Carbamic acid, ethyl ester: Human health tier II assessment

13 February 2015

CAS Number: 51-79-6

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.

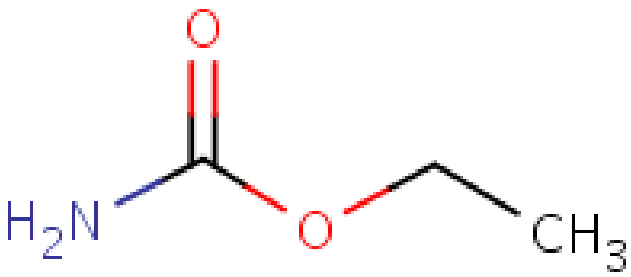
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	urethane ethyl carbamate ethyl urethane leucethane pracarbamine
Structural Formula	
Molecular Formula	C3H7NO2
Molecular Weight (g/mol)	89.1
Appearance and Odour (where available)	Colourless, almost odourless, columnar crystals or white granular powder
SMILES	C(N)(=O)OCC

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 United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments from the National Toxicology Program (NTP, 2014), the International Agency for Research on Cancer (IARC, 1974) and the Scientific Committee on Occupational Exposure Limits (SCOEL, 2012).

The chemical has reported site-limited uses:

- as an intermediate in the preparation of amino resins; and
- in organic synthesis.

The chemical has also reported non-industrial uses including as:

- an active ingredient of therapeutic agents (antineoplastic agent, sclerosing solution, hypnotic, topical bactericide, anaesthetic);
- in veterinary products;
- a solubiliser and co-solvent in manufacturing pesticides and fumigants; and
- a reagent in biochemical research.

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 4 (SUSMP, 2014) as follows: 'URETHANE' (excluding its derivatives) for therapeutic use'.

Schedule 4 chemicals are described as 'Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription' (SUSMP, 2014).

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) Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- EU Registration, Evaluation, Authorization and Restrictions of Chemicals (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 0.1 %'.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrase for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- R45 Carc. Cat 2 (carcinogenicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The chemical has a time weighted average (TWA) exposure limit of 0.002 mg/m^3 in the Netherlands (Galleria Chemica).

Health Hazard Information

Toxicokinetics

The chemical is rapidly metabolised in rats and mice and distributed evenly throughout the body (SCOEL, 2012).

Metabolic activation of the chemical was reported to be necessary for its tumorigenic effects (Hoffler et al., 2003). Two metabolic pathways have been identified through oxidative transformation. These were either by converting to vinyl carbamate and then to vinyl carbamate epoxide (both known to react with DNA); or by converting to ethanol and ammonia (Hoffler et al., 2003). Both pathways lead to carbon dioxide (CO_2) formation (Hoffler et al., 2003), as shown in rodent studies in which 90 % of the radiolabelled chemical was excreted within 24 hours as CO_2 in the expired air, while 6 % remained in the body and a similar amount was excreted in the urine (IARC, 1974; Hoffler et al., 2003). Urinary metabolites were quantitatively similar in rats, rabbits and humans (SCOEL, 2012), including N-hydroxy urethane (0.02–0.15 % of the administered dose), acety1-N-hydroxy urethane (0.1–0.6 %), ethy1 mercapturic acid (0.1–0.2 %), N-acetyl-S-ethoxy carbony1cysteine (0.9–2.1) and the unchanged chemical (0.5–1.7 %) (IARC, 1974).

The chemical was also reported to easily penetrate the placental barrier to have a short-term period of toxic activity (Nomura, 1974).

Acute Toxicity

Oral

The chemical has low to moderate acute oral toxicity in rats and mice.

The median lethal dose (LD50) was reported to be 1809 mg/kg bw for the rat (HSDB; RTECS), and 2500 mg/kg bw for the mouse (NTP, 1996; HSDB; RTECS). Details of these studies were not available.

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Following an overdose with this chemcial used as an anticancer agent, the chemical can cause adverse effects including a reduced number of white blood cells, granulocytes and platelet count, and incomplete bone marrow development (HSDB).

Corrosion / Irritation

Skin Irritation

No data are available.

Eye Irritation

No data are available.

Sensitisation

Skin Sensitisation

No data are available.

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause severe effects from repeated oral exposure to doses below 100 mg/kg bw/day. Although there were some haematological effects observed at 10 and 30 mg/kg bw/day in rats, most of the adverse effects were observed at 100 mg/kg bw/day or above.

