# Methane, isocyanato-: Human health tier II assessment

**03 July 2015**

## CAS Number: 624-83-9



## 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 | isocyanate, methyl-<br>isocyanic acid, methyl ester<br>iso-cyanatomethane<br>methyl carbonimide |
| Structural Formula |  |
| Molecular Formula | C2H3NO |
| Molecular Weight (g/mol) | 57.05 |
| Appearance and Odour (where available) | Colourless liquid with a sharp, unpleasant odour |
| SMILES | C(=O)=NC |

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

The chemical has reported site-limited use as a chemical intermediate in manufacturing carbamate pesticides, although use as an intermediate in other chemical manufacturing cannot be excluded.

# Restrictions

## Australian

The chemical, belonging to the group 'Isocyanates', is 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).

## International

The chemical is listed on the following (Galleria Chemica):

- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II—Part 1: List of substances which must not form part of the composition of cosmetic products;
- European Union (EU) Regulation (EC) No. 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- EU Cosmetic Directive 76/768/EEC Annex II—List of substances which must not form part of the composition of cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

# 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+; R26 (acute toxicity)
- T; R24/25 (acute toxicity)
- R42/43 (sensitisation)
- Xi; R37/38-41 (irritation)
- Repr. Cat. 3; R63 (reproductive and developmental toxicity)

### 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).

Exposure limits of 0.02–0.05 mg/m$^3$ TWA and 0.02–0.08 mg/m$^3$ STEL in various countries such as Canada, India, Ireland, South Africa, Switzerland and the US.

## Health Hazard Information

Methane, isocyanato- (CAS No. 624-83-9) is a highly reactive, volatile and flammable chemical mainly used to produce carbamate pesticides. The chemical reacts exothermically with water to produce carbon dioxide, methylamine, dimethylurea and/or trimethylbiuret. The reaction is relatively slow below 20 °C, but becomes violent at elevated temperatures or when acids or bases are present.

The chemical was responsible for the Bhopal disaster in India in 1984. Approximately 27 tonnes of the chemical were accidentally released due to water being introduced into a storage tank at the Union Carbide pesticide manufacturing facility. Thousands of people died following exposure to the toxic gas cloud. Debilitating health effects were seen in more than 200,000 survivors of the disaster (OEHHA, 2010).

### Toxicokinetics

Limited toxicokinetic data on the chemical suggest that there is a significant uptake and distribution of the chemical following exposure by inhalation.

Within minutes of exposure by inhalation, the chemical was detected in the venous and arterial blood of mice. Two hours after exposure by inhalation, the chemical was observed at high concentrations in the lungs, foetus, spleen, uterus and kidneys of pregnant mice. Following 24 hours of exposure, the chemical was mainly observed in the lungs, foetus and spleen of these animals. The chemical was eliminated from the blood within three days of exposure (OEHHA, 2010).

## Acute Toxicity

### Oral

The chemical is classified as hazardous with the risk phrase ‘Toxic if swallowed’ (T; R25) in the HSIS (Safe Work Australia). The available data support this classification.

The chemical has high acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) values are 51.5 and 120 mg/kg bw in rats and mice, respectively. Reported signs of toxicity included flaccid paralysis without anaesthesia, somnolence (drowsiness/sleepiness) and respiratory depression (NIOSH, 1994; ChemIDPlus; HSDB; RTECS).

### Dermal

The chemical is classified as hazardous with the risk phrase ‘Toxic in contact with skin’ (T; R24) in the HSIS (Safe Work Australia). The available data partly support this classification.

The chemical has moderate to high acute toxicity based on results from animal tests following dermal exposure. The LD50 values are 220, 1820 and 2780 mg/kg in rabbits, mice and rats, respectively. Reported sign of toxicity included dermatitis (SCOEL, 2006; NIOSH, 2014; ChemIDPlus; HSDB; RTECS).

