Hexane, 1,6-diisocyanato-: Human health tier II assessment

27 November 2014

CAS Number: 822-06-0

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.

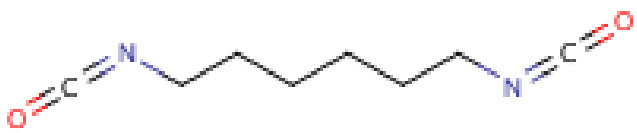
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	hexamethylene diisocyanate 1,6-diisocyanatohexane 1,6-hexanediol diisocyanate isocyanic acid, diester with 1,6-hexanediol
Structural Formula	
Molecular Formula	C8H12N2O2
Molecular Weight (g/mol)	168.2
Appearance and Odour (where available)	Clear, colourless to slightly yellow liquid with sharp, pungent odour
SMILES	C(=O)=NCCCCCCN=C=O

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, Authorisation and Restriction of Chemicals (EU REACH) dossiers; the Organisation for Economic and Co-operative Development Screening Information Dataset Initial Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic Countries (SPIN) database; eChemPortal: the United States (US) Environmental Protection Agency's Aggregated Computational Toxicology resource (ACToR), the Hazardous Substances Data Bank (HSDB), and the European Commission International Uniform Chemical Information Database (EC IUCLID).

The chemical has reported commercial uses including:

- as an industrial adhesive-binding and putty agent;
- as an absorbent and adsorbent; and
- in paints, lacquers and varnishes.

While these formulations are expected to contain the chemical mostly in reactive form, such as in prepolymers, limited amounts of free chemical might be present.

The chemical has reported site-limited use in manufacture of polyurethane products.

Restrictions

Australian

The chemical belongs to the group 'isocyanates' and is listed in the *Poisons Standard* (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) in Schedule 6 with the entry:

'ISOCYANATES, free organic, boiling below 300° C, except in:

(a) viscous polyurethane adhesives; or

(b) viscous polyurethane sealants;

containing not more than 0.7 per cent of free organic isocyanates boiling below 300°C.'

Schedule 6 chemicals are labelled as a ‘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.'

The chemical is listed in the Safe Work Australia, Model Work Health and Safety Regulations, Hazardous chemicals (other than lead) requiring health monitoring (Safe Work Australia, 2011).

International

International restrictions on the chemical include the European Commission Regulation (EU) No. 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food—Annex I: Substances. Restriction imposed at 1 mg/kg in final product expressed as isocyanate moiety.

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 (Acute toxicity);
- Xi; R36/37/38 (Irritation);
- Xi; R42 (Sensitisation); and
- Xn; R43 (Sensitisation).

Exposure Standards

Australian

The chemical has an exposure standard of 0.02 mg/m^3 time weighted average (TWA) and 0.07 mg/m^3 short-term exposure limit (STEL) as isocyanates, all (as -NCO).

International

The following exposure standards are identified (Galleria Chemica):

- An exposure limit (STEL) of 0.02–0.1 mg/m^3 in countries such as Switzerland, the United Kingdom, Hungary, China and Poland.
- An exposure limit (TWA) of 0.02–0.052 mg/m^3 in countries such as Spain, the United Kingdom, Poland, Ireland and China.

Health Hazard Information

Toxicokinetics

There are limited data on the toxicokinetics of the chemical. Isocyanates react rapidly with water to produce the relevant amines and carbon dioxide. Under conditions of long-term systemic exposure, the hydrolysis product hexamethylene diamine is expected to be the main species present.

The uptake of the radiolabelled chemical in the blood from the respiratory tract was immediate and increased linearly during exposure over a range of concentrations in animal studies (OECD, 2001).

In controlled studies in human volunteers, the chemical was rapidly absorbed via the respiratory tract and up to 39 % of the estimated inhaled dose was excreted in the urine (OECD SIDS, 2001). No chemical was detectable in plasma, and a relatively small amount was excreted in faeces and exhaled air.

