# Isocyanates: Human health tier II assessment

**03 July 2015**



## Chemicals in this assessment

| Chemical Name in the Inventory | CAS Number |
|---|---|
| **Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-** | 2778-42-9 |
| **Benzenesulfonyl isocyanate, 4-methyl-** | 4083-64-1 |
| **Cyclohexane, 2-heptyl-3,4-bis(9-isocyanatononyl)-1-pentyl-** | 68239-06-5 |

## 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

# Grouping Rationale

All the chemicals in this group are related as the toxicology is expected to be dominated by the isocyanate functional groups. Most toxicology data are available on benzene, 1,3-bis(1-isocyanato-1-methylethyl)- (TMXDI; CAS No. 2778-42-9) and assessing these chemicals as a group allows data to be read across from the data rich member. For any endpoint where data are not available for the chemicals in this group, data on methylenediphenyl diisocyanates (MDI) and toluene diisocyanates (TDI) (NICNASa; NICNASb) are also used for read across.

# Import, Manufacture and Use

## Australian

The following Australian industrial use was reported under previous mandatory and/or voluntary calls for information for cyclohexane, 2-heptyl-3,4-bis(9-isocyanatononyl)-1-pentyl- (CAS No. 68239-06-5).

Cyclohexane, 2-heptyl-3,4-bis(9-isocyanatononyl)-1-pentyl- has reported commercial use as a curing compound.

No specific Australian import, manufacture or use information has been identified for TMXDI (CAS No. 2778-42-9) or benzenesulfonyl isocyanate, 4-methyl- (tosyl isocyanate; CAS No. 4083-64-1).

## International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers, Galleria Chemica, the Substances and Preparations in Nordic countries (SPIN)

database, the Organisation for Economic Co-operation and Development High Production Volume chemical program (OECD HPV), the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR) and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

TMXDI and tosyl isocyanate have reported uses which may be domestic, including in:

- adhesives and sealants;
- anti-condensation agents;
- fillers;
- paints, lacquers and varnishes; and
- surface treatments.

TMXDI and tosyl isocyanate have reported commercial uses, including:

- in construction materials;
- in dust-binding agents;
- as process regulators; and
- in manufacturing polyurethane products.

TMXDI and tosyl isocyanate have reported site-limited use as intermediates.

No specific international import, manufacture or use information has been identified for cyclohexane, 2-heptyl-3,4-bis(9-isocyanatononyl)-1-pentyl-.

# Restrictions

## Australian

These chemicals, belonging to the group 'Isocyanates', are listed in the *Poisons standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2015) in Schedule 6 as follows:

'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 with 'Poison'. These are 'Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.' (SUSMP, 2015).

These chemicals, belonging to the group 'Isocyanates', are listed in the Model Work Health and Safety Regulations—Table 14.1: Hazardous chemicals (other than lead) requiring health monitoring (Safe Work Australia, 2014).

## International

TMXDI and tosyl isocyanate are listed on the Switzerland Ordinance of the Federal Department of Home Affairs (FDHA) on articles and materials Annex 6—List of permitted substances for the manufacture of packaging inks, subject to the requirements

set out therein (Galleria Chemica).

Restrictions for these chemicals according to the Switzerland Ordinance of the FDHA Annex 6 are that:

- '...no transfer of these substances to food or food simulants can be detected...'; and
- '...must not be detectable in a migration test in the lowest possible concentration at which a substance may be detected...' (Galleria Chemica).

No international restrictions have been identified for cyclohexane, 2-heptyl-3,4-bis(9-isocyanatononyl)-1-pentyl-.

# Existing Worker Health and Safety Controls

## Hazard Classification

One of the chemicals in this group, tosyl isocyanate (CAS No. 4083-64-1), is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- Xi; R36/37/38 (Irritation)
- Xn; R42 (Sensitisation)

## Exposure Standards

### Australian

The chemicals have exposure standards 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 of 0.02 mg/m$^3$ TWA in Ireland and South Africa, and 0.02–0.07 mg/m$^3$ STEL in Ireland, South Africa and Switzerland as isocyanates.