### Inhalation

The chemical is classified as hazardous with the risk phrase ‘Very toxic by inhalation’ (T+; R26) in the HSIS (Safe Work Australia). The available data support this classification.

The chemical has very high acute toxicity following inhalation exposure based on results from animal tests. The median lethal concentration (LC50) values are 0.014 and 0.028 mg/L in rats and mice, respectively, following six hours of exposure to the chemical as vapour. The LC50 is <0.012 mg/L in guinea pigs following four hours of exposure to the chemical as vapour (US EPA, 2012).

## Corrosion / Irritation

## Corrosivity

The chemical is classified as hazardous with the risk phrases ‘Irritating to skin’ (Xi; R38) and ‘Risk of serious eye damage’ (Xi; R41) in the HSIS (Safe Work Australia). The available data support an amendment to this classification (refer to **Recommendation** section).

Undiluted application of the chemical on intact rabbit skin resulted in necrosis at the site of application. In a separate study, moderate erythema and marked capillary injection were reported following an application of the chemical (10 % solution) to intact rabbit skin. Undiluted application of 1–10 mL/kg of the chemical resulted in oedema, necrosis and haemorrhaging in guinea pigs. In a separate study with guinea pigs, a single application of 25–100 % of the chemical in solution produced increasing dose-dependent erythema reactions (US EPA, 2012; NIOSH, 2014; RTECS).

In a standard Draize test with rabbits, administration of the chemical at 5 µL (concentration not provided) for 24 hours resulted in severe eye irritation. Observed effects included hazy cornea, injected iris, oedema, erythema, constriction of the pupil, conjunctival swelling, corneal injury, complete loss of sight, severe eyelid injury, haemorrhage and necrosis (US EPA, 2012; RTECS).

### Respiratory Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in the HSIS (Safe Work Australia). The available data support an amendment to this classification (refer to **Recommendation** section).

A study was conducted to assess sensory and pulmonary irritation in mice. To assess the sensory irritation properties of the chemical, the animals were exposed to the chemical at concentrations of 0.5–7.6 ppm for 90 minutes. The concentration that causes a 50 % decline in respiratory rate (RD50) for sensory irritation was established as 1.3 ppm based on the observed decreases in the respiratory rate. To assess pulmonary irritation, the animals were first fitted with tracheal catheters, then exposed to the chemical at concentrations of 0.4–7.3 ppm for 90 minutes. Pulmonary irritation in these animals was indicated by decreases in the respiratory rate. The RD50 for pulmonary irritation was established as 1.9 ppm (SCOEL, 2006).

In a separate respiratory irritation study, the RD50 for sensory irritation in mice was established as 2.9 ppm following a 30-minute exposure to the chemical. No further details of the study were provided (SCOEL, 2006).

### Observation in humans

Four human volunteers were exposed to the chemical by inhalation for 1–5 minutes. No effects were observed in the volunteers exposed to the chemical at a concentration of 0.4 ppm. At 2 ppm, no odour was detected, but eye irritation and lacrimation were reported. The symptoms of irritation were more pronounced at 4 ppm, and exposure to the chemical became unbearable at 21 ppm (NIOSH, 1994; SCOEL, 2006; ChemIDPlus; HSDB; RTECS).

In a separate human exposure study, seven volunteers were exposed to the chemical by inhalation at concentrations of 0, 0.3, 1, 2.5 or 5 ppm for approximately one minute. The volunteers experienced eye irritation and lacrimation when exposed to the chemical at 5 ppm for up to 50 seconds, with all effects disappearing within three minutes after exposure (NIOSH, 1994; HSDB).

