained in tissues and the gastrointestinal tract at the 24 h timepoint, with approximately 2 % of ^{14}C-DMT remaining in tissues at 72 h after dosing.

In male mice, the cumulative disposition of the chemical in 2.5 and 25 mg/kg bw groups was similar to that in rats at the same doses. Compared to males, female mice excreted slightly less (approximately 77 % of the total dose) in urine while amounts excreted in faeces and remaining in tissues and the gastrointestinal tract were similar. Data for mice receiving 250 mg/kg bw oral dose was not reported due to acute toxicity.

Absorption of the lower doses was estimated to be at or near 100 % based on comparison of oral and i.v. data. The main metabolite in male rat urine was p-(N-acetyl-hydroxyamino) hippuric acid. Other metabolites identified were N,N-dimethyl-p-toluidine N-oxide and N-methyl-p-toluidine. Metabolites in mouse urine were not reported (NTP, 2012).

Acute Toxicity

Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 3’ and hazard statement H301 (Toxic if swallowed) in the HCIS (Safe Work Australia). The reported median lethal doses (LD50) of 980–1650 mg/kg bw in rats and 139 mg/kg bw in mice support this classification.

Clinical signs of toxicity in rats included somnolence, respiratory depression, excessive blinking, piloerection and hunched posture (REACH; NTP, 2012; RTEC, 2012). Cyanosis due to methaemoglobin formation is the main cause of toxicity observed in humans (see ***Observations in humans*** section).

In a study performed in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, Sprague Dawley (SD) rats (5/sex/dose) were orally treated (gavage) with single doses of 1250, 1800, or 2500 mg/kg bw of the chemical. Mortality occured in all rats receiving 2500 mg/kg bw, males receiving 1800 mg/kg bw and one male and one female from the 1250 mg/kg bw dose groups within 2-3 days of treatment. The main clinical signs were reduced activity, hunched posture and salivation. The reported LD50 was 1650 mg/kg bw (REACH; US EPA, 2009a; US EPA 2009b).

Additionally, the following oral LD50 values have been reported for the chemical (no further study details available):

- 139 mg/kg bw in mice; and
- 980 mg/kg bw in rats (REACH; RTEC, 2012).

Dermal

The chemical is classified as hazardous with the hazard category ‘Acute Toxicity Category 3’ and hazard statement “Toxic in contact with skin’ (H312) in the HCIS (Safe Work Australia).

The available experimental data (LD50 was >2000 mg/kg bw) do not support this classification. However, considering that humans may be more sensitive than animals to chemical causation of methaemoglobinaemia than rabbits (NRC, 2000) and absorption of the chemical through skin could be a source of exposure (HSBD), the existing hazard classification is appropriate.

In a study performed in accordance with OECD (TG) 402, New Zealand White (NZW) rabbits (5/sex/dose) were exposed to the chemical by the dermal route at 2000 mg/kg bw. The reported LD50 was >2000 mg/kg bw. No other data are available (REACH, EPA, 2009).

Inhalation

The chemical is classified as hazardous with the hazard category 'Acute Toxicity Category 3' and hazard statement "Toxic if inhaled (H331) in the HCIS (Safe Work Australia). The available data support this classification. The reported median lethal concentrations were (LC50) of 1.4–1.92 mg/L/4h (253 ppm) in rats (NTP, 1999; REACH, RTEC).

In an acute toxicity study, SD rats (5/sex/dose) were exposed to 0.30, 0.99, 1.73, or 5.27 mg/L of DMT in air for 4 h. Clinical signs in rats exposed to 1.73 mg/L included hypoactivity, a comatose/prostrate condition, dyspnoea or rapid respiration, and salivation. Nasal discharge and red material around the nose were observed in the 0.30 and 0.99 mg/L groups. Mottled lungs, red ovaries, and gas-filled gastrointestinal organs were observed in the rats exposed to 1.73 or 5.27 mg/L. The reported LC50 was 1.4 mg/L/4h (NTP, 1999).

In an acute toxicity study, SD rats (5/sex/dose) were exposed to 0.11, 1.85, 1.92, 1.97 or 2.32 mg/L of DMT in air for 1, 3, 5, 8 and 15 days, 4h/day. Clinical signs in rats exposed to 2.32 mg/L included ataxia and tremor (time not specified). The reported LC50 was 1.92 m/L/4h (REACH).

