Guanidine, N,N'-diphenyl-: Human health tier II assessment

28 June 2013

CAS Number: 102-06-7

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.

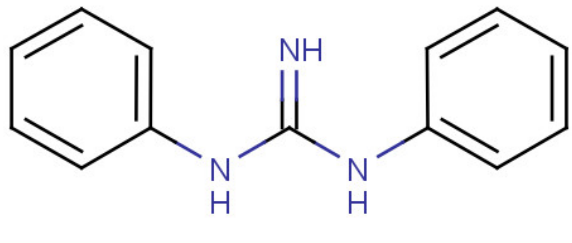
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Diphenyl guanidine 1,3-Diphenylguanidine Guanidine, 1,3-diphenyl-
Structural Formula	
Molecular Formula	C13H13N3
Molecular Weight (g/mol)	211.27
Appearance and Odour (where available)	Solid
SMILES	c1(NC(=N)Nc2ccccc2)ccccc1

Import, Manufacture and Use

Australian

The following Australian industrial use was reported under previous mandatory and/or voluntary calls for information.

The chemical has reported site-limited use including in:

- vulcanising agents.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), Galleria Chemica, Substances in preparations in the Nordic countries (SPIN) database.

The chemical has reported domestic use including in:

- fillers; and
- adhesives and binding agents.

The chemical has reported commercial use including in:

- tyre and general rubber goods production;
- polymer preparations;
- welding and soldering agents; and
- process regulators.

The chemical has reported site-limited use including in:

- vulcanising agents;
- plastics manufacturing; and
- manufacturing of bulk, large scale chemicals (including petroleum products).

Restrictions

Australian

No known restrictions have been identified.

International

The following restrictions have been identified through Galleria Chemica:

- EU Cosmetic Directive 76/768/EEC Annex II: List of substances which must not form part of the composition of cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain—Table 1.

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; R62 Repr. Cat. 3

Xn; R22 (acute toxicity)

Xi; R36/37/38 (irritation).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

A time weighted average (TWA) of 5–10 mg/m^3 in different countries such as USA (California), Canada (Ontario), Spain and Ireland.

Health Hazard Information

Toxicokinetics

The chemical is absorbed rapidly after oral uptake, but only slowly after dermal application. The substance is metabolised quickly and eliminated in the urine and faeces (OECD, 2007).

Acute Toxicity

Oral

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

The median lethal dose (LD50) is 350–460 mg/kg bw in rats (OECD, 2007). The signs of toxicity included reduced appetite and activity, weakness, collapse and death. During gross autopsy, haemorrhagic areas were observed in the lungs. Severe irritation of the gastrointestinal (GI) tract was also reported (OECD, 2007).

Dermal

The chemical is of low acute toxicity via the dermal route.

In an OECD Test Guideline (TG) compliant study, the dermal LD0 (lethal dose 0 % — dose at which no mortalities are expected) was > 2,000 mg/kg bw in rabbits (OECD, 2007). Transient dermal irritation and red discoloration of the pancreas or pancreatic lymph nodes were observed.

Inhalation

No data are available.

Corrosion / Irritation

Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). No data were identified to support or amend this classification.

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). The two available skin irritation studies indicate that the chemical is non-irritating to the skin. However, the acute dermal toxicity study in rabbits indicates that the chemical can cause skin irritation. Therefore, it is not recommended that the existing classification be amended.

In two studies (non-guideline), no skin irritation was observed in rabbits (n = 6) after application of the chemical (500 mg) to both the intact and abraded skin for up to 72 hours under occlusion (OECD, 2007; REACH).

Transient dermal irritation in rabbits was observed in the acute dermal toxicity study (OECD, 2007).

Eye Irritation

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

Three eye irritation studies in rabbits found the chemical to be slightly to moderately irritating with conjunctivitis and marked corneal opacity observed at 24, 48 and 72 hours. Effects were reversible within the observation period, between 7–14 days (OECD, 2007).

Sensitisation

Skin Sensitisation

The chemical is not a skin sensitiser.

Negative results were reported in a guinea pig maximisation test. Fifteeen guinea pigs received intradermal and cutaneous applications of the chemical for 10 days, and were left for 12 days without treatment prior to challenge. A cutaneous challenge was performed using a 25 % concentration (with occlusive dressing). No cutaneous reactions were observed at challenged sites after 24 and 48 hours (OECD, 2007).