In the Bhopal disaster, exposure to the chemical resulted in the deaths of thousands of people in the first few days. The cause of death was mainly due to pulmonary oedema, with other deaths due to secondary respiratory infections such as bronchitis and bronchial pneumonia. Other significant health effects reported were respiratory tract irritation, difficulty in breathing, severe visual impairment, and liver and kidney damage. The ground level concentrations of the chemical were estimated to be 0.12–86 ppm, but the toxic gas cloud contained other chemicals such as phosgene and hydrogen chloride. Therefore, it was not possible to delineate the exact cause of the health effects from the disaster (SCOEL, 2006; OEHHA, 2010; US EPA, 2012; HSDB).

## Sensitisation

### Respiratory Sensitisation

The chemical is classified as hazardous with the risk phrase 'May cause sensitisation by inhalation' (R42) in the HSIS (Safe Work Australia). The available data support this classification.

The US EPA (2012) concluded that the chemical is sensitising in guinea pigs. Guinea pigs were exposed to the chemical via inhalation, followed by a challenge exposure via epidermal application or intradermal injection. A sensitisation reaction was reported.

A study was conducted to determine the antibody production specific to the chemical using sera from 99 Bhopal survivors and sera from guinea pigs exposed to the chemical. Low and transient titres of antibodies specific to the chemical of the immunoglobulin (Ig) G, IgM, and IgE classes were detected in 11/99 human subjects, indicating that exposure to the chemical in the Bhopal disaster resulted in immunological responses. The guinea pigs also produced chemical-specific antibodies when tested with guinea pig serum albumin. The findings were concomitant with respiratory effects following exposure to the chemical (Karol & Kamat, 1987).

Although asthma resulting from exposure to the chemical has not been reported, NICNAS assessments of the structurally-related chemicals methylenediphenyl diisocyanates (MDI) and toluene diisocyanates (TDI), have found that both chemicals cause sensitisation from inhalation (NICNASa; NICNASb).

### Skin Sensitisation

The chemical is classified as hazardous with the risk phrase ‘May cause sensitisation by skin contact’ (R43) in the HSIS (Safe Work Australia). The available data support this classification.

The US EPA (2012) concluded that the chemical is sensitising in guinea pigs. In separate studies, guinea pigs were exposed to the chemical via epidermal exposure or intradermal injections, followed by a challenge exposure via epidermal application or intradermal injection. A sensitisation reaction was reported in each study.

In an intradermal sensitisation test, 16 guinea pigs were injected with 0.05 mL of the chemical diluted at 0.01 % in peanut oil, followed by a series of seven 0.1 mL sensitising injections. All animals showed immunological reactions 24–48 hours after receiving the injections (NIOSH, 2014; HSDB).

In a separate skin sensitisation test, five guinea pigs were challenged with nine applications of 5–25 % of the chemical in a solution of acetone and dioxane containing 13 % guinea pig fat on abraded skin during a three-week period. Another five animals received two intradermal injections of 1 % of the chemical in dimethyl phthalate seven days apart. Allergic dermatitis was observed in 9/10 animals, indicating that the chemical was a skin sensitiser in guinea pigs (NIOSH, 2014).

In cross-sensitisation studies, positive reactions were observed in 7/20 guinea pigs that were previously sensitised intradermally with eight applications of the chemical followed by a challenge with intradermal injections of TDI. Similarly, 15/16 guinea pigs that were injected intradermally with TDI, followed by an intradermal challenge with the chemical, showed cross-sensitisation (NIOSH, 2014).

## Repeated Dose Toxicity

### Oral

No data are available.

### Dermal

No data are available.

### Inhalation

The chemical is considered to be toxic following repeated exposure via inhalation exposure, warranting hazard classification.

The following repeated dose toxicity studies for the chemical do not meet the minimum required exposure duration of 28 days according to standard test guidelines. However, the studies are considered sufficient given the high toxicity observed following short-term repeated exposures. The chemical is very toxic (see **Acute toxicity**), highly irritating (see **Irritation**) and a respiratory sensitiser (see **Sensitisation**).

