Ethanethioamide: Human health tier II assessment

27 November 2014

CAS Number: 62-55-5

Preface

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

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

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

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

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

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

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

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

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Thioacetamide Acetothioamide TAA
Structural Formula	 Structural formula of Ethanethioamide
Molecular Formula	C2H5NS
Molecular Weight (g/mol)	75.13
Appearance and Odour (where available)	White crystalline solid, or colourless leaflets, with a slight odour of mercaptans.
SMILES	C(C)(N)=S

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 European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the International Agency for Research on Cancer (IARC) monographs; the United States National Toxicology Program (US NTP) 12th Report on Carcinogens (RoC); Galleria Chemica; the Substances and Preparations in the Nordic countries (SPIN) database; and eChemPortal data sources including the US National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported commercial use including as:

- an organic solvent in the leather, textile and paper industries; and
- a stabiliser in motor fuel containing tetraethyl lead.

The chemical has reported site-limited use including:

- in manufacturing pharmaceuticals;
- an accelerator in the vulcanisation of synthetic polybutadiene rubber; and
- as a laboratory chemical.

While the commercial uses listed above have been reported, these appear to be historical uses. The US NTP has stated that there is no evidence that the chemical is currently being used for these purposes (NTP RoC, 2011). The chemical is registered under the REACH legislation for 'intermediate use only' (REACH).

Restrictions

Australian

No known restrictions have been identified.

International

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

- 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
- Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

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):

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

Exposure Standards

Australian

No specific exposure standards are available.

Guidance on the interpretation of workplace exposure standards for airborne contaminants advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia, 2013).

International

No specific exposure standards have been identified.

Health Hazard Information

Toxicokinetics

Following oral administration (through the diet) of the radiolabelled chemical to male albino rats, radioactivity was found in the liver (highest levels detected), kidneys and adrenal gland (IARC, 1974). The majority of the chemical metabolised to acetate within 24 hours, with less than 1 % excreted unchanged in the urine. The IARC monograph indicates that the chemical could metabolise in vivo to acetamide, which is then hydrolysed to acetate. Thioacetamide-S-oxide has been identified as an intermediate (Arni, 1989). Results from tissue analysis reportedly found the liver to be three times more active than the kidney in converting the chemical to acetamide.

Acute Toxicity

Oral

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

The oral median lethal dose (LD50) was reported to be 301 mg/kg bw in rats (HSDB; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). No data are available to evaluate this classification.

Eye Irritation

The chemical is classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). No data are available to evaluate this classification.

Sensitisation

Skin Sensitisation

No data are available.

Repeated Dose Toxicity

Oral

Limited data are available to evaluate the non-cancer effects of the chemical. Cirrhosis of the liver and histopathologicial changes in the biliary system have been observed in repeated dose studies in rats and mice examining carcinogenicity (refer **Carcinogenicity** section). Effects in the biliary system were observed in rats following an 11-week exposure to the chemical in the diet at a concentration of 0.032 % (IARC, 1974).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemical is considered to be genotoxic. Most of the data obtained from experiments in vitro revealed negative results; positive results have been described below. The chemical has been demonstrated to exert a genotoxic effect in vivo in somatic cells (Arni, 1989). Classification is considered warranted (refer **Recommendation** section).

The chemical was negative in several strains of *Salmonella typhimurium* in the presence and absence of metabolic activation. Positive results were observed in strains TA100 and TA1535 with a liquid incubation system and in a forward mutation assay with *S. typhimurium.* The potential metabolite, thioacetamide-S-oxide, induced weak mutagenic effects in *S. typhimurium* strain TA100 in the absence of metabolic activation.

The chemical was positive in several in vitro assays. The chemical induced:

- mutants in the L5178Y/TK ± mouse lymphoma assay with effects reduced in the presence of activation;
- gene conversion and mitochondrial mutation in *Saccharomyces cerevisiae* (absence of activation);
- cell transformation in hamster and rat embryo cells;
- polyploidy in human liver cells (absence of activation); and
- chromosome bridges and acentric chromosome fragments in monkey kidney cells (absence of activation).

The chemical was also positive in an alkaline elution assay with rat hepatocytes (at high concentrations).

In vivo, the chemical has been shown to bind DNA in newborn mice but not adult mice and rats. An increase in the formation of chromosome bridges and acentric chromosome fragments were observed in the livers of rats treated orally or by intraperitoneal (i.p.) injections. The chemical and its potential metabolite, thioacetamide-S-oxide, were positive in the mouse micronucleus test with the metabolite reported to be the more active. Equivocal results have been observed in a *Drosophila melanogaster* recessive lethal test.

Carcinogenicity

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

Liver cancer (hepatocellular carcinoma) in rats and mice (of both sexes) and tumours of the bile duct (cholangiocellular tumours) in rats have been observed in long-term feeding studies (47 weeks to 18 months). Tumours were not observed in a 30-week study in hamsters (IARC, 1974; NTP RoC, 2011).

The International Agency for Research on Cancer (IARC) has classified the chemical as a Group 2B carcinogen: ‘Possibly carcinogenic to humans’ (IARC, 1974), while the US NTP has classified the chemical as 'Reasonably anticipated to be a human carcinogen' (NTP RoC, 2011).

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). A genotoxic mode of action cannot be excluded. The chemical could also cause skin and eye irritation and harmful effects following a single oral exposure.

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

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 may pose an unreasonable risk to workers unless adequate control measures to minimise exposure to the chemical 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 appropriate controls.

Guidance on the interpretation of workplace exposure standards for airborne contaminants advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia, 2013).

The data available support an amendment to the hazard classification in HSIS (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 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 hazards 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 eyes (Xi; R36)* Irritating to skin (Xi; R38)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)	Suspected of causing genetic defects - Cat. 2 (H341)
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 consumers

Products containing the chemical should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from oral, demal, 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 assist with meeting 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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Last update 27 November 2014