In a 13-week study, the chemical at concentrations of 0, 110, 330, 1100, 3300 or 10000 ppm in drinking water was provided ad libitum to Fischer 344 (F344) rats (n = 10/sex/dose). The ppm doses used in this study were calculated as equivalent to 0, 10, 30, 100, 300 and 900 mg/kg bw/day, respectively, using the European Food Safety Authority (EFSA) measures (EFSA, 2012). Seven males and four females at the highest dose and one female at 3300 ppm died before the end of the study. Significant adverse effects observed included lymphoid depletion in both sexes from 1100 ppm and bone marrow cell depletion at 10000 ppm; hepatocellular lesions (fatty changes, foci of alteration) from 3300 ppm in males and females; increased incidence and severity of nephropathy from 1100 ppm in females; and increased incidence (from 330 ppm) and increased severity of cardiomyopathy from 3300 ppm in females and 10000 ppm in males. Relative organ weights were greater in males and females at 1100 ppm than those of controls. The chemical also induced significant and dose-dependent leukopenia (decrease in the number of white blood cells), a secondary effect of lymphopenia (abnormally low level of lymphocytes in the blood), in male and female rats from 330 ppm and 110 ppm, respectively (NTP, 1996).

In a comparable study (NTP, 1996), B6C3F1 mice (n = 10/sex/dose) were administered the chemical in drinking water at doses of 0, 110, 330, 1100, 3300 or 10000 ppm for 13 weeks. The ppm doses used in this study were calculated as equivalent to 0, 16.5, 49.5, 165, 495 and 1500 mg/kg bw/day, respectively, using EFSA measures (EFSA, 2012). All mice treated with 10000 and 3300 ppm died during the study. Significant toxic effects occurred at 1100 ppm or greater in both sexes, including lung inflammation (serofibrinous exudation, macrophage accumulation), lymphoid depletion, nephropathy and cardiopathy. Alveolar epithelial hyperplasia occurred in the lungs of males at 330 and 1100 ppm and females at 1100 ppm (NTP, 1996). Most of the severe adverse effects were reported to be observed at 165 mg/kg bw/day or above.

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

In a clinical trial on patients with leukaemia or other types of somatic cancers, the chemical was administered as an oral treatment at doses of 1–6 g/day for up to 109 days. The common side effects were nausea, vomiting and diarrhoea. Leukopenia was observed in patients with somatic tumours. The observed decrease in white blood cells count was considered as a beneficial effect of the chemical on patients with leukaemia (SCOEL, 2012).

Genotoxicity

The chemical is considered to be genotoxic, warranting hazard classification.

Based on several mutagenicity studies, the NTP concludes that the chemical 'is clearly genotoxic in vitro and in vivo' (NTP, 1996). While both positive and negative results were reported for mutation induction in mammalian germ cells in vivo (NTP, 1996), results discussed under reproductive toxicity (see **Reproductive and developmental toxicity**) suggest the chemical reaches and causes heritable mutations in mice germ cells (Nomura, 1975), with a particular effect on oocytes, thus not detectable in the dominant lethal assay.

The chemical showed positive results in most of the in vitro assays (NTP, 1996). It induced:

- gene mutations in *Salmonella typhimurium* (strains not specified), only with metabolic activation, generally at very high doses (10 mg/plate);
- mixed results for gene conversions in *Saccharomyces cerevisiae*;
- sister chromatid exchanges (SCE) with or without metabolic activation in cultured Chinese hamster ovary cells (CHO) and rat ascite hepatoma cells;
- unscheduled DNA synthesis (UDS) and SCE in human cell cultures, with or without metabolic activation;
- no chromosomal aberrations in CHO cells; and
- no gene mutations in L5178Y mouse lymphoma cells or hamster V79 cells.

In the following in vivo assays (NTP, 1996), the chemical induced:

- micronuclei in erythrocytes of mice after 45 days of exposure to the chemical and in bone marrow cells of mice after 13 weeks of exposure to the chemical in drinking water (details not available);
- micronuclei in cells of rats exposed to 300 mg/kg bw of the chemical (Schlegel & MacGregor, 1984, cited in NTP, 1996) and in mice (details not available);