In a repeated dose inhalation toxicity study, Fischer 344 (F344) rats were exposed to the chemical as vapour at concentrations of 0, 1.13 or 2.98/2.79 (males/females) ppm (approximately 0, 0.0026 and 0.007/0.0065 mg/L), six hours/day for four days and observed up to 91 days following exposure. Treatment-related effects such as mortality, respiratory and olfactory epithelial regeneration, inflammation, epithelial erosion and/or fibrosis in the bronchi and bronchioles, alveoli and pulmonary atelectasis (complete or partial collapse of the lung), lymphocytic necrosis of the thymus, and atrophy of the spleen were observed in the animals in the high concentration group. A no observed adverse effect concentration (NOAEC) of 0.0026 mg/L was established in this study (US EPA, 2012; HSDB; RTECS).

In the same study, B6C3F1 mice were exposed to the chemical under the same conditions. Treatment-related effects such as inflammation of the mucosa of the nasal passages, respiratory and olfactory epithelial regenerations, and mural and/or intraluminal fibrosis of the bronchi were observed in the animals in the high concentration group. A NOAEC of 0.0026 mg/L was established in this study (US EPA, 2012; HSDB; RTECS).

In a separate repeated dose inhalation toxicity study, F344 rats (10 animals/sex/group) were exposed to the chemical as vapour at concentrations of 0, 0.15, 0.58 or 3.1 ppm (0, 0.00035, 0.0014 and 0.0072 mg/L), six hours/day for eight days (two four-day exposure periods separated by a two-day non-exposure period). No mortalities were reported in this study. Treatment-related effects including higher incidences of red crust or clear nasal discharge, impaired gait, arched back, significant weight loss, decreased food consumption, significantly increased absolute and relative lung weights and reddening of the lungs were observed in the animals exposed to 0.0072 mg/L of the chemical. Increased haemoglobin concentration and decreased oxygen saturation were also observed in the male rats of the 0.0072 mg/L group. Microscopic findings revealed effects to the lungs and respiratory tracts of the animals exposed to 0.0072 mg/L of the chemical, including increased incidences of rhinitis, epithelial cell degeneration in the olfactory mucosa of the nasal cavities, tracheitis, bronchiolitis, pneumonitis, submucosal fibroplasia in the lungs, reactive hyperplasia of the bronchial lymph nodes and squamous metaplasia in the nasal passages, tracheas and bronchioles. A NOAEC of 0.0014 mg/L was established in this study (US EPA, 2012; HSDB; RTECS).

## Genotoxicity

Based on the available genotoxicity data, the chemical was found to be clastogenic in both in vitro and in vivo tests, although results for germ cell mutation were negative, warranting hazard classification.

***In vitro studies***

In a bacterial reversal mutation assay, the chemical was assayed for gene mutation with *Salmonella typhimurium* (*S. typhimurium*) strains (TA98, TA100, TA1535 and TA1537) at concentrations of 0, 3.3, 10, 33, 100 or 333 µg/plate in the presence of a rat liver metabolic activation system, and 0, 0.3, 1, 3.3, 10, 33 or 100 µg/plate in the absence of a rat liver metabolic activation system. The cytotoxic concentrations were 33 and 333 µg/plate in the absence and presence of the metabolic activation, respectively. Negative findings were reported for this study (US EPA, 2012; HSDB).

In a separate bacterial reversal mutation assay, the chemical was assayed for gene mutation with *S. typhimurium* strains (TA97, TA98, TA100 and TA1535) at concentrations of 0, 3.3, 10, 33, 100 or 333 µg/plate in the presence of a rat liver metabolic activation system and 0, 3.3, 10, 33, 100 or 200 µg/plate in the absence of a rat liver metabolic activation system. The cytotoxic concentration was 100 µg/plate in the absence and presence of the metabolic activation. Negative findings were reported for this study (US EPA, 2012; HSDB).