Acute Toxicity

Oral

The chemical had moderate toxicity in animal tests following oral exposure. The median lethal dose (LD50) in male Wistar rats was 746–959 mg/kg bw. The data warrant a hazard classification.

In an animal study similar to OECD Test Guideline (TG) 401, the chemical was administered to 15 male animals/dose at 105, 263, 525, 788, 1050, 1575 or 2100 mg/kg bw followed by a 14-day observation period. All surviving animals in dose groups 263 mg/kg bw and above showed poor general condition and mild sedation. The LD50 was calculated as 959 mg/kg bw (REACH).

In another acute toxicity study similar to OECD TG 401, the chemical was administered by oral gavage to 20 male albino rats at 263, 525, 1050 or 2100 mg/kg bw followed by a 14-day observation period. All animals from the higher dose groups (1050 and 2100 mg/kg bw) died within four hours after application; survivors showed extreme sluggishness soon after dosing. The LD50 was calculated as 746 mg/kg bw (REACH).

Dermal

The chemical has low acute toxicity based on results from an acute dermal study conducted according to OECD TG 402. The LD50 in Wistar rats is >7000 mg/kg bw. Observed sub-lethal effects included rough hair, crusts, scars and hyperaemia (REACH).

Inhalation

The chemical is currently classified as hazardous with the risk phrase ‘Toxic by inhalation’ (Xn; R23) in the Hazardous Substances Information System (HSIS) (Safe Work Australia). The data available support an amendment to this classification (refer to **Recommendation** section) to reflect the findings reported below.

An acute inhalation toxicity study conducted according to OECD TG 403 reported a median lethal concentration (LC50) of 124 mg/m^3 (equivalent to 0.124 mg/L) for a four-hour exposure in rats (OECD, 2001; REACH). Reported signs of toxicity included bradypnoea, dyspnoea, a laboured breathing pattern, nostrils/muzzle with red encrustations, cyanosis, reduced motility, ungroomed coat, hypothermia, decreased body weights and haemorrhages in the lungs (REACH).

Corrosion / Irritation

Corrosivity

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38), 'Irritating to eyes' (Xi; R36) and 'Irritating to respiratory system' (Xi: R37) in HSIS (Safe Work Australia). The available data suggest that the chemical is corrosive (OECD, 2001) and support an amendment to the existing classifications (refer to **Recommendation** section) to reflect the findings reported below.

Skin effects

In a skin irritation/corrosion study, the chemical was applied under occlusive conditions to the intact skin of New Zealand White rabbits. The chemical produced severe erythema (mean score = 4) and oedema (mean score = 4). The effects were not reversible within the eight-day observation period. The application site was swollen and bloody, and all animals had induration and necrosis up to the last day of observation. While the test was done under occlusive conditions, the effects observed are clearly corrosive (REACH).

Eye effects

In an eye irritation/corrosion study in New Zealand White rabbits conducted according to OECD TG 405, the chemical was found to be highly irritating with conjunctivitis, irritation to the iris, marked-to-dense corneal opacity and chemosis observed at 72 hours and eight days after application. Effects were not reversible within the eight-day observation period and it is reported that all effects worsened during this time. Mean corneal and iris scores for several animals were not obtained as the eyes were completely swollen at 24, 28 and 72 hours into the observation period. It was also reported that damage to the eyes occurred within 30 seconds after application (based on the effects seen in the other eye rinsed with saline 30 seconds after application) (REACH).

Respiratory effects

In the inhalation acute toxicity study (refer **Acute toxicity: Inhalation** section), lung damage was reported with collapsed, dark red lungs suggesting a corrosive effect.

Observation in humans

In an inhalation study with human subjects, eye and respiratory irritation were observed.

Three male volunteers were tested in an inhalation study with short exposure to the chemical at 0.007, 0.035, 0.14 or 0.7 mg/m^3 concentrations. The results showed that the chemical at 0.14 mg/m^3 caused slight eye irritation in two volunteers and at 0.7 mg/m^3 caused eye and throat irritation (REACH).