Observation in humans

Cases of children ingesting acrylic nail solution containing the chemical DMT have been reported (Potter et al., 1988; Kao et al., 1997).

A 16 month old girl ingested about 15 mL of an artificial nail solution containing four parts acetone and one part of a mixture containing 98 % ethyl methacrylate monomer and 2 % DMT (approximately 6 mg DMT/kg bw). Vomiting was induced; however, 2.5 h later the mother noted blueness of lips and nail beds. At hospital the girl was diagnosed with acute cyanotic episode due to methaemoglobinaemia. The girl fully recovered from the episode. In vitro studies suggested that the activity of the chemical was probably due to its biochemical transformation to the toxic metabolite p-methylphenylhydroxylamine (Potter et al., 1998).

A 5 month old boy was accidentally fed approximately 30 mL of artificial nail solution containing unspecified concentrations of acrylic ester monomers and DMT. The child was noted to have breathing difficulties and excessive drooling. The boy was diagnosed with methaemoglobinaemia with a methaemoglobin value of 11 % (normal value is <2 %). After two days in hospital the boy had recovered (Kao et al., 1997).

Corrosion / Irritation

Skin Irritation

The chemical is reported to be mildly irritating to skin. The effects are not sufficient to warrant hazard classification.

In a study performed in accordance with OECD (TG) 404, White Vienna rabbits (3 female) were treated with 0.5 mL of the chemical applied to a 6 cm x 6 cm piece of gauze, which was held in contact with clipped rabbit skin (dorsal lumbar region) under semi-occlusive conditions for 4 h. After 24 h, the skin displayed mild erythema (average score, 1.33 of 4) and oedema (average score, 0.33 of 4). After 72 h the skin was free of irritation (REACH).

In another study, NZW rabbits (6, sex not reported) received 0.5 mL of undiluted chemical applied to shaved skin. Rabbits were scored for irritation according to Draize at 30 to 60 minutes, 24, 48, and 72 h, and 4-14 days following administration of the chemical. Very slight to well-defined erythema (grade 1; maximum score 2) was present in all six rabbits at study termination on day 14 (US EPA, 2009b). No further details are available.

Eye Irritation

The chemical may be slightly irritating to the eye. The effects are not sufficient to warrant hazard classification.

In a study performed in accordance with OECD (TG) 405, NZW rabbits (3 females) received 0.1 mL of the chemical applied to one eye while the other eye served as the control. After 24 h, one rabbit displayed some swelling above normal (grade 1; maximum score 3); no other effects were seen at this time-point. No effects of the chemical were observed 72 h after application (REACH).

In a study in NZW rabbits (3, sex not reported), 0.1 mL of the undiluted test substance was applied to one eye of each rabbit; the other eye served as the control. The treated eye was washed 30 seconds after DMT application followed by scoring according to Draize at 1, 24, 48, 72 h and 4 and 7 days after administration of the chemical. Severe conjunctival redness (grade 2; maximum score 4) was observed in one rabbit 1 h after application. No effects were seen seven days after application (US EPA, 2009b).

Sensitisation

Skin Sensitisation

Based on the available animal and human data (see ***Observation in humans*** section) the chemical is considered a skin sensitiser and warrants hazard classification (see ***Recommendation*** section).

In a skin sensitisation study performed according to a modified Buehler method, Hartley guinea pigs were exposed to the chemical at 50 % v/v in mineral oil once weekly for three weeks. Challenge with the maximum non-irritating concentration (10 % v/v) produced dermal responses in 60 % of the animals (US EPA, 2009b).

The profiling functionality of the OECD QSAR Toolbox v3.2 was used to determine the presence of potential structural alerts for skin sensitisation. The chemical did not have mechanistic alerts for skin sensitisation. However, the metabolite of DMT, N-methyl-p-toluidine (CAS 623-08-5) (see ***Toxicokinetics*** section) had a structural alert for protein conjugation (indicative of skin senstisation potential) via Michael type addition at nucleophilic centers on the protein.

Observation in humans

Sensitisation to the chemical has been demonstrated in dental patients and in patients with artificial hips.

