1,3-Benzenediamine: Human health tier II assessment

22 November 2013

CAS Number: 108-45-2

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.

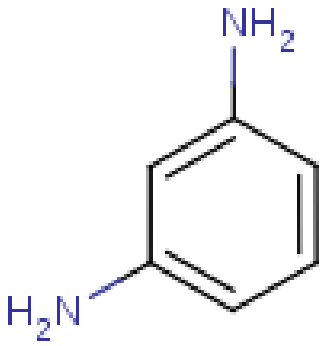
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	m-phenylenediamine 1,3-phenylenediamine 3-aminoaniline m-benzenediamine m-aminoaniline
Structural Formula	
Molecular Formula	C6H8N2
Molecular Weight (g/mol)	108.14
Appearance and Odour (where available)	White to slightly red crystalline powder.
SMILES	c1(N)cc(N)ccc1

Import, Manufacture and Use

Australian

The chemical is on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS).

The chemical has reported cosmetic use in permanent hair dye preparations.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; and eChemPortal: OECD High Production Volume chemical program (OECD HPV), the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR), and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported cosmetic use in hair dye preparations.

The chemical is listed as safe for use in hair dyes at concentrations up to 10 % (US Cosmetic Ingredient Review (CIR, 1997)—Cosmetic ingredients found safe, with qualifications).

The chemical has reported commercial use:

- as a component of dyes for leather and textiles;
- in rubber curing agents;
- as an accelerator for adhesive resins;
- in ion exchange resins;
- in photographic developing; and
- as an additive in gasoline.

The chemical has reported site-limited use:

- in manufacturing polymers (epoxy resin, aramid fibres);
- in manufacturing dyes and corrosion inhibitors; and
- as an intermediate in manufacturing rubber and antioxidants.

Restrictions

Australian

The chemical is not listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). However, there is a group entry in Schedule 6 and Appendix C of the SUSMP that includes this chemical:

- Schedule 6:

'PHENYLENEDIAMINES and alkylated phenylenediamines not elsewhere specified in these Schedules:

(a) in preparations packed and labelled for photographic purposes;

(b) in preparations packed and labelled for testing water **except** tablets containing 10 mg or less of diethyl-para-phenylenediamine or dimethyl-para-phenylenediamine in opaque strip packaging provided the directions for use include the statement, “Do not discard testing solutions into the pool"; or

(c) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye. written in letters not less than 1.5 mm in height; or

(d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement: WARNING - This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use. written in letters not less than 1.5 mm in height'.

Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.

- Appendix C:

'PHENYLENEDIAMINES in preparations for skin colouration and dyeing of eyelashes or eyebrows except when included in Schedule 6'.

Appendix C chemicals are substances of such danger to health as to warrant prohibition of sale, supply and use.

International

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

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- EU Commission Banned Hair Dye Substances: m-phenylenediamine;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;

- 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; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist").

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)

Xi; R36 (irritation)

Xi; R43 (sensitisation)

Muta. Cat. 3; R68 (mutagenicity)

Exposure Standards

Australian

The chemical has an exposure standard of 0.1 mg/m³ time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

- an exposure limit of 0.1 mg/m³ time weighted average (TWA) in USA, Canada, Norway, Spain, Iceland, Greece, Denmark and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical is rapidly absorbed through the skin in rats and dogs. In rats, it is metabolised in the liver into three main metabolites (N-acetyl-1,3-diaminobenzene, N,N'-diacetyl-2,4-diaminophenol and N, N'-diacetyl-1,3-diaminobenzene). Urine was reported to be the primary route of excretion (49 %) (HSDB; REACH).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in HSIS (Safe Work Australia). The available data support this classification.

The median lethal dose (LD50) is 280–650 mg/kg bw in rats; 67.7 mg/kg bw in mice; 450 mg/kg bw in guinea pigs; 437 mg/kg bw in rabbits; and 562 mg/kg bw in wild birds (ChemIDPlus; HSDB).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in HSIS (Safe Work Australia). The available data support this classification.

The LD50 in mice is 90 mg/kg bw (CIR, 1997).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in HSIS (Safe Work Australia). Although the median lethal concentration (LC50) available indicates a lower hazard classification, considering the high mortality in the six-hour study (dose not reported), the existing classification is considered appropriate.