# Health Hazard Information

## Toxicokinetics

There are no toxicokinetic data available for the chemicals in this group. Tosyl isocyanate reacts rapidly with water to form corresponding carbamic acid, which in turn undergoes immediate decomposition to form carbon dioxide and p-toluenesulfonamide (CAS No. 70-55-3). Following oral exposure to p-toluenesulfonamide, rapid elimination via the urine has been observed (REACHa).

## Acute Toxicity

### Oral

The chemicals in this group are expected to have low acute toxicity following oral exposure.

TMXDI has low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) for TMXDI in Sprague Dawley (SD) rats is >5000 mg/kg bw. Observed sub-lethal effects included soft faeces, wet perianal areas, inactivity, crusty muzzles, diarrhoea, lethargy, piloerection and ataxia (IUCLID, 2005; US EPA, 2009; REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals have been identified as having low acute toxicity in animal tests (NICNASa; NICNASb).

### Dermal

The chemicals in this group are expected to have low acute toxicity following dermal exposure.

TMXDI has low acute toxicity based on results from animal tests following dermal exposure. The LD50 for TMXDI in New Zealand White rabbits is >2000 mg/kg bw. Observed sub-lethal effects included dermal irritation (IUCLID, 2005; US EPA, 2009; REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals have been identified as having low acute toxicity in animal tests (NICNASa; NICNASb).

### Inhalation

The chemicals in this group are considered to be very toxic following inhalation exposure, warranting hazard classification.

In an acute inhalation toxicity study conducted according to OECD Test Guideline (TG) 403, SD rats (five animals/sex/group) were exposed to TMXDI as an aerosol at concentrations of 0, 0.020, 0.053, 0.094 or 0.316 mg/L for four hours. A median lethal concentration (LC50) of 0.027 mg/L was established in this study. Reported signs of toxicity included lethargy, respiratory abnormalities, partial closing of the eyes, peripheral vasodilation, piloerection and salivation (IUCLID, 2005; US EPA, 2009; REACHb).

In a separate acute inhalation toxicity study conducted according to OECD TG 403, English smooth-haired guinea pigs (five animals/sex/group) were exposed to TMXDI as an aerosol at concentrations of 0, 0.195, 0.233, 0.355 or 0.457 mg/L for one hour. An LC50 of 0.24 mg/L (four-hour equivalent of exposure: 0.06 mg/L) was established in this study. Reported signs of toxicity included death, lethargy, gasping/rales, discharge from the eyes, nose or mouth, and collapsed lungs (IUCLID, 2005; US EPA, 2009; REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals are concluded to be toxic and very toxic by inhalation, respectively (NICNASa; NICNASb).

## Corrosion / Irritation

### Respiratory Irritation

Tosyl isocyanate is classified as hazardous with the risk phrase ‘Irritating to respiratory system’ (Xi; R37) in the HSIS (Safe Work Australia). The available data support the extension of this classification to the chemicals in this group.

In a study conducted to assess sensory and pulmonary irritation, four male Swiss Webster mice were exposed to TMXDI as vapour at concentrations of 0.5, 1.1, 1.3 or 2.5 ppm for three hours. The concentration which produced a 50 % decrease in respiratory rate (RD50) was established as 1.7 ppm (approximately 0.017 mg/L). Clinical signs of toxicity included periocular wetness, decreased motor activity and/or an unkempt appearance, which lasted for several days (REACHb).

In the same study, four male SD rats were exposed to TMXDI as vapour at concentrations of 0.56, 0.84, 1.4 or 2.2 ppm for three hours. The RD50 was established as 3.7 ppm (approximately 0.037 mg/L) in the study. Clinical signs of toxicity included ocular

and nasal irritation, audible breathing, subcutaneous red discolouration around the eyes and reddened ears, which lasted for several days (REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals have been identified to cause respiratory irritation (NICNASa; NICNASb).