A 60 year old man without history of contact dermatitis had a total hip replacement. The bone cement used during surgery contained methyl methacrylate monomer and poly(methyl methacrylate). Benzoyl peroxide was used as a catalyst and DMT as an accelerator. Patch tests were performed on the patient’s back using separated individual components of the bone cement. A positive result to DMT with palpable erythema was noted at both 48 and 96 h after application. There was no reaction to any of the other tested materials including various metals, polyethylene and individual components of the bone cement. The man had handled a lot of different glues potentially containing DMT in his work, which may have contributed to sensitisation (Haddad et al., 1995).

In a study of 70 patients with hip replacements and 25 patients without prostheses, allergic responses to the chemical and other prosthesis components were evaluated. There were no allergic responses to the prosthesis components including polyethylene, metals, methyl methacrylate, benzoyl peroxide or hydroquinone. In this study, 7 out of the 15 patients suffering from aseptic hip loosening had an allergic reaction to DMT, suggesting that sensitisation may be due to the chemical leaching out of the prosthesis (Haddad et al., 1996).

Several cases of hypersensitivity to the chemical DMT have been found in patients suffering from burning mouth syndrome (BMS). This syndrome is common in patients wearing dentures that may contain DMT.

In a study of 22 BMS patients (19 females, 2 males) wearing dentures or with acrylic fillings, positive reactions to methyl methacrylate, DMT, formaldehyde, hydroquinone, cobalt chloride, and nickel sulfate were observed. Three patients reacted positively to DMT in the patch test. In one of the patients the BMS complaints resolved completely after fitting a denture based on polyurethane that did not contain DMT (Dutree-Meulenberg et al, 1991).

In another patch-test study of dental materials, a dental student, with blistering and swelling of the finger tips following contact with dental materials used in prostheses, displayed sensitivity to the chemical (Santosh et al., 1999).

In a case study, a female patient with BMS demonstrated a positive reaction to DMT and to scrapings of her own dentures. Her symptoms disappeared after removal of the dentures (Verschueren et al., 1991).

In another case study, a female patient suffering from BMS tested positive to the chemical in a patch-test. The patient had no reactions to any other substances in the dental test series. The symptoms of BMS diminished after removal of the dentures (Tosti et al., 1990).

Repeated Dose Toxicity

Oral

The chemical is classified as hazardous with hazard category 'Category 2 Specific target organ toxicity (repeated exposure)' and hazard statement H373 (May cause damage to organs through prolonged or repeated exposure) in the HCIS (Safe Work Australia). The available data supports this classification.

In a 13 week oral gavage study (standard NTP methodology), F344 rats (10/sex/dose) were given daily doses of the chemical DMT in corn oil at 0, 62.5, 125, 250, 500 or 1000 mg/kg bw, 5 days a week for 14 weeks. No rats in the 1000 mg/kg bw/day dose group survived past day 3 and in the 500 mg/kg bw/day dose group one male mortality occurred.

The main clinical findings associated with exposure to the chemical included cyanosis, abnormal breathing, and lethargy in groups administered 250 mg/kg bw/day or greater. The final mean bodyweights were significantly decreased in all surviving rats. The dose-dependent haematology findings were consistent with anaemia and methaemoglobinaemia. Liver weights were significantly increased in all surviving males and females. Incidence of hepatocellular hypertrophy was significantly increased in both sexes at doses of 125 mg/kg bw/day and above and increased liver pigmentation was seen at doses 62.5, 125, and 500 mg/kg bw/day. Hepatocyte necrosis was present in females exposed to the chemical at 62.5, 250, and 500 mg/kg bw/day. In the kidney, significantly increased incidences of pigmentation were detected at doses above 62.5 mg/kg bw/day. Nephropathy was present in the 125, 250 and 500 mg/kg bw/day dose groups. In males, congestion of the spleen was observed in all doses and in females at doses above 250 mg/kg bw/day. The incidence of bone marrow hyperplasia was increased in all dose groups. A lowest observed adverse effect level (LOAEL) 62.5 mg/kg bw/day was reported based on effect on multiple organs (NTP, 2012).