The LC50 is reported as 3.2 mg/L in rats (with 95 % confidence limits of 2.6 and 4.1 mg/L) (CIR, 1997). In the four-hour (nose only exposure) study, red ocular discharge and nasal discharge were observed at concentrations from 0.72 to 3.9 mg/L. Lung noise and tremors were noted at 2 mg/L and laboured breathing was observed above 3.2 mg/L.

In another study following six hours of exposure to the chemical, 9/10 rats died within 24 to 48 hours after exposure (dose not available). Necropsy indicated pronounced pulmonary congestion with occasional haemorrhages in all animals (CIR, 1997).

Corrosion / Irritation

Skin Irritation

The data available indicate the chemical is a slight skin irritant in New Zealand White rabbits. However the irritation scores are below the level for classification. The study in guinea pigs indicates the chemical is an irritant at 10 % concentration, but the irritation scores are not available to consider this study for classification of the chemical.

In a skin irritation study, 0.5 g of the chemical was applied on shaved skin (occlusive patch) of New Zealand White rabbits (n=6) for four hours. The chemical produced a mild skin irritation (mean scores were 1.5, 1.7 and 0.3 for erythma; and 0, 0.7 and 0 for oedema at 1, 24 and 48 hours, respectively following the patch removal) (REACH).

In another skin irritation study, six albino rabbits were treated with the chemical (dose not reported) on abraded and intact skin (occlusive) for 24 hours. No skin irritation was reported throughout the 72-hour observation period (scores not available) (REACH).

In a 48-hour occlusive patch test, 0.1, 5 or 10 % concentrations of the chemical were applied to the flanks of nine Hartley albino guinea pigs. Skin irritation was observed in 4/9 animals treated at 10 % concentration. No skin irritation was observed at 0.1 or 5 % concentrations (CIR, 1997).

Eye Irritation

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

In an eye irritation study (OECD TG 405), 0.01 g of the chemical was instilled in one eye each of two New Zealand White rabbits. Only the eyes of one rabbit were washed after 20 seconds. Severe effects occurred in the treated eyes within 72 hours after exposure and persisted for at least 24 hours. These effects included severe conjunctival redness, conjunctival blistering, moderate corneal opacity and iritis, nictitating membrane haemorrhaging and epithelial sloughing of the cornea. Severe chemosis was observed in the treated unwashed eye. The mean scores are not available. However, the maximum scores reported up to seven days are: 3 for cornea, 1 for iris and 4 for conjunctivae. The effects were reversible seven days after the treatment. The chemical was considered to be an eye irritant (REACH).

In another study (similar to OECD TG 405), 0.01 g of the chemical was instilled in one eye each of two albino rabbits. Only the treated eye of one rabbit was washed after 20 seconds. Ocular effects (such as cloudiness, development of blood vessels, redness, swelling and discharge) occurred within 72 hours after exposure and persisted for at least 24 hours (mean scores not available). Treated eyes became normal within the 14-day observation period. The chemical was considered to be a moderate eye irritant (REACH).

Sensitisation

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in HSIS (Safe Work Australia). The data available support this classification.

In a local lymph node assay (LLNA) (equivalent to OECD Test Guideline (TG) 429), groups of female CBA mice were topically treated with 0.25 µL of the chemical at 2, 5 and 10 % concentrations once a day for three days. The chemical was a skin sensitiser at all tested concentrations. The effect concentration for tripling response (EC3) was calculated as 0.49 % (REACH).

The chemical was sensitising when 25 and 35 % concentrations were tested on intact and abraded skin of guinea pigs (number not reported). Mild to intense redness of the skin (erythematous reactions) were observed in both intact and abraded skins (CIR, 1997).

In a sensitisation study, 1 % concentration of the chemical was topically applied to the nape of Hartley albino guinea pigs (n=9), three times a week for two weeks (occlusive patch for 48 hours). After two weeks of non treatment, the animals were challenged with 0.1 and 1 % concentrations of the chemical applied on to the flanks of the animals (occlusive patch for 48 hours). The chemical induced mild sensitisation (CIR, 1997).