- SCE in rats, mice and hamsters exposed to 400 mg/kg bw (Sharief et al., 1984, cited in NTP, 1996);
- chromosomal aberrations in cells of mice exposed to intraperitoneal (i.p.) injections of 1000 to 200 mg/kg bw of the chemical (Dean, 1969);
- sex-linked recessive lethal mutations and reciprocal translocations in germ cells of male *Drosophila melanogaster* fed with the chemical (study details not available);
- dose-related increases in spermatogonial cell SCE frequencies of mice (study details not available), however lower than in bone marrow and liver cells (Roberts & Allen, 1980, cited in NTP, 1996);
- significant decreases in testicular DNA synthesis of mice (study details not available); however, the test is reported to give positive results for all types of carcinogens (Seiler, 1977, cited in NTP, 1996);
- no germ cell mutations in male mice administered a single i.p. injection of 1750 mg/kg (Russell et al., 1987, cited in NTP, 1996);
- no sperm-head abnormalities in mice daily exposed to five injections of 1000 mg/kg; and
- no mutations in several dominant lethal tests on mice (details not available).

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 tests. The NTP reported that the chemical is 'reasonably anticipated to be a human carcinogen' (NTP, 2014).

In a two-year study, B6C3F1 mice (n = 48/sex/dose) were administered the chemical in drinking water at doses of 0, 10, 30 or 90 ppm (equivalent to 0, 0.9, 2.7 and 8.1 mg/kg bw/day). Results showed 'clear evidence of carcinogenic activity' (NTP, 2004), based on increased incidences of liver, lung, Harderian gland, skin and forestomach neoplasms, and haemangiosarcomas of the liver and heart in male mice; and increased incidences of liver, lung, Harderian gland, mammary gland and ovarian neoplasms, and haemangiosarcomas of the liver and spleen in female mice. Significant decreases in survival rate were reported for both sexes, especially in female mice with 1/48 survivors in the 90 ppm group compared with 38/48 in the control group (NTP, 2004).

The chemical has been found to be carcinogenic in mice, rats and hamsters via oral, dermal, inhalation, subcutaneous and intraperitoneal exposure according to many studies. It produced lung tumours, lymphomas, hepatomas, melanomas and vascular tumours, and enhanced skin carcinogenesis in mice when given orally and topically (IARC, 1974).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not considered to have reproductive or developmental toxicity. Adverse effects on reproductive parameters or rodent foetus development were only observed at high doses and/or with subcutaneous exposure (which is not a relevant route of exposure for humans).

In the 13-week NTP study (see **Repeat dose toxicity**), the only effect to the reproductive system was a significant decrease in epididymal spermatozoal concentration and motility in male rats that received the chemical in drinking water at 1100 and 3300 ppm (~100 and 300 mg/kg bw/day). Male mice also showed similar effects at 1100 ppm (~165 mg/kg bw/day). Female mice had ovarian atrophy at 1100 ppm, with follicle degeneration at higher doses (NTP, 1996).

Groups of pregnant mice were administered a single subcutaneous (s.c.) injection of the chemical at 1000 or 1500 mg/kg bw on gestation days (GD) 3, 5, 7, 8, 9, 10, 11, 12, 13, 15 or 17. A third group received the chemical once at 500 mg/kg bw on GD 3, 7, 8, 9, 10, 11 or 12. When administered on GD 3, the chemical caused preimplantation loss from 1000 mg/kg bw. Complete resorption of all embryos was observed at 1500 mg/kg bw when administered on GD 7. Organ anomalies (lung and liver) were observed only at the highest dose from GD 8, during the early stage of organogenesis. The incidence of embryonic deaths and malformations was significant only at 1500 mg/kg bw (34–94 %), dropping to zero at 1000 mg/kg bw (Nomura, 1974).

When pregnant mice were treated with a single s.c. injection of the chemical at 1000 mg/kg bw on GD 17, a significant increase of tumours in the offspring was reported. When the male and female offpsring were mated with untreated mice, the F2 generation developed a greater incidence of lung tumours than the control group, suggesting that the chemical had damaged the foetal germ cells of the first offspring and tumours had been transmitted to the next generation (Nomura, 1975). When male and female mice receiving a single s.c. injection of the chemical at 1500 mg/kg bw were mated with untreated mice, malformations (open eyelids, kinky tails, cleft palates and dwarfism) and a significantly higher number of lung tumours were observed in foetuses. The incidence of tumours and malformations was higher in the offspring of treated females than in the offspring of treated males, suggesting damage not only to chromosomes but also to components of oocytes (Nomura, 1975).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity and mutagenicity).

No data are available on local effects of the chemical.

Public Risk Characterisation

Given the industrial uses identified (internationally) 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

During product formulation, oral, dermal and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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]
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)	May cause genetic defects - Cat. 1B (H340)
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 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;
- 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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