In a 13 week oral gavage study (standard NTP methodology), B6C3F1/N mice (10/sex/dose) were given daily doses of the chemical DMT in corn oil at 0, 15, 30, 60, 125 or 250 mg/kg bw/day, 5 days a week for 14 weeks. Only one male receiving the highest dose survived to the end of the study. In the 125 mg/kg bw dose group 5 mortalities occurred (3 males, 2 females) before the end of the study. Clinical findings included abnormal breathing, thinness, lethargy, cyanosis, and ruffled fur in males and females at 125 and 250 mg/kg bw/day. Slight but significant reductions in erythrocytes and haematocrit were observed in male mice from the lowest dose group. Methaemoglobinaemia was observed in both sexes at doses of 30 mg/kg bw/day and above. The liver and lung weights of both sexes at doses of 125 mg/kg bw/day and above were significantly increased. Histopathological changes were observed in liver, respiratory epithelia and thymus. Other treatment-related lesions included lymph node atrophy and bone marrow hyperplasia. Overall, the effects of the chemical in mice were similar to those in rats but less severe. A LOAEL of 30 mg/kg bw/day was reported based on haematological effects (NTP, 2012).

Dermal

The chemical is classified as hazardous with hazard category 'Category 2 Specific target organ toxicity (repeated exposure)' and hazard statement H373 (May cause damage to organs through prolonged or repeated exposure) in the HCIS (Safe Work Australia).

No publicly available data are available for the chemical. However, the chemical has potential to induce methaemoglobinaemia and this may be common to all routes and the systemic exposure may occur via the dermal route (HSBD). Therefore, the classification is not amended.

Inhalation

The chemical is classified as hazardous with hazard category 'Category 2 Specific target organ toxicity (repeated exposure)' and hazard statement H373 (May cause damage to organs through prolonged or repeated exposure) in the HCIS (Safe Work Australia).

No publicly available data are available for the chemical. However, the acute toxicity study showed bioavailability of the chemical via inhalation route (see ***Acute Toxicity: Inhalation*** section) and the chemical has potential to induce methaemoglobinaemia. Therefore, the classification is warranted for the chemical.

Genotoxicity

Based on the weight of evidence from available studies reported below, the chemical does not warrant classification for mutagenicity.

In vitro studies

Several in vitro assays were conducted using the chemical. These included:

- Negative in vitro point mutation results in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 at concentrations up to 1,000 µg/plate, with or without metabolic activation (NTP, 2012).
- Negative in vitro point mutation results in *S. typhimurium* strains TA98 and TA100 and *Escherichia coli* WP2 uvrA/pKM101at concentrations up to 1,500 µg/plate, with or without metabolic activation (NTP, 2012).
- Negative in vitro point mutation results in *S. typhimurium* strains TA97, TA98, or TA100 at concentrations up to70 µg/plate, with or without metabolic activation (Taningher et al., 1993).
- Positive in vitro point mutation results in *S. typhimurium* strain TA1535. The tested doses were 10-100 µg/plate with metabolic activation and 33-3333 µg/plate without metabolic activation (NTP, 1999).
- Positive results for gene mutation in the thymidine kinase (tk) locus in L5178Y mouse lymphoma cells treated with DMT at 0.018-0.044 µl/ml with metabolic activation and 0.05-0.24 µl/ml without metabolic activation (NTP, 1999)
- Positive in vitro micronuclei induction in Chinese hamster V79 cells at concentrations of 0.9 and 1.2 mM (Taningher et al., 1993).

In vivo studies

The chemical gave mostly negative results for in vivo genotoxicity assays:

- Positive results in the DNA damage alkaline comet assay in liver cells from SD rats orally exposed to the chemical at 60 mg/kg bw/day for 4 days (NTP, 2012).
- Negative results in the DNA damage alkaline comet assay in leukocytes and liver from B6C3F1/N mice orally exposed to the chemical at 30 to 75 mg/kg bw/day for 4 days (NTP, 2012).
- Negative results in a micronucleus test with no significant increase in micronucleated erythrocytes or reticulocytes in B6C3F1/N mice orally exposed to the chemical at 15 to 125 mg/kg bw/day for 3 months (NTP, 2012).
- Negative results in a micronucleus test with no significant increase in micronucleated erythrocytes or reticulocytes in B6C3F1/N mice orally exposed to the chemical at 30 to 75 mg/kg bw/day for 4 days (NTP, 2012).

Carcinogenicity

The chemical gives evidence of carcinogenic activity in experimental rat and mouse NTP studies, warranting hazard classification (see ***Recommendation*** section).

The chemical is also classified as 'Possibly carcinogenic to humans' (Group 2B) by the International Agency for Research on Cancer (IARC).

