Carbamic chloride, dimethyl-: Human health tier II assessment

13 February 2015

CAS Number: 79-44-7

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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

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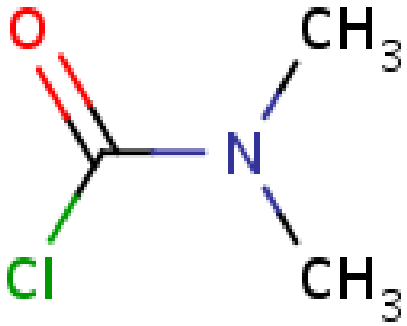
Acronyms & Abbreviations

Chemical Identity

Synonyms	dimethylcarbamoyl chloride dimethylcarbamyl chloride (dimethylamino)carbonyl chloride carbamyl chloride, N,N-dimethyl- N,N-dimethylcarbamic acid chloride
Structural Formula	
Molecular Formula	C3H6ClNO
Molecular Weight (g/mol)	107.5
Appearance and Odour (where available)	Clear, colourless liquid
SMILES	C(=O)(Cl)N(C)C

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 the European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers; Galleria Chemica; the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments including the National Toxicology Program (NTP, 2014) and the International Agency for Research on Cancer (IARC, 1999; IARC, 1976).

The chemical has reported site-limited use as an intermediate in the manufacture of dyes, pharmaceuticals and pesticides.

Restrictions

Australian

No known restrictions have been identified.

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;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products; and
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

The chemical is also listed on the EU REACH Regulation (EC) No 1907/2006 Annex XVII—Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles, as follows: the chemical 'shall not be placed on the market, or used, as substance, as a constituent of other substances, or in mixture, for supply to the general public when the individual concentration in the substance or mixture is equal to or greater than 0.001 %'.

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, Xn; R22 (acute toxicity)
- Xi; R36/37/38 (irritation)
- Carc. Cat 2; R45 (carcinogenicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The chemical has a time weighted average (TWA) exposure standard of 0.005 ppm in Canada, Ireland, Spain and United States of America (USA) (Galleria Chemica).

Health Hazard Information

Toxicokinetics

The chemical was rapidly hydrolysed to dimethylamine, hydrogen chloride (HCl) and carbon dioxide (CO_2) when in contact with water (IARC, 1999).

Acute Toxicity

Oral

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

A median lethal dose (LD50) of 1170 mg/kg bw was reported in rats when the chemical in oil was orally administered. Signs of toxicity were not reported (IARC, 1976).

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Toxic by inhalation’ (T; R23) in the HSIS (Safe Work Australia). The available data support this classification.

A median lethal concentration (LC50) of 180 ppm/6h (0.8 mg/L/6 hours) was reported in rats exposed to the chemical (physical state not available) (HSDB).

Rats could tolerate an atmosphere saturated with the chemical (concentration not stated) at 20°C for eight minutes, to survive 14 days post-exposure. However, all rats (n = 6) exposed for one or two hours died. Reported signs of toxicity included damage to mucous membranes of the nose, throat and lungs and difficulty in breathing (IARC, 1976).

Corrosion / Irritation

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 this classification.

Rats exposed to the chemical exhibited damage to mucous membranes of the nose, throat and lungs and difficulty in breathing (IARC, 1976).

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in the HSIS (Safe Work Australia). The available data suggest a corrosive effect but are not sufficient to recommend an amendment to the classification.

The undiluted chemical produced irritation on rat and rabbit skin, with subsequent degeneration of the epidermis and outer dermal structure (IARC, 1976).

Eye Irritation

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

Conjunctivitis and keratitis were observed in rabbit eyes following application of the chemical (IARC, 1976).

Observation in humans

Eye irritation was observed in workers exposed to the chemical (details not available) (IARC, 1976).

Sensitisation

Skin Sensitisation

Based on the limited information available, the chemical is not considered to be a skin sensitiser.

Skin sensitisation tests conducted with the chemical in guinea pigs gave negative results (details not available) (IARC, 1976).