Observation in humans

Patients with contact dermatitis (many of whom suffered from rubber intolerance), occasionally reacted positively to the chemical in the patch test. The results were considered to be cross reactions rather than a direct sensitising effect of the chemical (OECD, 2007).

Repeated Dose Toxicity

Oral

Based on the information available, the chemical is not considered to cause serious damage to health from repeated oral exposure.

Rats and mice that consumed feed containing the chemical for 90 days had no histological effects (see below for details). However, some effects indicative of reduced nutrient intake were observed. These were consistent with similar changes observed in other studies of feed restricted rats and mice (OECD, 2007).

In two 90-day feeding studies in rats, an increase in mortality rate at 3000 ppm (181 mg/kg bw/day) and decreased body weight gain (>10%) and food consumption (> 12 %) at 500 ppm (32 mg/kg bw/day) and above were observed. All female rats in the 3000 ppm group died during one study. The no observed adverse effect level (NOAEL) was 150 ppm (11 mg/kg bw/day) in rats, based on decreased body weight gain and food consumption (OECD, 2007; NTP, 1995).

In a 90-day feeding study in mice, decreased body weight gain (> 7 %) was seen at 750 ppm (114 mg/kg bw/day) and above. Decreased body weight gain was considered to be due to the poor palatability of the chemical. No treatment related effects were seen on organs, haematological and clinical chemistry parameters, or urinalysis. A NOAEL of 500 ppm (75 mg/kg bw/day) was determined based on decreased body weight gain and food consumption (OECD, 2007).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the results of in vitro and in vivo genotoxicity studies, the chemical is not considered genotoxic.

The chemical demonstrated negative results in 8/10 Ames tests and in vitro mammalian cell assays (such as gene mutation and cytogenetic assay). An equivocal response was observed in a single Ames test, along with a positive result in a host-mediated mutagenicity assay that was not reproducible (OECD, 2007).

Negative results were reported for in vivo assays, including a rat (oral) bone marrow cytogenetic test at 300 mg/kg bw/day, and a mouse (oral) micronucleus assay up to 3000 ppm (OECD, 2007).

Carcinogenicity

Based on the limited data available, the chemical is not considered a carcinogen.

The chemical was freely administered in the diet at doses of 20, 60, 180 and 540 ppm to groups of male and female C57BLxDB hybrid mice (n = 30 per sex) for 21 months. No neoplastic or non-neoplastic pathological effects attributable to the treatment were observed in any dose group. No further information is available (OECD, 2007).

In another study, C57BLxDB hybrid mice were fed the chemical at 4 or 8 mg/kg bw/day for 32 weeks. At the termination of dosing no tumours were observed. After 16 weeks, 3/50 mice in the low dose group developed lymphatic adenocarcinomas,

while the high dose group and the control group showed no such tumours. Treatment also caused enlarged spleens in all treated mice, but this effect subsided after termination of treatment. No further details are available (REACH).

Reproductive and Developmental Toxicity

The chemical is classified hazardous as a Category 3 substance toxic to reproduction, with the risk phrase 'Possible risk of impaired fertility' (Xn; R62) in HSIS (Safe Work Australia). The available data support this classification.

Mice (ICR) that received the chemical at 0, 0.25, 1, 4 or 10 mg/kg bw/day by gavage on gestation days 0 to 18, showed no maternal toxicity. The mean number of implants was reduced in females receiving the highest dose. There were no treatment related effects on the percentage of dead foetuses, litter size, sex ratio or mean body weight at any dose level (NTP, 1995).

In studies with Syrian golden hamsters and mice (C57BL/J6 x DBA2), the incidence of abnormal sperm was increased after about four weeks of exposure to the chemical in acidified drinking water at 4 or 8 mg/kg bw/day. Mice exposed to the chemical (at both dose levels) for 5 weeks or longer had reduced sperm counts and decreased testis weights. Histopathological observations reported irregular shaped seminiferous tubules with no defined basement membrane, a loss of interstitial cells and decreased spermatids and spematozoa in the tubule lumen (NTP, 1995).

In another study, mice (C57BL/J6 x DBA2) received the chemical in acidified drinking water at 0, 4 or 8 mg/kg bw/day. After five weeks of exposure, significant decreases were observed in fertility indices and the number of implants per pregnant mouse in both dose groups. The number of dead foetuses per pregnancy was also increased significantly (NTP, 1995).

