Carbamothioic acid, ethyl-, O-(1-methylethyl) ester: Human health tier II assessment

03 July 2015

CAS Number: 141-98-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

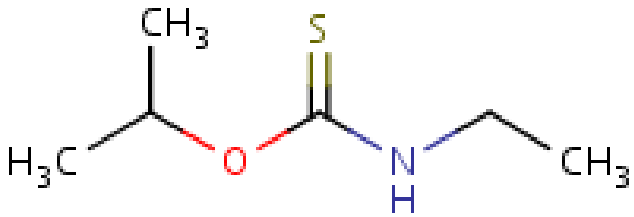
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	o-isopropylethyl thiocarbamate isopropyl ethyl thionocarbamate ethylcarbamothioic acid, O-(1-methylethyl) ester
Structural Formula	
Molecular Formula	C6H13NOS
Molecular Weight (g/mol)	147.241
Appearance and Odour (where available)	Yellow liquid
SMILES	C(=S)(NCC)OC(C)C

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the chemical.

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 and the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemical has reported site-limited use as an ore flotation agent in the mining industry.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

No toxicokinetic data are available on the chemical.

The chemical belongs to the thiocarbamate group. In general, thiocarbamates are absorbed via the skin, mucous membranes, respiratory and gastrointestinal tracts, with rapid elimination via expired air and urine. Thiocarbamates are also rapidly metabolised, producing either mercapturic acid compounds or compounds that enter the carbon metabolic pool (IPCS, 1988).

Acute Toxicity

Oral

The chemical has moderate acute toxicity based on results from animal tests following oral exposure, warranting hazard classification. The median lethal dose (LD50) in rats is 568 mg/kg bw. Observed sub-lethal effects included reduced motility and muscle tone, ataxia, dyspnoea and in one animal treated at 2067 mg/kg bw, necrosis. No details on the site of necrosis were provided (REACH).

Dermal

The chemical has low acute toxicity based on results from animal tests following dermal exposure. The LD50 in rabbits is >2000 mg/kg bw. No details on observed sub-lethal effects were provided (REACH).

Inhalation

The chemical has low acute toxicity based on results from animal tests following inhalation exposure. The limited data provided in this report were not sufficient to warrant hazard classification. The median lethal concentration (LC50) in rats following a four-hour exposure is 20 mg/L. No details on observed sub-lethal effects were provided (REACH).

Corrosion / Irritation

Skin Irritation

The chemical is considered to be a skin irritant following in vitro tests, warranting hazard classification.

In an in vitro skin corrosion test conducted according to the Organisation for Economic Co-operation and Development Test Guideline (OECD TG) 431, the chemical, at a concentration of 95.7 %, was applied topically to a three-dimensional human skin model (EST-1000) for three minutes or one hour. A test chemical is not considered to be corrosive when the cell viability is ≥50 % after a three-minute exposure and ≥15 % after a one-hour exposure. The chemical was concluded to be non-corrosive, as the cell viability was calculated to be 88.4 % and 34 % in the three-minute and one-hour exposure periods, respectively (REACH).

In an in vitro skin irritation test conducted according to OECD TG 439, the chemical, at a concentration of 95.7 %, was applied topically to a three-dimensional human skin model (EST-1000) for 20 minutes. A test chemical is considered to be a skin irritant if the cell viability after exposure and post-treatment incubation is ≤50 %. The chemical was concluded to be a skin irritant as the cell viability was calculated to be 10.2 % following exposure (REACH).

Eye Irritation

Limited data are available. The available data suggest that the chemical is not an eye irritant.

In an eye irritation test conducted according to OECD TG 405, the chemical (concentration not specified) was instilled into one eye each of three Himalayan rabbits. The eyes were rinsed with 20 mL of sodium chloride solution 24 hours after instillation. Grade one corneal opacity (mean score: 0.67), irritation of the iris (mean score: 0.33), conjunctival redness (mean score: 1) and chemosis (mean score: 1) were observed in the animals, with all symptoms fully reversed within 72 hours. The chemical was concluded to be non-irritating to the eyes (REACH).

Sensitisation

Skin Sensitisation

Limited data are available. The available data suggest that the chemical is not a skin sensitiser.