Observation in humans

The chemical induced skin sensitisation in patch tests in 8/38 workers with dermatitis (CIR, 1997).

A scratch test in workers (number not available) showed adverse reactions to the chemical (CIR, 1997).

Repeated Dose Toxicity

Oral

Although there were treatment-related effects in rats in the 90-day study at doses within the hazard classification range, the incidence and severity of these effects are not sufficient to warrant a hazard classification.

In a 90-day study (non-guideline), groups of 20 rats were administered the chemical (by gavage) at 0, 2, 6 or 18 mg/kg bw/d. The following effects were reported at 18 mg/kg bw/d: liver degeneration (significant in one case with nuclear pyknosis, where the nucleus of the cell shrinks and the chromatin condenses to a solid, structureless mass), a dose-dependent significant increase (percentage increase not available) in the absolute and relative liver weights in females and males, and increased kidney weight in females. There were no mortalities. The no observed adverse effect level (NOAEL) was reported as 6 mg/kg bw/d (IUCLID, 2000; REACH).

In a four-week study (non-guideline), groups of rats (n=5/sex) were administered the chemical by gavage at 0, 10, 30 or 100 mg/kg bw/d. There were no mortalities. Increased kidney weights were observed at 10 and 30 mg/kg bw/d (not dose-dependent) and sedation was observed at =30 mg/kg bw/d (IUCLID, 2000; REACH; CIR 1997).

Dermal

The two studies available have limited value?one tested a formulation containing a very low concentration of the chemical and the other study had high, non treatment-related mortility rates in mice. The data available are insufficient to make a conclusion regarding the potential of the chemical to cause serious damage to health from repeated dermal exposure.

Dermal application of 1 mL/kg bw/d of an oxidative dye formulation containing 1.5 % of the chemical (with 3 % of hydrogen peroxide) to 12 rabbits for 13 weeks did not induce toxicity (CIR, 1997).

In a two-year study, 0.2 or 1 mg of the chemical was applied to the skin of mice (strains: C57BL/6Bd and C3Hf/Bd; n=20/sex and 40/sex respectively) three times a week. No treatment-related effects were reported. The mortality was comparable to the control groups (between 10–50 % in both strains) except in C57BL/6Bd male mice where there were no mortalities in the control group (compared with 10–35 % in the treated groups). No explanation was available for the high mortality rates observed in most control and treatment groups (IUCLID, 2000).

Inhalation

No data are available.

Observation in humans

Occupational exposure to the chemical for 5–10 years caused dysuria (painful urination) in 13.4 % of a group of workers (number of workers not reported) (CIR, 1997).

Genotoxicity

The chemical is classified as hazardous—Category 3 mutagenic substance—with the risk phrase ‘Possible risk of irreversible effects’ (Xn; R68) in HSIS (Safe Work Australia). The available data support this classification. There are no positive in vivo germ cell data to consider upgrading this existing classification.

Many in vitro studies showed positive results with the chemical (REACH; IUCLID, 2000; CIR, 1997):

- Ames assay (similar to OECD TG 471) with four strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, and TA100—the chemical was mutagenic in strain TA1538 with metabolic activation at all tested doses (1, 10, 50, 100, 250, 500, 750, and 1000 µg/plate). All other strains produced negative results with or without metabolic activation;

- In another Ames assay with *S. typhimurium* strains TA97 and TA98, the chemical was mutagenic with metabolic activation from doses of 1–10000 µg/plate;
- Sister chromatid exchange (SCE) assay (non-guideline study)—positive in mammalian cells (cell type not reported) at concentrations 5, 16.7, 50, 75.4, 100.5, 150 and 166.7 µg/mL without metabolic activation and 500, 1666.7 and 5000 µg/mL with metabolic activation;
- Microscreen assay (non-guideline study) for lambda prophage induction in *Escherichia coli* B/r.WP2(lambda)—the chemical was mutagenic without metabolic activation at 175 µg/well;
- Chromosomal aberration test in Chinese hamster ovary cells (CHO)—the chemical was mutagenic without metabolic activation at concentrations of 246.5, 502.5, 747.0 and 1000.0 µg/mL but not mutagenic with metabolic activation at 2513.0, 3750.0 and 5000.0 µg/mL;
- In another mammalian chromosomal aberration test with Chinese hamster lung cells (CHL) (similar to OECD TG 473), the chemical was mutagenic without metabolic activation at concentrations of 15 µg/mL and 30 µg/mL, and with metabolic activation at 125 µg/mL;
- Chromosomal aberration test in human lymphocytes—positive at concentrations of 5, 50 and 200 µg/mL; and
- Forward mutational assay in L5178Y mouse lymphoma cells—positive at concentrations of 25, 50 and 100 µg/mL.