### Skin Irritation

Tosyl isocyanate is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). The available data support the extension of this classification to the chemicals in this group.

In a dermal irritation study, undiluted TMXDI was applied occlusively to the abraded skin of New Zealand White rabbits (five animals/sex) at a concentration of 2000 mg/kg bw for 24 hours with observation for 14 days. One of 10 animals died on day four after treatment. On day 14, the mean irritation score was 3.9/8. No treatment-related significant effects were observed in post-mortem examinations. The chemical was concluded to be moderately irritating to rabbit skin (REACHb).

In a separate dermal irritation study, 0.5 mL of undiluted TMXDI was applied occlusively to the intact and abraded skin of six male New Zealand White rabbits for 24 hours and observed for 14 days. Erythema and oedema were observed in all animals at 72 hours after treatment. By day six, eschar formation was observed and persisted at all but two sites on one animal until the study was terminated. A primary dermal irritation index of 3.3/8 was established. The chemical was concluded to be moderately irritating to rabbit skin (IUCLID, 2005; US EPA, 2009; REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals have been identified to cause skin irritation (NICNASa; NICNASb).

### Eye Irritation

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

In an eye irritation study, 0.1 mL of TMXDI was instilled into the right eyes of nine rabbits. Six rabbits received no further treatment while three rabbits had their eyes rinsed for 60 seconds, 30 seconds after the chemical was instillation. No corneal damage or iritis was observed in the study. Discharge, chemosis (Draize scores of >3) and conjunctival redness (Draize scores of >2) were observed in the animals. Irritation to the conjunctivae appeared to dissipate but was not fully reversed by day 14 when the study was terminated. The mean overall irritation scores were 15.1/100 and 13.6/100 in animals with and without washout treatment, respectively. The chemical was concluded to be irritating to rabbit eyes (IUCLID, 2005; US EPA, 2009; REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals have been identified to cause eye irritation (NICNASa; NICNASb).

### Observation in humans

In a clinical and immunological evaluation of 96 workers employed at facilities that manufactured or used TMXDI, approximately 40 % of workers experienced some symptoms, mostly upper respiratory or ocular irritation (Grammer et al., 1993; HSDB; REACHb).

## Sensitisation

### Respiratory Sensitisation

Tosyl isocyanate is classified as hazardous with the risk phrase 'May cause sensitisation by inhalation' (Xn; R42) in the HSIS (Safe Work Australia). The available data support the extension of this classification to the chemicals in this group.

In a respiratory sensitisation study, female Hartley guinea pigs (12 treated animals and eight control animals) were exposed to TMXDI as an aerosol at concentrations of 0 or 30 µg/L, three hours/day for five consecutive days. On days 22, 23 and 26 following induction exposure, the animals were challenged with a 20-minute exposure to 15–20 µg/L of guinea pig serum albumin (GPSA) followed by a 20-minute exposure to 15–20 µg/L of TMXDI-GPSA conjugate, with a recovery period of 30 minutes between exposures. Mortalities were observed in 4/12 treated animals. Clinical observations included periocular, perioral and perinasal wetness, respiratory difficulties, diminished motor activity and a greater incidence and degree of alveolar histiocytosis in the lungs. An immediate pulmonary hypersensitivity response was not observed in the study; thus, the chemical was concluded to be non-sensitising (REACHb).

In a range-finding study, 12 female English smooth-haired guinea pigs were exposed to TMXDI by inhalation at a concentration of 36 µg/L, three hours/day for five consecutive days. A number of untreated animals served as the control group. The animals were challenged on days 22, 23 and 26 after induction exposure with a 20-minute inhalation exposure to TMXDI–GPSA conjugate at concentrations of 15–20 µg/L. A topical challenge dose (100 µL of TMXDI) was also applied on day 24 and skin reaction was observed at six, 22 and 46 hours after treatment. Lethargy and nasal and oral discharge were observed in the treated animals. Topical and respiratory challenges did not result in sensitisation responses. The chemical was concluded to be non-sensitising in guinea pigs (IUCLID, 2005; US EPA, 2009; REACHb).