In a local lymph node assay (LLNA) conducted similarly to OECD TG 429 by employing the lymph node cell count and weight method instead of the standard radioactive labelling method to measure cell proliferation, the chemical was applied topically to female NMRI mice (six animals/group) at concentrations of 5, 10 or 25 %. A stimulation index (SI) of 1.4 or above is considered to be a positive response. The SIs for lymph node cell count were 0.971, 1.067 and 1.139, and for lymph node weight were 0.948, 1.172 and 1.103, at concentrations of 5, 10 and 25 %, respectively. The positive control produced expected increases in lymph node cell count and lymph node weight (SIs of 1.838 and 1.431, respectively). The chemical was concluded to be non-sensitising in this study (REACH).

Repeated Dose Toxicity

Oral

Limited data are available. The available data suggest that the chemical has low to moderate repeated dose toxicity, based on results from animal tests following oral exposure. The available information was not sufficient to warrant hazard classification.

In a dose-range finding study, Crl:CD(SD) rats (five animals/sex/group) were administered the chemical at concentrations of 0, 31, 103 or 309 mg/kg bw/day by oral gavage for 14 consecutive days. A 10 % reduction in body weight gain was observed at 309 mg/kg bw/day, while food consumption was decreased by 9 % and 22 % in the 103 and 309 mg/kg bw/day groups, respectively. Signs of toxicity were observed at 309 mg/kg bw/day, including slight ataxia, piloerection, slightly reduced motility and slight to moderate salivation. A no observed effect level (NOEL) of 31 mg/kg bw/day was established in this study (REACH).

Based on the dose-range finding study, a combined repeated dose and reproduction/developmental toxicity study was conducted according to OECD TG 422. In this study, Crl:CD(SD) rats (10 animals/sex/group) were administered the chemical at concentrations of 0, 30, 100 or 300 mg/kg bw/day by oral gavage, daily for two weeks before mating up until the day of euthanasia in males (a minimum of 28 days) or up to at least gestation day (GD) three in females. A no observed adverse effect level (NOAEL) of 30 mg/kg bw/day for repeated dose toxicity was established in this study. No details on the toxicity effects were provided (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Only in vitro genotoxicity data are available for the chemical. Based on the available in vitro data, the chemical is not expected to be genotoxic.

In a bacterial reverse mutation assay conducted according to OECD TG 471 in five *Salmonella typhimurium* strains (TA98, TA100, TA102, TA1535 and TA1537), the chemical was tested at concentrations of 10, 26, 103, 257, 1029 or 2571 µg/plate in the absence and presence of a rat liver metabolic activation system. The chemical did not induce mutagenic effects at any concentration tested (REACH).

In a mammalian cell gene mutation test conducted according to OECD TG 476, the chemical was tested up to cytotoxic concentrations (concentrations not specified) in Chinese hamster lung fibroblasts (V79), in the absence and presence of a rat liver metabolic activation system. The chemical did not result in mutagenic effects in this study (REACH).

In a mammalian chromosome aberration test conducted according to OECD TG 473 in human peripheral lymphocytes, the chemical was tested at concentrations of 10, 26, 103, 257, 1029 or 2571 µg/mL in the absence and presence of a rat liver metabolic activation system for 24 and four hours, respectively. The chemical did not result in an increase in chromosomal aberrations (REACH).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Limited data are available. Based on the available data, the chemical is expected to be a reproductive toxicant, warranting hazard classification.

In a combined repeated dose and reproduction/developmental toxicity study conducted according to OECD TG 422, Crl:CD(SD) rats (10 animals/sex/group) were administered the chemical at concentrations of 0, 30, 100 or 300 mg/kg bw/day by oral gavage, daily for two weeks before mating until the day of euthanasia in males (a minimum of 28 days) or up to at least gestation day (GD) three in females. The chemical resulted in significant increases in post-implantation loss in all treated animals (3.6, 26.9, 96.4 and 100 % at 0, 30, 100 and 300 mg/kg bw/day, respectively). The effects did not appear to correlate with parental toxicity. No further details were provided. A lowest observed adverse effect level (LOAEL) of 30 mg/kg bw/day for developmental toxicity was established in this study (REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include a systemic long-term effect (reproductive toxicity), a systemic acute effect (acute toxicity from oral exposure) and a local effect (skin irritation).

Public Risk Characterisation

Given that there are no consumer 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

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

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)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Irritating to skin (Xi; R38)	Causes skin irritation - Cat. 2 (H315)
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 oral and dermal 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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