Mouse lymphoma L5178Y cells were exposed to the chemical at concentrations of 0, 0.5, 0.75, 1, 1.5, 2 or 3 nL/mL in the absence of a rat liver metabolic activation system. The cytotoxic concentration was 3 nL/mL. Genetic mutations were reported at all concentrations tested (US EPA, 2012).

In a sister chromatid exchange (SCE) assay, Chinese hamster ovary (CHO) cells were exposed to the chemical at concentrations of 0, 0.3, 0.9, 3.1 or 9.2 µg/mL in the absence and presence of a rat liver metabolic activation system and 0, 0.7, 1.5, 3 or 6 µg/mL in the absence of a rat liver metabolic activation system. Cells exposed to 6 or 9.2 µg/mL of the chemical were not scored due to toxicity. The chemical induced a concentration-dependent increase in SCEs at 0.9, 3.0 and 3.1 µg/mL in the absence and presence of the metabolic activation (US EPA, 2012; HSDB).

In a cytogenetic assay, CHO cells were exposed to the chemical at concentrations up to 25 or 30.5 µg/mL in the absence or presence of a rat liver metabolic activation system, respectively. Cells exposed to 25 or 30.5 µg/mL of the chemical were not scored for chromosomal aberrations due to cytotoxicity. The chemical induced chromosomal aberrations at all other test concentrations tested (US EPA, 2012; HSDB).

***In vivo studies***

In a cytogenetic assay, male B6C3F1 mice were exposed to the chemical via inhalation at concentrations of 0, 3, 10 or 30 ppm (approximately 0, 0.007, 0.023 and 0.07 mg/L) for two hours. A separate group of male and female B6C3F1 mice were exposed to the chemical at concentrations of 0, 1, 3 or 6 ppm (approximately 0, 0.0023, 0.007 or 0.014 mg/L), six hours/day for four consecutive days. No significant increases in chromosomal aberrations, SCEs or micronuclei were observed in the bone marrow cells of the animals that were exposed to the chemical for two hours. However, these animals showed significant delays in cellular proliferation. Delays in bone marrow cell proliferation were observed in the animals repeatedly exposed to 0.014 mg/L of the chemical and also in males exposed to 0.007 mg/L of the chemical in the four-day exposure treatment. A decreased rate of erythropoiesis and significant increases in chromosomal aberrations and SCEs were also observed in these animals. In males repeatedly exposed to 0.014 mg/L of the chemical, significant increases in micronuclei were observed. The chemical was concluded to induce chromosomal aberrations, SCEs and micronuclei in the four-day exposure study (US EPA, 2012).

In a dominant lethal mutation study, CD-1 mice (30 males/group) were exposed to the chemical as vapour at concentrations of 0, 1 or 3 ppm (approximately 0, 0.00233 and 0.007 mg/L), six hours/day for four consecutive days. The animals were mated with untreated females for eight weeks following final exposure to the chemical. No treatment-related effects were observed and the chemical was concluded to not induce dominant lethal mutations in this study (US EPA, 2012).

Negative findings were reported in a *Drosophila melanogaster* sex-linked recessive lethal mutation assay following administration of the chemical via inhalation (14 ppm), oral (600 µg/mL) or injection (260 or 350 µg/mL) exposure (Shelby et al., 1987; SCOEL, 2006; HSDB).

## Carcinogenicity

Limited data are available on the chemical. The available data are not sufficient to indicate the carcinogenic potential of the chemical.

In a study examining the long-term carcinogenic effects following a single exposure to the chemical, F344 rats and B6C3F1 mice were exposed to the chemical by inhalation at concentrations of 0, 1, 3 or 10 ppm for two hours and observed for up to two years. Male rats exposed to the chemical had marginally increased rates of phaeochromocytomas in the adrenal cortex and adenomas of the pancreatic acinar cells. It is noted that the correlation to exposure is weak and it is unknown if these tumours would progress to malignancies following chronic exposures to the chemical (SCOEL, 2006; US EPA, 2012; HSDB).

## Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 3 substance toxic to reproduction—with the risk phrase ‘Possible risk of harm to the unborn child’ (Repr. Cat. 3; R63) in the HSIS (Safe Work Australia). The available data support this classification.

In a reproductive and developmental toxicity study, Charles Foster rats (five females/group) were exposed to the chemical as vapour at concentrations of 0, 0.212, 0.265 or 0.353 ppm (approximately 0, 0.000495, 0.000618 or 0.000824 mg/L) for 30 minutes and then mated with untreated males. The dams were euthanised on gestational day (GD) 20 and all foetuses were examined for abnormalities. No effects on maternal food and water intake or mortality were observed in the dams. Maternal body weights on GD 20 were decreased in the treated animals. A toxicologically significant increase in total resorption was observed in the group exposed to 0.000824 mg/L of the chemical. In all treated groups, there were reductions in foetal weights, lengths and widths. Gross abnormalities such as everted and inverted claws, blood clot formation, wrinkled skin, kinked tails, wrist drop, knee and shoulder joint defects and clubbed hind limbs were increased in the treated animals. Visceral and skeletal abnormalities were increased in the offspring of the treated animals, including cleft palate, partial or non-ossified skull bones, rib malformations and liver enlargement. While the developmental effects were seen at doses associated with maternal toxicity, the type and level of observed foetal effects indicated developmental toxicity (US EPA, 2012; HSDB).

In a separate reproductive and developmental toxicity study, pregnant CD-1 mice (39–44 females/group) were exposed to the chemical as vapour at concentrations of 0, 1 or 3 ppm (approximately 0, 0.0023 and 0.007 mg/L), six hours/day on GDs 14–17. No maternal toxicity was observed. A statistically significant increase in the number of dead foetuses at birth was observed in both exposure groups. In the 0.007 mg/L group, pup mortality was significantly increased during lactation. No effects on pup body weight were observed. A lowest observed adverse effect concentration (LOAEC) of 0.0023 mg/L was established for this study (SCOEL, 2006; US EPA, 2012; HSDB; RTECS).

Pregnant Swiss Webster mice (11–18 females/treatment group; 24 females/control group) were exposed to the chemical as vapour at concentrations of 0, 2, 6, 9 or 15 ppm (approximately 0, 0.0047, 0.014, 0.021 or 0.035 mg/L) for three hours on GD 8. Increases in total resorption were observed in all exposed groups, and in the groups exposed to 0.021 or 0.035 mg/L of the chemical, the total resorption was >75 %. Decreased foetal and placental weights were observed in all exposed animals that retained pregnancy. Increased incidences of visceral abnormalities and decreased skeletal lengths were observed in the foetuses of the animals exposed to 0.021 or 0.035 mg/L of the chemical. A LOAEC of 0.0047 mg/L for developmental toxicity was established for this study (SCOEL, 2006; US EPA, 2012; HSDB; RTECS).

***Observation in humans***

In several epidemiology studies conducted following exposure to the chemical in the Bhopal disaster, increased spontaneous abortions, stillbirths, pre-term babies born with birth defects and organ defects, and decreased placental and foetal weights were

observed. In a well-controlled study, adolescent males that were exposed to the chemical in the disaster had significantly decreased physical growth. However, it is noted that conclusions were limited given the small number of boys (n = 3) recruited in this study (OEHHA, 2010).

### Other Health Effects

#### Neurotoxicity

Several studies have suggested the potential of the chemical as a neurotoxin. In a study with mice, intraperitoneal (i.p.) injections of the chemical produced an imbalance of both brain and plasma amino acid concentrations, indicating neurotoxic and systemic effects. Several in vitro studies also showed that the chemical was able to affect brain and muscle cells. However, the clinical relevance of this finding was not clear (SCOEL, 2006).