The following in vivo genotoxicity studies are available for the chemical (REACH, IUCLID, 2000):

- In a micronucleus assay, a group of Swiss mice (n=10) received intraperitoneal (i.p) injections of the chemical at 50, 100, 200, 250, 500 or 1000 mg/kg bw, twice at 24-hourly intervals. The chemical showed a dose-dependent increase in micronucleated polychromatic and normochromatic erythrocytes in bone marrow cells, cytotoxicity in mice ≥500 mg/kg bw and mortality at 1000 mg/kg bw;
- In another micronucleus assay (similar to OECD TG 474) in mice (Crl: CD-1(1CR)BR) that received the chemical twice (24 hours apart) by oral gavage doses of 16, 33 or 65 mg/kg bw/day, no statistically significant increase of micronucleated polychromatic erythrocytes (MPE) was observed. A significant depression in the ratio of young, polychromatic erythrocytes to mature, normochromatic erythrocytes was observed at 65 mg/kg bw/day; and
- In a dominant lethal assay (similar to OECD TG 478) male rats (Holtzman Albino rats) received intraperitoneal injections of the chemical three times a week for 10 weeks at 12.5, 25, 50 or 100 mg/kg bw/day. Weakly positive results were obtained in several dominant lethality parameters at 12 to 50 mg/kg bw/day. However, when the test was repeated, all dominant lethality criteria showed negative results at 25 to 100 mg/kg bw/day.

Carcinogenicity

The data available are not sufficient to make a conclusion about the carcinogenicity of the chemical. Although the 78-week drinking water study in mice indicated a NOAEL for carcinogenicity, considering the high tumour incidences reported in control groups compared with the treatment groups, the reliability of this non-guideline study is too questionable to make a conclusion.

The International Agency for Research on Cancer (IARC) stated that no evaluation of carcinogenicity of this chemical can be made as it has only been tested as a constituent of a hair-dye formulation in mice using skin painting, and in rats by subcutaneous injection ('was inadequately tested') (IARC, 1978). IARC concluded that 'No evaluation of the carcinogenicity of this compound or of its hydrochloride can be made'. Therefore, the chemical falls under Group 3 (Not classifiable as to its carcinogenicity to humans) (IARC, 1978— last updated March 1998).

Several carcinogenicity studies (non-guideline) are available for the chemical with limited information (IUCLID, 2000). Apart from one two-year study in Sprague Dawley (SD) rats, others did not indicate any increased tumour incidences related to the treatment. SD rats (n=30/sex), which received the chemical in subcutaneous injections at doses of 8.33 or 25 mg/kg bw (in 1 mL/kg peanut oil), once a week for two years showed an increased number of malignant tumours at the site of injection in both groups (78 % and 58 % respectively) (IUCLID, 2000).

In a carcinogenicity study (non-guideline), two groups of B6C3F1 mice (n=50/sex or n=56–59/sex) were dosed with the chemical at 0.02 % (calculated intake as 23 and 19.8 mg/kg bw/day for females and males, respectively) or 0.04 % (calculated intake as 41.8 and 38.2 mg/kg bw/day for females and males, respectively) in drinking water for 78 weeks. The survival rates were over 86 % at the end of the study in all groups. No neoplastic effects were reported at any dose level. However, it was reported that the incidences of hepatocellular tumours, hyperplastic liver nodules and lung adenomas were significantly lower in all treated groups compared with the control groups (REACH; IUCLID, 2000). The no observed adverse effect levels (NOAEL) for carcinogenicity were reported as 38.2 mg/kg bw/day for male mice and 41.8 mg/kg bw/day for female mice (REACH).