In a separate range-finding study, eight female English smooth-haired guinea pigs were exposed to TMXDI by inhalation at a concentration of 24 µg/L, three hours/day for five consecutive days. A number of untreated animals served as the control group. A topical challenge dose (25 µL of TMXDI) was applied on day eight and skin reaction was assessed at 24 and 48 hours after treatment. Laboured respiration, nasal and oral discharge, and slightly prominent bronchial and cervical lymph nodes were observed in the treated animals. Clear erythema responses were observed after the challenge dose. The RD50 for the chemical was established as >125.5 µg/L (REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals have been identified to cause respiratory sensitisation (NICNASa; NICNASb).

### Skin Sensitisation

Based on the available data, TMXDI is considered to be a skin sensitiser, warranting hazard classification. The available data support the extension of this classification to the chemicals in this group.

In a Buehler test in Hartley guinea pigs (5–10 animals/group), TMXDI was first applied non-occlusively to the intact skin of five animals at concentrations of 0, 0.00625, 0.0125, 0.025, 0.05 or 0.1 % for a primary skin irritation phase. Skin irritation was observed at concentrations of ≥0.025 % at 24 and 48 hours. Based on the result of the irritation phase, 0.36 mol/L of the chemical was applied non-occlusively to the skin of the 10 animals. Challenge and rechallenge applications were performed with the chemical five and 14 days, respectively, after the induction application at concentrations of 0, 0.00625, 0.0125, 0.025, 0.05 or 0.1 %. Dose-dependent enhanced skin reactions were observed at the treated sites. Positive results were seen at the initial challenge, while the response was lower upon rechallenge. The chemical was concluded to be a skin sensitiser in this study (IUCLID, 2005; US EPA, 2009; REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals have been identified as skin sensitisers (NICNASa; NICNASb).

### Observation in humans

In a clinical and immunological evaluation of 96 workers employed at facilities that manufactured or used TMXDI, very low levels of immunoglobulin G (IgG) serum antibodies against the chemical were identified in 7 % of workers, all of whom were highly exposed to the chemical. No work-related asthma was reported (Grammer et al., 1993; HSDB).

## Repeated Dose Toxicity

### Oral

Limited data are available. TMXDI is considered to have low repeated dose toxicity, based on results from an animal test following oral exposure. The effects were not sufficient to warrant hazard classification.

In a combined repeated dose reproductive/developmental toxicity study, SD rats (10 animals/sex/group) were administered TMXDI at concentrations of 0, 15, 150 or 250 mg/kg bw/day by gavage for 19 days (males) or 40–41 days (females). Increased salivation during pre- and post-dosing were observed in the animals at 150 and 250 mg/kg bw/day. Reductions in body weight and food consumption and increased incidences of diarrhoea, diuresis, piloerection, hunched posture and tiptoe gait were observed in the animals at 250 mg/kg bw/day. Piloerection, hunched posture and tiptoe gait were also observed occasionally in the animals at 150 mg/kg bw/day. Isolated incidences of increased salivation during pre- and post-dosing and tiptoe gait were observed in the animals at 15 mg/kg bw/day. Based on these findings, a no observed adverse effect level (NOAEL) of 150 mg/kg bw/day was established for systemic toxicity (IUCLID, 2005; US EPA, 2009; REACHb).

No data are available for MDI. In the NICNAS assessment of TDI, the chemicals were not identified to cause serious health damage by repeated oral exposure (NICNASa; NICNASb).

### Dermal

No data are available for the chemicals in this group.

### Inhalation

Based on the available data, TMXDI is considered to be toxic following repeated inhalation exposure, warranting hazard classification. The available data support the extension of this classification to the chemicals in this group.