Sensitisation

Respiratory Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by inhalation’ (Xn; R42) in HSIS (Safe Work Australia).

In a study to examine respiratory sensitisation, eight Dunkin–Hartley Pirbright White female guinea pigs were exposed to a 27.4 mg/m^3 concentration of the chemical for five consecutive days by inhalation for three hours/day. The animals showed increased eosinophilia of the airways and lung-associated lymph nodes, as well as a marked increase in IgG1-antibodies. Bronchiolitis and allergic airway hyper-responsiveness were observed in histopathological investigations following the 28-day recovery period (REACH).

Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (Xn R43) in the HSIS (Safe Work Australia). Skin sensitisation was observed in a mouse lymph node assay, mouse ear swelling test, and in guinea pig maximisation and Buehler tests (IUCLID, 2000; OECD, 2001; REACH). The available data support this classification.

Observation in humans

A range of case reports/workplace studies suggest that the chemical is a skin and respiratory sensitiser in humans (IUCLID 2000; OECD 2001; REACH).

Respiratory sensitisation

In case reports and systematic examinations, workers with occupational exposure to the chemical through spray applications of polyurethane coatings based on prepolymers including the chemical showed clinical asthmatic reactions, bronchial hyper-reactivity, alveolitis, changes in lung functions and occurrence of IgG or IgE antibodies against the chemical bound to human serum albumin (REACH).

Skin sensitisation

Occupational allergic contact dermatitis was observed in six workers from a fabric finish industry undergoing patch testing with 1 % of the chemical dissolved in petrolatum (IUCLID, 2000).

Allergic contact dermatitis was also observed on the hands of a 50 year old non-atopic male car painter using paints containing the chemical. The chemical tested positive with a patch test of 0.1 % and 0.02 % of the chemical dissolved in petrolatum (REACH).

Repeated Dose Toxicity

Oral

In one limited study, the lowest observed adverse effect level (LOAEL) was determined based on the local effect of ulcerative gastritis at 300 mg/kg bw/day (REACH).

In a repeated oral dose study, a 5 % solution of the chemical in peanut oil was administered by gavage for 10 days at a dose level of 300 mg/kg bw/day to six male Albino ChR-CD rats. The animals showed diarrhoea and salivation, and were uncomfortable after most treatments. No clinical signs were observed during the 10 day recovery period. Ulcerative gastritis was observed in rats sacrificed on the tenth day. Following recovery period there were signs of healing gastritis. The LOAEL based on the local effects was 300 mg/kg bw/day (REACH).

Dermal

No data are available.

Inhalation

On repeated inhalation exposure to the chemical the respiratory tract is the target organ with nasal cavity lesions particularly seen. Based on the available data, hazard classification for repeated inhalation toxicity is recommended.

In a two year study according to OECD TG 453, Fischer 344 (F344) rats were exposed to the chemical (60 animals/dose) at concentrations of 0, 0.005, 0.025 or 0.164 ppm (equivalent to 0, 0.035, 0.175, 1.15 mg/m^3) for 6 hours/day for 5 days/week as a vapour. The respiratory tract was the target of the chemical with histopathological changes seen in the nasal cavity and to a lesser extent the lungs. The most significant adverse effect reported was olfactory epithelial degeneration with a no observed adverse effect concentration (NOAEC) of 0.035 mg/m^3 and a lowest observed adverse effect concentration (LOAEC) of 0.175 mg/m^3. Lung lesions included epithelialisation, interstitial pneumonia or macrophage accumulation in alveolar space at 0.175 and 1.15 mg/m^3 in both sexes. However, no clear concentration-response relationship was observed in the lung (OECD, 2001).

In a 90-day study according to OECD TG 413, F344 rats were exposed to the chemical (20 animals/dose) at concentrations of 0, 0.01, 0.04 or 0.14 ppm (equivalent to 0, 0.068, 0.272 or 0.952 mg/m^3) for 6 hours/day for 5 days/week as a vapour. The respiratory tract was the target of the chemical with histopathological changes seen in the anterior nasal cavity. A LOAEC of 0.068 mg/m^3 was determined in both males and females (REACH).