In another study, 1.5, 3.0 or 6.0 % (w/v) of the chemical in acetone was applied to the shaved skin of mice (strain: C3Hf/Bd; n=25/sex), three times a week (total of 2.25, 4.5 or 9 mg chemical in each animal a week, respectively) for two years. The chemical did not induce skin tumours (CIR, 1997).

Dermal application of 0.5 mL of a hair dye formulation containing 1.5 % of the chemical (mixed with hydrogen peroxide (concentration not indicated) at 1:1 ratio) to a group of Swiss Webster mice (n=50/sex) once a week for 21 months did not induce tumours. The skin tumour incidence in both treated and control groups was low and not statistically significantly different. However, application of the chemical at the same concentration to shaved skin of the back of SD rats (n=60/sex) twice a week for two years (in a multigeneration reproduction study) caused non-neoplastic lesions in the treated and control groups (both males and females). These lesions were reported to be commonly found in ageing SD rats. The incidence of adenocarcinoma or carcinoma in the mammary glands of treated animals was comparable with the control groups (CIR, 1997; IUCLID, 2000).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to have reproductive or developmental toxicity. All reported foetal effects are likely to be secondary to maternal toxicity.

In a reproductive and developmental toxicity study (similar to OECD TG 414), three groups of 25 female rats (OFA (SD) SPF) were orally dosed with the chemical at 10, 30 or 90 mg/kg bw/day on gestation days 5–16. At the highest dose, 6/25 dams died and statistically significant body weight changes were observed. Reduction in the number of litters with live pups, lower average body weight of live pups, increased total resorptions and increased number of early and late dying embryos were also observed at the highest dose, compared with the control group. There were no major malformations. No statistically significant effects were observed in foetuses of dams of other treatment groups. The NOAEL for maternal toxicity and foetal developmental toxicity was 30 mg/kg bw/day (REACH; CIR, 1997).

In a similar study (non guideline), three groups of SD female rats were orally dosed (gavage) with the chemical (in propylene glycol) at 0, 45, 90 or 180 mg/kg bw/day on gestation days 6–15. No mortality was observed. At 180 mg/kg bw/day, a significant decrease in mean maternal weight gain and an increased number of foetal resorptions (not statistically significant) were observed. The numbers of foetal implantations and foetal anomalies were not significantly different from the controls (IUCLID, 2000; REACH; CIR, 1997). Details and effects on other treatment groups are lacking.

In a multigeneration reproduction study, 0.5 mL of a hair dye formulation containing 1.5 % of the chemical, mixed with an equal volume of hydrogen peroxide (6 %), was applied on shaved skin on the back of SD rats (six groups, n=40/sex) twice a week until each rat was 100 days old. Three additional groups were used as controls. The rats were paired and mated for 15 days. The fertility, gestation, survival and live birth indices were comparable to the control groups in all generations. No toxicological signs related to the treatment were noted. Only mild dermatitis was observed intermittently throughout the treatment period in each generation (CIR, 1997).

Other Health Effects

Neurotoxicity

Based on the available data, the chemical is not considered neurotoxic.

In a neurotoxicity study, three groups of 20 CDBR rats were dosed with the chemical at 0, 5, 10 or 20 mg/kg bw/day for 90 days in drinking water. No abnormalities in the nervous system or skeletal muscle were observed. Reductions in horizontal motor activity counts in male rats dosed at 10 or 20 mg/kg bw/day and, reduced vertical motor activity counts in male rats dosed at 20 mg/kg bw/day were observed (not statistically significant). The chemical did not induce changes in horizontal or vertical motor activity counts in female rats at any of the tested dose levels. The no-observed effect level (NOEL) was reported as 5 mg/kg bw/day (CIR, 1997).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (mutagenicity);
- local effects (skin sensitisation and eye irritation); and
- systemic acute effects (acute toxicity from oral, dermal and inhalation exposure).

The data available are not sufficient to make conclusions on carcinogenicity and repeated dose toxicity of the chemical.

Public Risk Characterisation

The chemical is reported to be used in permanent hair dye preparations in Australia.

Many countries including Canada, New Zealand and the European Union have prohibited the use of this chemical in cosmetics.