Male and female F344/N rats and B6C3F1 mice were administered the chemical in feed at doses of 250, 500, 750, 1500 or 3000 ppm for 13 weeks. Female rats exhibited uterine hypoplasia and a prolonged reproductive cycle in the 750 ppm group (approx. 49 mg/kg bw/day) and 1500 ppm group (approx. 95 mg/kg bw/day) compared with controls. All female rats in the 3000 ppm group (approx. 181 mg/kg bw/day) died during the study. In male rats, only the 1500 ppm group (approx. 100 mg/kg bw/day), showed diminished sperm motility. Alterations in reproductive organs (e.g. secretory depletion of the prostate gland, hypospermia, reduced spermatogenesis) were occasionally found in male rats at 3000 ppm. In mice, a prolonged reproductive cycle in females and decreased sperm motility in males were observed at 3000 ppm. At these higher concentrations, the effects on reproductive organs could be secondary to malnutrition and exhaustion (OECD, 2007; NTP, 1995).

Male and female SD rats were dosed with the chemical daily by oral gavage (5, 15 or 25 mg/kg bw/day) for four weeks before mating, during mating, gestation and until day five after birth. At 25 mg/kg bw/day, males showed low mean body weight gain over the treatment period and females had low mean food consumption during gestation and lactation. Mean pup body weights on day five of lactation and body weight gains over the lactation period were lower at the highest dose, although there were no treatment-related clinical signs or pup mortality. A NOAEL of 15 mg/kg bw/day for parental toxicity, a no observed effect level (NOEL) of 25 mg/kg bw/day for reproductive performance (mating and fertility) and a developmental NOEL of 15 mg/kg bw/day were reported (REACH).

There were no significant adverse effects on fertility or reproductive performance in male mice (Swiss CD-1) when administered the chemical by gavage prior to mating, at up to 16 mg/kg bw/day for eight weeks (OECD, 2007; NTP, 1995). Females were not dosed with the chemical at any time during the study.

The chemical induced foetotoxicity at maternotoxic doses (50 mg/kg bw/day) in female rats (Charles River COBS CD), which received a single daily gavage dose from days six through 15 of gestation. Foetotoxicity was shown by a significantly reduced mean foetal body weight and by a slight increase in post implantation loss at this dose. The maternal NOAEL was 25 mg/kg bw/day and developmental NOEL was 5 mg/kg bw/day (REACH).

Risk Characterisation

Critical Health Effects

The main critical effects to human health are irritation to the eyes, skin and respiratory system. The chemical is harmful if ingested and has potential reproductive toxicity.

Public Risk Characterisation

Although some domestic uses, such as in fillers, adhesives and binding agents have been identified overseas (use concentrations not available), no Australian domestic uses were reported under the mandatory or volunteer calls for information.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered low if adequate control measures to minimise occupational exposure to the chemical 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 appropriate controls. The existing hazard classification for worker health and safety is considered adequate.

NICNAS Recommendation

Current risk management measures are considered adequate for the protection of public health and workers. No further assessment is required.

Regulatory Control

Public Health

Considering the available information to indicate low public exposure from this chemical no regulatory controls are recommended. However, if new information becomes available, NICNAS may recommend risk management measures for public safety.

Work Health and Safety

The existing hazard classification for worker health and safety is considered appropriate 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	Harmful if swallowed (Xn; R22)*	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	Suspected of damaging fertility - Cat. 2 (H361f)

[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, 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;
- 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.

References

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.nohsc.gov.au/pdf/Standards/approved_criteriaNOHSC1008_2004.pdf

REACH Dossier on 1,3-diphenylguanidine (CAS 102-06-7). Accessed at January 2013 at http://apps.echa.europa.eu/registered/data/dossiers/DISS-9877a14e-89ce-6031-e044-00144f67d031/AGGR-483a2d65-be88-4466-a139-1bbfe6da4f89_DISS-9877a14e-89ce-6031-e044-00144f67d031.html#section_1.1

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

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

National Toxicology Program (NTP) 1995. Technical report on toxicity studies of 1,3-diphenylguanidine (CAS No. 102-06-7) administered in feed to F344/N Rats and B6C3F mice. Assessed January 2013 at http://ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox042.pdf

OECD (2007). SIAR on on Guanidine, 1,3-diphenyl- (102-06-7). Accessed January 2013 at http://webnet.oecd.org/HPV/UI/Search.aspx

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

Substances in Preparations in Nordic Countries (SPIN). Accessed January 2013. http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx

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