In a subchronic inhalation toxicity study conducted according to OECD TG 413, CD-1 mice (10 animals/sex/group) were exposed to TMXDI as vapour at concentrations of 0, 0.4, 0.8 or 1.6 ppm (approximately 0, 0.004, 0.008 or 0.015 mg/L, respectively), six hours/day, five days/week for 13 weeks. The mortality incidences were 5, 20 and 80 % in the animals exposed to 0.4, 0.8 and 1.6 ppm of the chemical, respectively. The exposed animals exhibited nasal cavity lesions including necrosis, ulceration, squamous metaplasia and inflammatory changes. Pulmonary changes including congestion, haemorrhage and in some animals, bronchiolar submucosal fibrosis, were also observed. Respiratory difficulties, reddened ears and paws, blepharospasm and alopecia were observed in animals at 0.8 and 1.6 ppm. Increases in absolute and relative lung weights were observed at all concentrations. A lowest observed adverse effect concentration (LOAEC) of 0.4 ppm (equivalent to 0.004 mg/L) for mice was established in this study (IUCLID, 2005; US EPA, 2009; REACHb).

In the same study, SD rats (10 animals/sex/group) were exposed to TMXDI under similar conditions. The incidence of mortality was 15 % in the animals exposed to 1.6 ppm of the chemical. The exposed animals exhibited nasal cavity lesions including necrosis, ulceration, squamous metaplasia and inflammatory changes. Pulmonary changes including congestion, haemorrhage and in some animals, bronchiolar submucosal fibrosis, were also observed. Respiratory difficulties and reddened ears and paws were observed in animals at 0.8 and 1.6 ppm. Increased mean corpuscular volume and erythrocyte count, and decreased albumin concentration, glucose concentration and urine volume were observed in animals at 0.4, 0.8 and 1.6 ppm. Increases in absolute and relative lung weights were observed at all concentrations. A LOAEC of 0.4 ppm (equivalent to 0.004 mg/L) for rats was established in this study (IUCLID, 2005; US EPA, 2009; REACHb).

In a repeated dose inhalation toxicity study, SD rats (five animals/sex/group) were exposed to TMXDI as an aerosol at concentrations of 0, 0.0005, 0.0015 or 0.005 mg/L, six hours/day, five days/week for four weeks. In the animals exposed to 0.005 mg/L of the chemical, significant increases in serum calcium and phosphorus levels were observed in male rats, while significant increases in relative lung weights were observed in female rats. Subacute/chronic inflammation in the lungs and the appearance of hyperplastic and metaplastic changes in the bronchi were also observed in these animals. A no observed adverse effect concentration (NOAEC) of 0.0015 mg/L was established in this study (IUCLID, 2005; US EPA, 2009; REACHb).

In the NICNAS assessment of MDI, the chemicals have been identified to cause severe effects to the lungs by prolonged exposure through inhalation (NICNASa). In the NICNAS assessment of TDI, systemic toxicity was not identified following repeated inhalation exposure to the chemicals (NICNASb).

### Genotoxicity

No in vivo genotoxicity studies are available for the chemicals in this group. The negative results from the available in vitro studies and data for MDI and TDI indicate that the chemicals in this group are not considered to be genotoxic.

In a bacterial reverse mutation assay conducted according to OECD TG 471, TMXDI was assayed for gene mutation with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 at concentrations of 0.3, 1, 3, 10 or 30 µg/plate in the absence and presence of a rat liver metabolic activation system. Negative findings were reported in this study (IUCLID, 2005; US EPA, 2009; REACHb).

In a mammalian chromosomal aberration study conducted according to OECD TG 473, Chinese hamster ovary (CHO) cells were exposed to TMXDI at concentrations of 0–40 µg/mL in the absence and presence of a rat liver metabolic activation system. The chemical did not induce chromosomal aberration in this study (IUCLID, 2005; US EPA, 2009; REACHb).

A mammalian cell gene mutation study was conducted according to OECD TG 476 in the mouse lymphoma L5178Y cell line (thymidine kinase (tk) locus). The chemical was tested up to a maximum concentration of 12.5 µg/mL in the absence and presence of a rat liver metabolic activation system. The chemical did not induce a toxicologically significant increase in the frequency of mutations in this study (REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals have been identified as non-genotoxic (NICNASa; NICNASb).