Genotoxicity

The chemical is not genotoxic in both in vitro and in vivo studies.

In vitro studies

In an Ames test, the chemical was tested at 6, 12, 20, 25, 50 or 150 µL per plate for point mutation in *Salmonella typhimurium* strains TA 98, 100, 1535 and 1537, with or without metabolic activation. The chemical had no mutagenic activity in any of the strains tested (REACH, OECD, 2001).

In a mammalian cell gene mutation assay, the chemical was not genotoxic in the Chinese hamster ovary (CHO) cells with or without metabolic activation (REACH; OECD, 2001).

In vivo studies

In a chromosomal aberration assay, 10 CD-1 mice/sex/dose were exposed to 0, 0.14, 0.80 or 1.47 ppm once for six hours. There were no treatment related deaths. Mice exposed to the mid and high doses showed considerable weight loss. However, there was no significant increase in micronucleated polychromatic erythrocytes. Therefore, the chemical showed no clastogenic activity.

Carcinogenicity

The chemical is not carcinogenic.

In a two year study conducted according to OECD TG 453, F344 rats were exposed to the chemical (60 animals/dose) at concentrations of 0, 0.005, 0.025 or 0.164 ppm (equivalent to 0, 0.035, 0.175 or 1.15 mg/m^3) for 6 hours/day for 5 days/week as a vapour (refer **Repeated Dose Toxicity** section for details). No carcinogenic effects were observed in this study up to 1.15 mg/m^3 (OECD 2201, REACH).

Reproductive and Developmental Toxicity

There is no evidence of reproductive or developmental toxicity of the chemical.

In a combined reproductive/developmental/neurotoxicity study (OECD TG 422) with the chemical, Sprague Dawley (SD) rats were exposed whole body to either 0, 0.005, 0.053 or 0.299 ppm (equivalent to 0, 0.034, 0.361 or 2.03 mg/m^3) during the 14-day premating phase, 14-day mating phase and a 21-day gestation phase. Histopathological changes were observed in the nasal cavity at the mid and high doses. No effects on any reproductive/developmental or neurological parameters were observed at any dose level. Therefore, the no observed effect concentration (NOEC) for reproductive/developmental or neurological effects was established at 2.03 mg/m^3 (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include local effects, particularly respiratory and skin sensitisation and eye and respiratory corrosion. Both acute and repeat dose toxicity may arise from the cytotoxic nature of the chemical.

Public Risk Characterisation

The chemical is used industrially to process polymers used in products with potential domestic use (eg. adhesives, binding agents, surface coatings and surface treatment). Inhalation and dermal routes are the likely routes of exposure for the public

through consumer use of products containing the chemical. When completely cured, free isocyanate functional groups are not available for reaction. Articles such as vinyl furniture and those coated with polyurethane lacquer containing the chemical are considered to be completely cured; hence, they are considered non-toxic.

In Australia, the chemical is currently listed on Schedule 6 of the Poisons Standard. Strong warning statements, safety directions and first aid instructions apply to any domestic products containing the chemical. The current controls are considered adequate to minimise the risk to public health posed by any domestic use of this chemical. Therefore, the risk to public health is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation oral, dermal, ocular and inhalation 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 critical systemic acute and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise oral, dermal, ocular and inhalation 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.

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **Recommendation** section).

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemical should be labelled in accordance with state and territory legislation (SUSMP, 2014).

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) Very toxic by inhalation (T+; R26)	Harmful if swallowed - Cat. 4 (H302) Fatal if inhaled - Cat. 1 (H330)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Causes burns (C; R34)	Corrosive to the respiratory tract (AUH071) Causes severe skin burns and eye damage - Cat. 1C (H314)
Sensitisation	May cause sensitisation by inhalation (Xn, R42)* May cause sensitisation by skin contact (Xi; R43)*	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)

[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 could 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 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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