Hydrazine, 1,2-diphenyl-: Human health tier II assessment

27 November 2014

CAS Number: 122-66-7

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

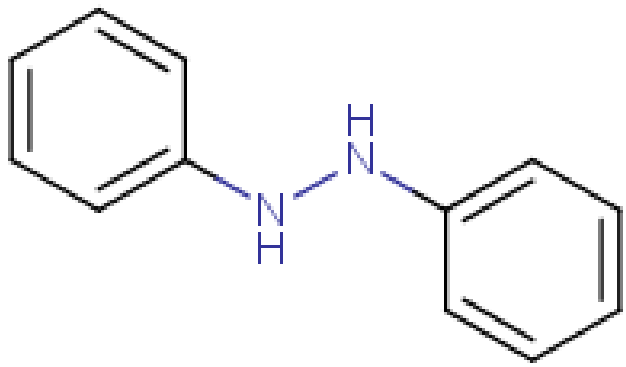
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	hydrazobenzene 1,2-diphenylhydrazine benzene,1,1'-hydrazobis- N,N'-bianiline N,N'-diphenylhydrazine
Structural Formula	
Molecular Formula	C12H12N2
Molecular Weight (g/mol)	184.24
Appearance and Odour (where available)	Colourless crystals
SMILES	c1(NNc2ccccc2)ccccc1

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through Galleria Chemica, the United States Environmental Protection Agency's (US EPA) Aggregated Computer Toxicology Resource (ACToR), the US National Library of Medicine's Hazardous Substances Data Bank (HSDB) and various international assessments (ATSDR 1999; ATSDR 2009).

The chemical has reported commercial uses including as:

- an additive for motor oil;
- a reductant in reclamation of rubber; and

- a composant of photochromic resins.

These uses were described as minor direct uses compared with the intermediate use.

The chemical has reported site-limited use as an intermediate in manufacturing dyes (as a precursor for benzidine).

The chemical has reported non-industrial uses as:

- an intermediate in the manufacture of pharmaceuticals; and
- a desuckering agent for tobacco plants.

Restrictions

Australian

No known restrictions have been identified for the chemical.

International

The chemical is included in the group entry 'Hydrazine (302-01-2), its derivatives and their salts' in the European Union (EU) Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products.

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):

- Xn; R22 (acute toxicity)
- R45 Carc. Cat 2 (carcinogenicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Only limited hazard data are available on acute and repeated dose toxicity, and no hazard data are available on local effects (skin and eye irritation and skin sensitisation), or reproductive and developmental toxicity of the chemical.

Toxicokinetics

The metabolites of the chemical were analysed following administration to Wistar rats using different exposure routes. Following oral administration at 200 or 400 mg/kg bw, the unchanged chemical, benzidine, aniline and two hydroxy derivatives of benzidine were identified in the rats' urine after 24 hours. Following intraperitoneal (i.p.) administration at 100 or 200 mg/kg bw, the unchanged chemical, aniline, benzidine, p-aminophenol and o-

aminophenol were detected in the urine after 24 hours. Only the unchanged chemical and one phenolic compound were detected following intravenous administration at 4 or 8 mg/kg bw. Therefore, it is suggested that the chemical transformation to benzidine takes place in the stomach due to acidity (MAK, 2012; HSDB).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase 'Harmful if swallowed' (Xn; R22) in the HSIS (Safe Work Australia). The available data support this classification.

A median lethal dose (LD50) of 959 mg/kg bw was determined in rats following oral gavage administration of the chemical in a water suspension (ATSDR, 1990).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

No data are available.

Eye Irritation

No data are available.

Sensitisation

Skin Sensitisation

No data are available.

Repeated Dose Toxicity

Oral

The available data indicate that the chemical caused high mortalities in rodents at the doses tested. However, apart from intestinal haemorrhage observed in mice, the causes of these mortalities were not stated in these studies, nor any sublethal effects (NCI, 1978). Therefore, it is not possible to make a conclusion about the repeated dose oral toxicity of the chemical.

In a four-week feeding study, Fischer 344 (F344) rats died at doses higher than ~0.1 % in the diet (approximately 125–130 mg/kg bw/d). No gross compound-related abnormalities or mortalities were reported at 0.03 % (approximately 36 mg/kg bw/day) in males and 0.01 % (approximately 12 mg/kg bw/day) in females (NCI, 1978).