### Carcinogenicity

No data are available for the chemicals in this group.

### Reproductive and Developmental Toxicity

Limited data are available. The available data suggest that the chemicals in this group are not reproductive or developmental toxicants based on results from an animal test following oral exposure, and data for MDI and TDI.

In a combined repeated dose reproductive/developmental toxicity study, SD rats (10/sex/group) were administered TMXDI at concentrations of 0, 15, 150 or 250 mg/kg bw/day by gavage throughout maturation, mating, gestation and up to postnatal day (PND) four. The animals were paired within their dose groups after 14 days of treatment to produce litters. The study was terminated on PND five with all surviving animals euthanised and examined macroscopically. Increased salivation, piloerection, hunched posture and tiptoe gait were observed in the animals treated with 150 or 250 mg/kg bw/day of the chemical. At 250 mg/kg bw/day, slight reductions in body weight gain were observed in the males. There were no effects of treatment on fertility, mating performance, pre-coital interval, gestation or parturition length, live birth, litter size, pinna unfolding, surface righting reflex, sex ratio or survival of offspring throughout lactation. No significant histopathological changes were observed in the reproductive organs of adults when the study was terminated. The mean pup weight was significantly decreased on PNDs one and four in the animals at 250 mg/kg bw/day, leading to a decrease in the total mean litter weight compared with controls. Based on this study, a NOAEL of 250 mg/kg bw/day for reproductive and developmental toxicity was established (IUCLID, 2005; US EPA, 2009; REACHb).

In the NICNAS assessments of MDI and TDI, both groups of chemicals are not considered to be specific reproductive or developmental toxins (NICNASa; NICNASb).

## Risk Characterisation

### Critical Health Effects

The critical health effects for risk characterisation include systemic acute and repeated exposure effects (toxicity from inhalation exposure) and local effects (skin sensitisation and respiratory sensitisation). The chemicals can also cause skin, eye and

respiratory irritation.

### Public Risk Characterisation

Cyclohexane, 2-heptyl-3,4-bis(9-isocyanatononyl)-1-pentyl- has reported potential commercial use in Australia as a curing compound. Internationally, the chemicals in this group have reported uses which could possibly be domestic (e.g. as adhesives, fillers, paints, lacquers and varnishes). Inhalation and dermal routes are the likely routes of exposure for the public through consumers using products containing the chemicals.

The chemicals in this group are currently listed on Schedule 6 of the SUSMP. A strong warning statement, first aid instructions and safety directions apply to any domestic products containing the chemicals. The current controls are considered adequate to minimise the risk to public health posed by domestic products containing the chemicals; therefore, the chemicals are not considered to pose an unreasonable risk to public health.

### Occupational Risk Characterisation

During product formulation, 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemicals 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 these chemicals 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 chemicals should be labelled in accordance with state and territory legislation (SUSMP, 2015).

#### Work Health and Safety

The chemicals are 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] |
|---|---|---|

| Hazard | Approved Criteria (HSIS)[a] | GHS Classification (HCIS)[b] |
|---|---|---|
| Acute Toxicity | Very toxic by inhalation (T+; R26) | Fatal if inhaled - Cat. 1 (H330) |
| 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) |
| 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 dermal, ocular and inhalation exposure to the chemicals 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 chemicals are 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 chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemicals, 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

# References

Galleria Chemica. Accessed March 2015 at **http://jr.chemwatch.net/galeria/**

Grammer LC, Shaughnessy MA, Davis RA 1993. Exposure to TMXDI (meta) aliphatic isocyanate and TMI (meta) unsaturated aliphatic isocyanate. Clinical and immunological evaluation of 96 workers. Journal of Occupational Medicine 35(3):287-90.

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed March 2015 at **http://toxnet.nlm.nih.gov**.