In Australia, a chemical group (phenylenediamines) including this chemical is listed on Schedule 6 and Appendix C of the SUSMP, with restriction and prohibition on its use in specific cosmetic products and other domestic uses such as photographic purposes and water testing in pools. The Schedule 6 entry in the SUSMP allows phenylenediamines to be included in hair dye preparations and in eyelash and eyebrow tinting products with specific requirements.

If this chemical is included in cosmetic products containing N-nitrosating agents, carcinogenic N-nitrosamine compounds could be formed (SCCS, 2012).

Considering the hazard properties of this chemical, it will cause unreasonable risks to consumers if used in hair dyes and eyelash and eyebrow tinting products. Other potential domestic uses indicated in the SUSMP may not cause unreasonable risks to public considering the specified labelling requirements.

Occupational Risk Characterisation

Given the critical health effects (mutagenicity, skin sensitisation, acute toxicity and eye irritation), the chemical may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemical are implemented. Based on the available data, the hazard classification in HSIS is considered appropriate.

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in hair dye products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through classification and labelling.

Assessment of the chemical is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

At present, the chemical falls within the scope of the listing of 'phenylenediamines' in Schedule 6 of the SUSMP for use in hair dye preparations under specified conditions.

Considering the severe health effects possible from exposure to this chemical (i.e. skin sensitisation, potential mutagenicity) and in the absence of conclusive data on carcinogenicity and repeated dose toxicity, it is recommended that this chemical be excluded from the 'phenylenediamines' group entry in Schedule 6 of the SUSMP for its use in hair dye preparations and eyelash and eyebrow tinting products. A separate Appendix C entry is recommended to prohibit the use of this chemical in hair dye preparations, eyelash and eyebrow tinting products.

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Toxic 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)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)*	Causes serious eye irritation - Cat. 2A (H319)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)

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

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise

risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

References

Aggregated Computational Toxicology Resource (ACToR). 1,3-benzenediamine (108-45-2). Accessed September 2013 at http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=209D492764071DBA7ADE54B9C12A6802

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

ChemIDPlus Advanced. Accessed September 2013 at http://chem.sis.nlm.nih.gov/chemidplus/

Cosmetic Ingredient Review (CIR) 1997. Final report on the safety assessment of m-phenylenediamine and m-phenylenediamine sulfate. International Journal of Toxicology 16(suppl.1) pp. 59 - 115.

Cosmetics Directive (CosIng). 1,3-benzenediamine (108-45-2). Accessed September 2013 at http://ec.europa.eu/consumers/cosmetics/cosing/

Galleria Chemica. Accessed at September 2013 at http://jr.chemwatch.net/galleria/

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed on September 2013 at http://toxnet.nlm.nih.gov.

International Agency for Research on Cancer (IARC) 1978. Some Aromatic Amines and Related Nitro Compounds(Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals), volume 16. 1,3-benzenediamine (108-45-2). Accessed September 2013 at http://monographs.iarc.fr/ENG/Monographs/vol16/volume16.pdf

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2007. List of Chemicalsused as Dyes in Permanent and Semi-Permanent Hair Dyes in Australia.

Personal Care Product Council (INCI Dictionary). Accessed September 2013 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

REACH Dossier. m-phenylenediamine (108-45-2). Accessed September 2013 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed September 2013 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Scientific Committee on Consumer Safety (SCCS) Opinion on Nitrosamines and Secondary Amines in Cosmetic Products, 2012. Adopted at its 14th plenary meeting of 27 March 2012. Accessed June 2013 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_090.pdf

Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) 2012. Australian Government. Department of Health and Ageing. Therapeutic Goods Administration, (the SUSMP 3) No. 3, 2012. Accessed September 2013 at http://www.comlaw.gov.au/Details/F2012L01200

Substances in Preparations in Nordic Countries (SPIN). 1,3-benzenediamine (108-45-2). Accessed September 2013 at http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx

The International Uniform Chemical Information Database (IUCLID) 2000. Dataset on substance ID 108-45-2. European Commission 18 February 2000. Accessed October 2013 at http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/108452.pdf.

Last update 22 November 2013

Share this page