1,2-Benzenediamine: Human health tier II assessment

22 November 2013

CAS Number: 95-54-5

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.

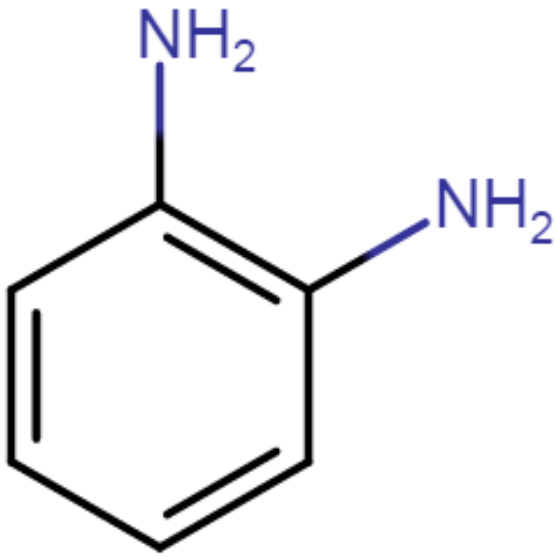
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	o-phenylenediamine (OPD) 1,2-phenylenediamine 1,2-diaminobenzene 2-aminoaniline
Structural Formula	
Molecular Formula	C6H8N2
Molecular Weight (g/mol)	108.143
Appearance and Odour (where available)	Light brown solid flakes
SMILES	c1(N)c(N)cccc1

Import, Manufacture and Use

Australian

No specific Australian use, import or manufacturing information has been identified.

International

The following international uses have been identified through European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; 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 site-limited use including:

- in manufacturing chemical substances such as dyes and photographic developing agents (as an intermediate that will be consumed during synthesis); and
- in manufacturing lubricants and corrosion inhibitors (SPIN)

Non-dispersive or closed system use is indicated for the chemical (IUCLID, 2000).

The chemical will be handled under strictly controlled conditions (Galleria Chemica).

Restrictions

Australian

The chemical is not listed in the Poisons Standard—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 phenylenediamine not elsewhere specified in these Schedules:

(c) in hair 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;

(d) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled 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;

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

The 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;

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; R25 (acute toxicity)

Xn; R20/21 (acute toxicity)

Xi; R36 (irritation)

Xi; R43 (sensitisation)

Carc. Cat. 3; R40 (carcinogenicity)

Muta. Cat. 3; R68 (mutagenicity)

Exposure Standards

Australian

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

International

The following exposure standards are identified (Galleria Chemica):

TWA of 0.1 mg/m³ in Canada, USA, Hong Kong and New Zealand; and

occupational exposure limit (OEL) of 0.1 mg/m³ in Japan.

Health Hazard Information

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Toxic if swallowed' (T; R25) in HSIS (Safe Work Australia). This classification is consistent with the data available for cats. The median lethal dose (LD50) varies with different species and rats seem to be less sensitive to the chemical than cats.

The LD50 in cats is reported as >50 and <250 mg/kg bw with symptoms including respiratory disturbance, agitation, methaemoglobinaemia (inability of the blood to carry oxygen and gives a blue colour to the skin and lips), saltatory spasms (abrupt involuntary movement) and mottled livers (IUCLID, 2000 and REACH).

The LD50 reported for other species are (ChemIDplus Advanced, REACH):

- 510 mg/kg bw in rats with convulsions and muscle weakness at sublethal doses;
- 1365 and 1418 mg/kg bw in female and male SPF-Wistar-K rats, respectively;
- 366 mg/kg bw in mice;
- 360 mg/kg bw in guineapigs; and
- 133 mg/kg bw in wild birds.

Dermal

The chemical is classified as hazardous with the risk phrase 'Harmful in contact with skin' (Xn; R21) in HSIS (Safe Work Australia). Although the available data in rats do not support this classification, information available in rabbits supports the classification.

The dermal LD50 in rats is >5000 mg/kg bw (IUCLID, 2000). However, the lowest published lethal dose (dermal LDLo) in rabbits is 1500 mg/kg bw, with effects in salivary glands (structural or functional), haematuria (blood in urine) and ataxia (lack of control over bodily movements) at sublethal doses (ChemIDplus Advanced).

Inhalation

The chemical is classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in HSIS (Safe Work Australia). The available data support this classification.

The median lethal concentrations (LC50) reported are: 1873 mg/m³ in rats and >91 mg/m³ with four hours' exposure in mice (IUCLID, 2000; ChemIDplus Advanced and REACH). Details are not available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is not considered a skin irritant.