International Uniform Chemical Information Database (IUCLID) Dataset 2005. 1,3-bis(1-isocyanato-1-methylethyl)benzene (CAS No. 2778-42-9). Accessed March 2015 at **http://www.epa.gov/hpv/pubs/summaries/isocyani/c13996rr3.pdf**

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (a). Human health Tier II assessment for methylenediphenyl diisocyanates. Australian Government Department of Health and Ageing. Accessed March 2015 at **http://www.nicnas.gov.au**

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (b). Human health Tier II assessment for toluene diisocyanates. Australian Government Department of Health and Ageing. Accessed March 2015 at **http://www.nicnas.gov.au/**

Registration, Evaluation and Authorisation of Chemicals (REACH) Dossier (REACH a). Toluene-4-sulphonamide (CAS No. 70-55-3). Accessed March 2015 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

Registration, Evaluation and Authorisation of Chemicals (REACH) Dossier (REACH b). 1,3-bis(1-isocyanato-1-methylethyl)benzene (CAS No. 2778-42-9). Accessed March 2015 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed March 2015 at **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**.

Safe Work Australia (SWA). Model Work Health and Safety Regulations. Accessed June 2015 at **http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/616/Model-WHS-Regulations-January-2014.pdf**

Substances in Preparations in Nordic Countries (SPIN). Accessed March 2015 at **http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx**

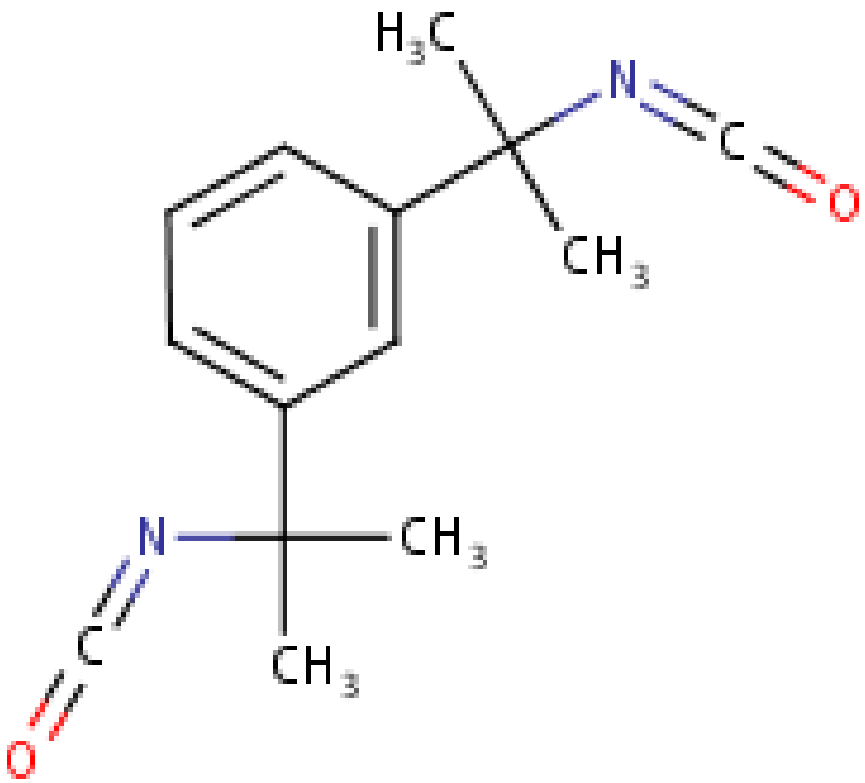
The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2015. Accessed June 2015 at **http://www.comlaw.gov.au/Details/F2015L00128**

US Environmental Protection Agency (US EPA, 2009). Screening level hazard characterization. Isocyanic Acid, m-phenylenediiso-propylidene (CASRN: 2778-42-9). Accessed March 2015 at **http://www.epa.gov/hpvis/hazchar/2778429_Isocyanic%20acid,m-phenylenediisopropylidene_Sept2009.pdf**