In B6C3F1 mice receiving the chemical for four weeks in the diet, two males and all females died at their highest respective doses of ~0.4 % and 5 % in the diet (approximately 850 and 10000 mg/kg bw/day respectively). Mice that died had experienced intestinal haemorrhages. No gross compound-related abnormalities or deaths were reported at 0.04 % in the diet (approximately 80 mg/kg bw/day) in either sex. No other treatment-related effects were reported. Histopathological examinations of the animals were not performed (NCI, 1978).

In a chronic carcinogenicity study (see **Carcinogenicity**), F344 rats receiving the chemical in the diet up to 0.03 % in males and 0.01 % in females for 78 weeks (15 and 5 mg/kg bw/day respectively) showed no signs of toxicity apart from a significantly high mortality rate in the female rats at the highest dose tested (NCI, 1978).

When B6C3F1 mice were administered the chemical up to 0.04 % in the food for 78 weeks (approximately 60 mg/kg bw/day), no compound-related signs of toxicity were observed apart from a significantly high mortality rate at the highest dose (NCI, 1978).

Approximate conversions of percentages to mg/kg bw/day were based on the European Food Safety Authority measures (EFSA, 2012).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The available data are insufficient to draw a conclusion on the genotoxic potential of the chemical.

Most of the available in vitro tests indicate positive results for genotoxicity with metabolic activation:

- weakly positive results in a bacterial gene mutation assay in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with metabolic activation only (Dunkel et al., 1985, cited in ATSDR, 1990);
- positive results in another bacterial gene mutation assay in *S. typhimurium* with metabolic activation only (Haworth et al., 1983, cited in ATSDR, 1990);
- negative results in a gene mutation assay in *Escherichia coli* WP2uvrA with and without metabolic activation (Dunkel et al., 1985, cited in ATSDR, 1990); and
- positive results with metabolic activation only in a chromosome aberration test and a sister chromatid exchange (SCE) assay which used Chinese hamster ovary (CHO) cells (Galloway et al., 1987, cited in ATSDR, 1990).

Limited in vivo data were available:

- the chemical inhibited testicular DNA synthesis in mice administered a single i.p. dose of the chemical at 100 mg/kg bw (Seiler, 1977, cited in ATSDR, 1990); and
- negative results were obtained in a sex-linked recessive lethal mutation assay in *Drosophila melanogaster* when administered the chemical in feed or by injection (Yoon et al., 1985, cited in ATSDR, 1990).

Carcinogenicity

The chemical is currently classified as a Category 2 carcinogen with the risk phrase ‘May cause cancer’ (T; R45) in the HSIS (Safe Work Australia). The available data support this classification.

The chemical has been 'reasonably anticipated to be a human carcinogen' since 1981 according to the National Toxicology Program (NTP, 2014), based on a rodent study described below (NCI, 1978).

The chemical was administered in the feed of F344 rats and B6C3F1 mice (n = 50/sex/dose) for 78 weeks. The doses administered were 0.008 % and 0.03 % (4 and 15 mg/kg bw/day, respectively) in male rats and 0.004 % and 0.01 % (2 and 5 mg/kg bw/day, respectively) in female rats; 0.008 % and 0.04 % in male mice (12 and 60 mg/kg bw/day, respectively) and 0.004 % and 0.04 % (6 and 60 mg/kg bw/day, respectively) in female mice. Approximate conversions of percentage to mg/kg bw/day were based on EFSA measures (2012). The chemical was considered carcinogenic in F344 rats, causing significantly increased incidence of hepatocellular carcinoma and Zymbal's gland squamous-cell neoplasms in male rats at both doses, and neoplastic nodules of the liver and mammary adenocarcinomas in female rats at the highest dose. The chemical was also considered carcinogenic in female mice (significantly increased hepatocellular carcinomas at the highest dose), but not in male mice (NCI, 1978).

When applied topically to mice at an estimated dose of 63 mg/kg bw/day for 442 days, the chemical induced an increased incidence of tumours (lung and liver adenomas and hemangiomas; a total of 22 % compared with 17 % in the control group) (Pliss, 1974, cited in ATSDR, 1990 and NTP, 2014).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic long-term effects (carcinogenicity); and
- systemic acute effects (acute toxicity from oral exposure).

No data or only limited data are available on most of the other health hazard end points.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the chemical is considered not to pose an unreasonable risk to public health.

Occupational Risk Characterisation

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

Given the carcinogenicity of the chemical, it could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Work Health and Safety

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

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

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

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