The chemical (500 mg mixed with 0.3 mL physiological saline) was applied (semi-occlusive) for four hours to the shaved skin of three New Zealand White rabbits (OECD TG 404). Mean (24, 48 and 72 h) erythema and oedema scores were 0.3–0.7 and 0, respectively indicating the chemical is only slightly irritating to rabbit skin (REACH).

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.

The chemical (100 mg) was applied to one eye each of three New Zealand White rabbits. The eyes were rinsed after 24 hours of exposure (OECD TG 405) and examined after 1, 24, 48, and 72 hours, and 7 and 14 days. The mean scores (24, 48 and 72 h) reported are: 2.3, 3.0 and 3.3 for chemosis in individual rabbits; 3.0 for conjunctival redness; 2.0-2.3 for corneal opacity and 1.0 for iritis. All effects were fully reversible within 7–14 days. The chemical is therefore considered to be an eye irritant in rabbits (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 positive results reported in the studies below support this classification.

The chemical was tested using two modified guinea pig maximisation tests: an open epidermal induction and challenge test and a quasi-intradermal induction test. In both these tests, the chemical was injected into the foot pad of guinea pigs. The challenge phase used a topical application of 10 µL of the chemical in the lumbar area. The sensitisation rates were reported as 30 % in the epidermal induction test (7/24 animals showing positive reactions) and 75 % in the intradermal test (18/24 animals showing positive reactions). The chemical was therefore reported to be a skin sensitiser (IUCLID, 2000 and REACH).

Repeated Dose Toxicity

Oral

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

In a 28-day study (OECD Test Guideline (TG) 407), male rats (strain ChR-CD) received the chemical at 0, 400, 1000, 2000 or 4000 ppm in drinking water, with 3–14 day intervals between each exposure. The only treatment-related effect reported was weight loss in rats (35 % less than the control group after week one) at 4000 ppm. Weight gain was rapid during the non-treatment periods (3–14 days intervals) during the study. Rats in the 1000 or 2000 ppm groups consumed less water and had transient decreases in the mean body weight gain. The chemical was reported as non-palatable to rats. The no observed adverse effect level (NOAEL) was reported as 400 ppm (REACH).

In a 90-day study (US EPA OTS 798.6200 and EPA OTS 798.6400), rats were administered the chemical at oral gavage doses of 0, 20, 40 or 80 mg/kg bw/day. There were no mortalities or treatment-related effects in treated rats, apart from reduced average body weight gain (not statistically significant) and staining of the fur around the abdomen area in female rats of the highest dose group (REACH). The NOAEL can be considered as 80 mg/kg bw/day.

Dermal

Only limited data are available.

The chemical was applied to the skin of six male albino rabbits at 300 mg/kg/day (occlusive) for six hours a day for 10 days, over a two-week period. Two animals died during the study (on day six and during week two). The chemical was a strong irritant and produced haemorrhagic areas under the skin and acute suppurative conjunctivitis (discharge of pus from the eyes). The haemoglobin and haematocrit levels were also decreased during the treatment period. All animals appeared normal during the recovery period (REACH).

Inhalation

Only limited data are available.

Male rats (ChR-CD) were exposed (whole body) to the chemical as an aerosol at 0.08 mg/L for four hours a day for 10 days. Growth rate was retarded during the exposure but became normal during the recovery period. Rats showed irregular respiration during the exposure. No other treatment-related effects were observed (REACH).

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. Reliable in vivo studies showing effects on germ cells are lacking to consider upgrading this existing classification.

There are many in vitro studies indicating positive results for the chemical (REACH):

- In Ames assays (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 from 250 µg/plate. All other strains produced negative results with or without metabolic activation at doses 1, 10, 50, 100, 250, 500, 750, and 1000 µg/plate. Another assay with *S. typhimurium* strains TA97, TA98, and TA100 were negative without metabolic activation (at doses from 100 to 10000 µg/plate), but were positive with metabolic activation. Strain TA1535 showed negative results with or without metabolic activation;
- Comet assay (non-guideline study)—positive with a dose response in human (male) lymphocytes at 5, 10, 15, 20, 30, 40 millimolar (mM);
- Sister cromatid exchange (SCE) assay (non-guideline study)—positive in human (male) lymphocytes at concentrations 5, 10, 15 and 20 mM; and
- Mammalian chromosome aberration tests—two tests indicated positive results (test one (with significant deviations from OECD TG 473) in Chinese hamster cells with or without metabolic activation; test two (OECD TG 473) in Chinese hamster ovary cells at concentrations of 187, 374, 748 and 1122 µg/mL without metabolic activation).