Experimental data

In a carcinogenicity study according to NTP guidelines, F344/N rats (50/sex/dose) were orally treated (gavage) with 0, 6, 20, or 60 mg/kg bw/day of DMT, 5 days per week for 105 weeks. Survival of males at highest dose was significantly reduced compared to vehicle control rats. Survival of female rats was non-significantly reduced at the highest dose. The incidence of liver tumours was significantly increased males and females at the highest dose and non-neoplastic liver lesions occurred frequently in the 20 and 60 mg/kg bw/day groups. In the nose, adenoma and/or carcinoma were observed in 60 mg/kg bw/day males; adenoma also occurred in female rats exposed to 6 or 60 mg/kg. All dosed animals had increased incidence of follicular cell adenoma or carcinoma of the thyroid (NTP, 2012).

In a carcinogenicity study according to NTP guidelines, B6C3F1/N mice (50/sex/dose) were orally treated (gavage) with 0, 6, 20, or 60 mg/kg bw/day of DMT, 5 days per week for 105 weeks. Survival of 60 mg/kg bw/day females was significantly reduced compared to the control group. Mean body weights of 60 mg/kg males and females were reduced by more than 10 % of compared to control mice at week 89 and week 65, respectively. The liver tumour incidence was significantly increased in 20 and 60 mg/kg bw/day females, and in 60 mg/kg bw/day males. Females in the 20 and 60 mg/kg bw/day dose groups had an increased incidence of adenoma and carcinoma in the lung and tumours in the forestomach. Neoplastic lesions of the olfactory epithelium were seen in 60 mg/kg bw/day males and 20 and 60 mg/kg bw/day females (NTP, 2012).

In a toxicogenomics study aimed to elucidate potential early carcinogenic mechanisms, male F344/N rats (5/dose) were orally treated (gavage) with 0, 1, 6, 20, 60 or 120 mg/kg bw/day of DMT for 5 days. Hyperplasia of the nasal epithelium was observed in the two highest dose groups. Gene transcript profiles of the nasal epithelium were consistent with a response to oxidative stress, cell proliferation and signals for apoptosis (Dunnick et al., 2016). In the liver, mild toxicity (individual cell death) and dose-related gene transcript changes were observed. Similar to the nasal epithelium, transcriptomic changes in the liver were characteristic of a response to oxidative stress (Dunnick et al., 2017). Transriptomic profiling of nasal epithelia and liver suggest that oxidative damage may contribute to the carcinogenic effects of DMT.

Reproductive and Developmental Toxicity

No reproductive or developmental toxicity data are available for the chemical. Based on the available data from an oral repeat dose toxicity study in F344 rats (see ***Repeat dose toxicity*** section), the chemical may have effects in male and female reproductive systems at higher doses.

The oestrous cycle was disrupted in female rats in the 125 and 250 mg/kg bw/day groups. The females had an extended dioestrus stage compared to the vehicle control group. Reduced weights of the testes, whole epididymis and the cauda epididymis were observed in males in the 250 mg/kg bw/day dose group. However, there were no significant differences in testicular spermatid or epididymal sperm numbers of male rats administered 62.5, 125, or 250 mg/kg bw/day when compared to vehicle controls (NTP, 2012).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (including carcinogenicity), systemic acute effects and local effects of skin sensitisation.

Public Risk Characterisation

The chemical has reported cosmetic use in Australia in nail preparations and domestic use in glues, at concentrations below 1 %. Provided that normal precautions are taken to avoid prolonged skin contact, exposure will be very low and the risk to the public posed by cosmetic or domestic products containing the chemical is not considered to be unreasonable at these low concentrations.

Occupational Risk Characterisation

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal and inhalation exposures 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 existing hazard classification for worker health and safety requires amendment to include the classification for carcinogenicity and skin sensitisation (see ***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

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2017).

Work Health and Safety

The chemical is recommended for classification and labelling aligned with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Toxic if swallowed - Cat. 3 (H301)* Toxic in contact with skin - Cat. 3 (H311)* Toxic if inhaled - Cat. 3 (H331)*
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)*
Carcinogenicity	Not Applicable	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 consumers

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

Advice for industry

Control measures to minimise the risk from oral, dermal and inhalation exposures 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 eliminating 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 may 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;
- 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.

References

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