***Observation in humans***

A cognitive function study was conducted on 52 Bhopal survivors one year after the disaster. Subjects who were exposed to high levels of the chemical scored lower values on cognitive tests including motor ability, associate learning, and the Standard Progressive Matrix (SPM), a test that measures the ability to think logically. In a separate study, clinical indications of central, peripheral and vestibular neurological damages and impaired short-term memory were observed in Bhopal survivors. It is noted that in these survivors, calculating the estimated exposure to the chemical was not possible due to confounding factors and other health factors such as depression could have contributed to the symptoms observed (SCOEL, 2006).

## Risk Characterisation

### Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (genotoxicity, reproductive and developmental toxicity), systemic acute effects (acute toxicity from oral, dermal and inhalation exposure) and local effects (skin and respiratory sensitisation; and skin, eye and respiratory irritation). The chemical can also cause harmful effects following repeated inhalation exposure.

### Public Risk Characterisation

Given the uses identified for the chemical as an intermediate in manufacturing other chemicals including carbamate pesticides, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

### 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 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 health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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, 2015).

### 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 | Toxic if swallowed (T; R25)* Toxic in contact with skin (T; R24)* Very toxic by inhalation (T+; R26)* | Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Fatal if inhaled - Cat. 1 (H330) |
| Irritation / Corrosivity | Causes burns (C; R34) | May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335) Causes severe skin burns and eye damage - Cat. 1B (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) |
| Genotoxicity | Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68) | Suspected of causing genetic defects - Cat. 2 (H341) |
| Reproductive and Developmental Toxicity | Repro. Cat 3 - Possible risk of harm to the unborn child (Xn; R63)* | Suspected of damaging the unborn child - Cat. 2 (H361d) |

[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 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.

# References

ChemIDPlus Advanced. Accessed March 2015 at http://chem.sis.nlm.nih.gov/chemidplus/

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

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

Karol MH and Kamat SR 1987. The antibody response to methyl isocyanate: experimental and clinical findings. Bulletin Europeen de Physiopathologie Respiratoire 23(6):591-597.

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/

Office of Environmental Health Hazard Assessment (OEHHA) 2010. Evidence on the developmental and reproductive toxicity of methyl isocyanate. Accessed March 2015 at http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/073010MIC.pdf

Registry of Toxic Effects of Chemical Substances (RTECS). Isocyanic acid, methyl ester (CAS No. 624-83-9), RTECS number: NQ9450000. Accessed March 2015 at http://ccinfoweb2.ccohs.ca/rtecs/records/NQ9450000.html

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

Scientific Committee on Occupational Exposure Limits (SCOEL). Recommendation on occupational exposure limits for methyl isocyanate SCOEL/SUM/118 (September 2006). Accessed March 2015 at http://ec.europa.eu/social/BlobServlet?docId=3875&langId=en

Shelby MD, Allen JW, Caspary WJ, Hawort S, Ivett J, Kligerman A, Luke CA, Mason JM, Myhr B, Tice RR, Valencia R, Zeiger E 1987. Results of in vitro and in vivo genetic toxicity tests on methyl isocyanate. Environmental Health Perspectives 72:183-187.

The National Institute for Occupational Safety and Health (NIOSH) 1994. Methyl isocyanate (624-83-9). Accessed March 2015 at http://www.cdc.gov/niosh/idlh/624839.html

The National Institute for Occupational Safety and Health (NIOSH) 2014. NIOSH Skin Notation (SK) Profiles. Methyl Isocyanate (CAS No. 624-83-9). Accessed March 2015 at http://www.cdc.gov/niosh/docs/2014-145/pdfs/2014-145.pdf

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

US Environmental Protection Agency (US EPA, 2012). Screening-level hazard characterization. Methane, isocyanato- (CASRN: 624-83-9). Accessed March 2015 at http://www.epa.gov/chemrtk/hpvis/hazchar/624839_Methane,isocyanato_HPV1%20HC_Dec%202012.pdf

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

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