Positive results are reported for the following in vivo genotoxicity studies (REACH):

- In a micronucleus assay (OECD TG 474) in mice (NMRI Hoe NMRKf (SPF71)) that received the chemical twice (24 hours apart) by oral gavage at doses of 0, 2.5, 25 or 250 mg/kg bw, a significant increase of micronucleated polychromatic erythrocytes (MPE) was observed (six hours after the second dose) at the highest dose in both male and female mice;
- Another micronucleus assay (similar to OECD TG 475) showed a dose-dependent increase of MPE in mice (NMRI) bone marrow and peripheral blood, following two (24 hours apart) intraperitoneal injections of the chemical (in 0.9 % NaCl) at 108, 216 and 324 mg/kg bw. No increase was observed at 27 and 54 mg/kg bw doses six hours after the second injection;
- In two other micronucleus assays (no TG indicated), Chinese hamsters and albino guinea pigs, which received two intraperitoneal injections of the chemical 24 hours apart, showed a significant increase of micronucleated polychromatic erythrocytes (MPE) (at 216 and 324 mg/kg bw in Chinese hamsters and a dose-dependent increase in guinea pigs from 108, 216 and 324 mg/kg bw). No increases of MPE were reported at 54 and 108 mg/kg bw in Chinese hamsters; and
- In male mice (NMRI) that received the chemical at 0, 100, 200 or 400 mg/kg bw as intraperitoneal injections, increased occurrence of diploid sperm cells were seen at the two higher doses (no TG indicated).

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase 'Limited evidence of carcinogenic effect' (Xn; R40 in HSIS (Safe Work Australia). The limited data available support this classification.

No reliable carcinogenicity data/studies are available.

In a non-guideline study, the chemical was administered orally (in the diet) to male CD rats at 2000 or 4000 mg/kg bw/day for 18 months, with a six-month recovery period. Increased incidence of liver tumours was reported at 4000 mg/kg bw/day (5/16 animals). The study was of limited quality (no necropsy evaluations were carried out for rats that died during the study and histopathological evaluations were conducted only on selected tissues) (REACH).

Another study indicated bladder papillomas in rats subcutaneously exposed to the chemical for 125 days (details not available) (REACH).

Reproductive and Developmental Toxicity

Based on the limited data available, no conclusion can be made on the reproductive and developmental toxicity of the chemical.

In a non-guideline study, maternal rats received the chemical orally at 0.5 or 1.5 mg/kg bw/day on gestation days 6–15. No reproductive effects or foetal effects in pups were reported (details not available) (REACH).

Male mice that were treated once, intraperitoneally, with the chemical at 100, 200 or 400 mg/kg bw showed an increased occurrence of diploid sperm cells at the two higher doses. The no observed effect level (NOEL) is reported as 100 mg/kg bw (details not available) (REACH).

Other Health Effects

Neurotoxicity

Based on the available data, the chemical is not considered to cause neurotoxicity.

In a 90-day study (US EPA OTS 798.6200 and EPA OTS 798.6400), rats were administered the chemical at oral gavage doses of 0, 20, 40 or 80 mg/kg bw/day and tested for neurobehavioural effects (one week before dosing and 4, 8 and 13 weeks after dosing). There were no neuropathological abnormalities in the nervous system or skeletal muscle, or effects on ocular tissues at the end of the treatment period in sacrificed rats. At 80 mg/kg bw/day, an increased incidence of enhanced tail pinch response was observed in male rats. All parameters evaluated in the functional observation battery (FOB) were unaffected by the treatment (IUCLID, 2000 and REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects—mutagenicity and potential carcinogenicity;
- local effects—eye irritation and skin sensitisation; and
- systemic acute effects—acute toxicity by oral, dermal and inhalation routes.

Public Risk Characterisation

Given the main use of the chemical as an intermediate to manufacture other chemicals, it is unlikely that the public will be exposed to the chemical. It is expected that the chemical will not be present in final consumer products, although it is likely to have properties that would make it useful for applications such as hair dyes.

Many countries including Canada, New Zealand and the European Union have prohibited the use of this chemical in cosmetics. In Australia, a chemical group (phenylenediamine) including this chemical, is listed on Schedule 6 and Appendix C of the SUSMP, with restriction/prohibition of its use in specific cosmetic preparations. The Schedule 6 entry in the SUSMP allows phenylenediamine to be included in hair dye preparations and in eyelash and eyebrow tinting products with specific requirements.

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.

Occupational Risk Characterisation

Given the critical health effects (carcinogenicity, mutagenicity and skin sensitisation), 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 and eyebrow/eyelash tinting 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, genotoxicity and

carcinogenicity) it is recommended that this chemical be excluded from this group entry in Schedule 6 of the SUSMP. A separate Appendix C entry is recommended to prohibit the use of this chemical in hair dye preparations and in 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)* Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Toxic if swallowed - Cat. 3 (H301) Harmful in contact with skin - Cat. 4 (H312) Harmful if inhaled - Cat. 4 (H332)
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)
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 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 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

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

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