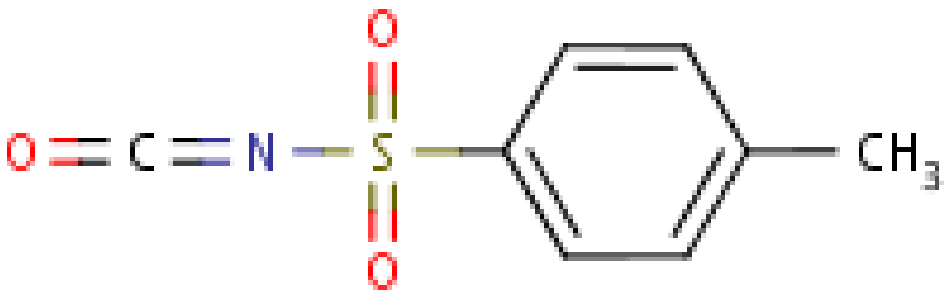
US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR). Accessed March 2015 at **http://actor.epa.gov/actor/faces/ACToRHome.jsp**

Last Update 03 July 2015

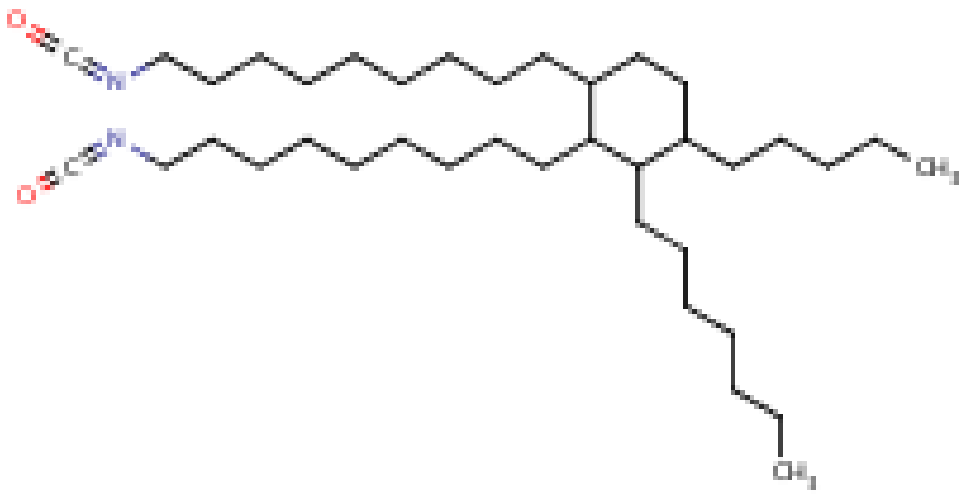
## Chemical Identities

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-**<br>1,3-bis(alpha-isocyanatoisopropyl)benzene<br>alpha,alpha,alpha',alpha'-tetramethyl-m-phenylenedimethylene diisocyanate<br>m-bis(1-isocyanato-1-methylethyl)benzene<br>m-tetramethylxylene diisocyanate (TMXDI)<br>isocyanic acid, m-phenylenediisopropylidene ester |
| CAS Number | 2778-42-9 |
| Structural Formula |  |
| Molecular Formula | C14H16N2O2 |

| | |
|---|---|
| Molecular Weight | 244.29 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Benzenesulfonyl isocyanate, 4-methyl-**<br>p-toluenesulfonyl isocyanate<br>4-isocyanatosulphonyltoluene<br>tosyl isocyanate<br>4-toluene sulfonyl isocyanate |
| CAS Number | 4083-64-1 |
| Structural Formula |  |
| Molecular Formula | C8H7NO3S |
| Molecular Weight | 197.21 |

| | |
|---|---|
| Chemical Name in the Inventory and Synonyms | **Cyclohexane, 2-heptyl-3,4-bis(9-isocyanatononyl)-1-pentyl-**<br>2-heptyl-3,4-bis(9-isocyanatononyl)-1-pentylcyclohexane |
| CAS Number | 68239-06-5 |

| | |
|---|---|
| Structural Formula |  |
| Molecular Formula | C38H70N2O2 |
| Molecular Weight | 586.98 |

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