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available data, the chemical is considered to have genotoxic potential warranting hazard classification.

The chemical is a direct-acting alkylating agent that can react with DNA. It was reported to have a 'wide spectrum of genotoxic activity' (IARC, 1999).

In the following in vitro assays, the chemical induced:

- positive and negative results for gene mutation in different strains of S*almonella typhimurium* (IARC, 1999);
- gene mutations at the *tk* locus in mouse lymphoma L5178Y cells (Jotz & Mitchell, 1981, cited in IARC, 1999);
- positive and negative results in sister chromatid exchange assays in Chinese hamster ovary (CHO) cells (IARC, 1999);
- chromosomal aberrations in CHO cells (Natarajan & Van Kesteren-van Leeuwen, 1981, cited in IARC, 1999), but not in rat liver cells (Dean, 1981, cited in IARC, 1999).

Mixed results were observed in the following in vivo assays:

- induction of micronuclei in ICR mice intraperitoneally (i.p.) injected with a single dose of the chemical at 160 mg/kg bw (Kirkhart, 1981, cited in IARC, 1999) and in B6C3F1 mice treated with two i.p. doses of the chemical at 130 mg/kg bw/day (Salamone et al., 1981, cited in IARC, 1999);
- negative results for induction of micronuclei in CD1 mice treated with two i.p. doses of the chemical at 160 mg/kg bw/day (Tsuchimoto & Matter, 1981, cited in IARC, 1999);
- negative results in a sister chromatid exchange assay in CBA mice treated with a single i.p. dose of the chemical at 100 mg/kg bw/day (Paika et al., 1981, cited in IARC, 1999); and
- induced sex-linked recessive lethal mutations in male *Drosophila melanogaster* injected with the chemical at 10000 ppm (Yoon et al., 1985, cited in IARC, 1999) or 2500 ppm (Foureman et al., 1994, cited in IARC, 1999), but there were no heritable translocations at either dose levels.

Carcinogenicity

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

The IARC has classified the chemical as ‘Probably carcinogenic to humans’ (Group 2A), based on sufficient evidence for carcinogenicity in animal testing. The NTP anticipated the chemical to be a human carcinogen (NTP, 2014).

In a six-week inhalation study, 50 male Sprague Dawley (SD) rats were exposed (whole-body) to 1 ppm of the chemical (4.4 mg/m^3), six hours/day for five days/week (total of 30 exposures). The mortality-corrected incidence of nasal cancers was 12 % and 17 %, after 480 and 600 days of exposure, respectively (Snyder et al., 1986, cited in IARC, 1999).

In a lifetime inhalation study, 100 male Syrian golden hamsters were exposed (whole body) to 1 ppm of the chemical, six hours/day for five days/week. Squamous cell carcinomas of the nasal tract were reported in 51 % of exposed animals, compared with none in the control group (Sellakumar et al., 1980, cited in IARC, 1999).

Female Swiss mice (n = 50) were dermally exposed to 2 mg of the chemical in 0.1 mL of acetone, three times a week for up to 615 days. Most mice developed tumours (32/50) at the site of administration (one papilloma, 27 squamous carcinomas, four keratoacanthomas), 350 days after the first exposure, compared with none in the control group (Van Duuren et al., 1987, cited in IARC, 1999).

When the chemical (in 0.1 mL tricaprylin) was injected subcutaneously at 0.43 mg or 4.3 mg, once a week for 365 days, 9/30 and 22/30 female Swiss mice developed tumours at the site of injection, respectively, compared with 2/30 in one of the control groups (Van Duuren et al., 1987, cited in IARC,

1999).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

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

The chemical can also cause skin, eye and respiratory tract irritation.

Public Risk Characterisation

Given the uses identified for the chemical, 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

Given the critical 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

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)* Toxic by inhalation (T; R23)*	Harmful if swallowed - Cat. 4 (H302) Fatal if inhaled - Cat. 2 (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)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from 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;
- 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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