Ethane, 1,1,1,2-tetrachloro-: Human health tier II assessment

13 February 2015

CAS Number: 630-20-6

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

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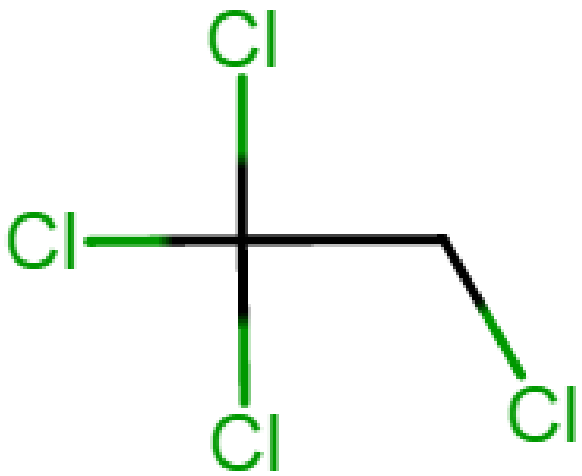
Acronyms & Abbreviations

Chemical Identity

Synonyms	1,1,1,2-Tetrachloroethane asym-tetrachloroethane
Structural Formula	
Molecular Formula	C2H2Cl4
Molecular Weight (g/mol)	167.85
Appearance and Odour (where available)	Colourless liquid solvent with a sweet odour
SMILES	C(Cl)(Cl)(Cl)CCl

Import, Manufacture and Use

Australian

The National Pollutant Inventory (NPI) holds data for all sources of the chemical in Australia.

The chemical has reported site-limited use as a solvent in producing wood stains and varnishes.

International

The following international uses have been identified through Galleria Chemica; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (International Agency for Research on Cancer (IARC) and National Toxicology Program (NTP)).

The chemical has reported site-limited uses including:

- as a feedstock or chemical intermediate in manufacturing trichloroethylene, tetrachloroethylene, and 1,2-dichloroethylene;
- as a solvent in manufacturing bleaches, paints removers and varnishes; and
- for cleaning and degreasing metals.

The chemical has reported non-industrial uses including in insecticides, herbicides and soil fumigants.

Restrictions

Australian

This chemical (tetrachloroethane) is listed in Schedule 7 of the *Poisons Standard—The Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2014).

Schedule 7 chemicals are labelled with 'Dangerous Poison'. These are 'substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply' (SUSMP, 2014).

International

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

- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’).

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

The following exposure standards are identified (Galleria Chemica).

Time weighted average (TWA):

- 5 mg/m^3 in Latvia.

Health Hazard Information

Toxicokinetics

The chemical can be absorbed following oral, dermal and inhalation exposure. The blood to air partition coefficient for humans and rats was estimated to be 30 and 42, respectively, indicating respiratory uptake under equilibrium conditions. Empirical regression models predicted the tissue to air partition coefficients in humans to range from 1.4 (kidneys) to 56 (fat), suggesting that the chemical is widely distributed to tissues following systemic delivery (IARC, 2014).

Rats and mice were orally administered the chemical at doses of 25 or 200 mg/kg bw/day and 100 or 400 mg/kg bw/day, respectively for four weeks. After 48 hours, the administered dose was eliminated as urinary metabolites (60 % in rats, 77 % in mice), unchanged in exhaled air, and as carbon dioxide (1 % in rats, 2 % in mice). The identified urinary metabolites in rats, mice, rabbits and guinea pigs were trichloroethanol (major) and trichloroacetic acid (minor). In the absence of oxygen, reductive metabolism in rat liver produced the minor metabolites 1,1-dichloroethylene and 1,1,2-trichloroethane (IARC, 2014; HSDB).

Acute Toxicity

Oral

The chemical has moderate acute oral toxicity in animal studies and warrants hazard classification.

The reported oral median lethal dose (LD50) values were 670–800 mg/kg bw in rats and 1500 mg/kg bw in mice. No compound-related, gross pathological effects were observed (NTP, 1983; HSDB).

In an acute oral study, rabbits were exposed to the chemical at a dose of 500 mg/kg for 24 hours. Elevated enzyme activities, blood cholesterol and total lipid levels were reported at 72 hours after exposure (HSDB).

Dermal

No data are available.

Inhalation

The chemical has moderate acute inhalation toxicity in animal studies and warrants hazard classification.

The median lethal concentration (LC50) was 2500 mg/m^3 in rats and rabbits following four hours exposure to the chemical vapour (HSDB).

Corrosion / Irritation

Skin Irritation

No data are available.

The chemical was reported to be slightly irritating to rabbit skin following dermal exposure (HSDB).

Eye Irritation

No data are available.

The chemical was reported to be slightly irritating to the ocular mucous membranes in rabbits (HSDB).

Sensitisation

Skin Sensitisation

There is an alert for protein binding using the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure Activity Relationship (QSAR) application toolbox for nucleophilic substitution to alkyl halides. The electron-deficient carbon attracts nucleophiles and reacts with proteins via substitution by a protein amino group on the carbon, with subsequent displacement of the halide ion (Roberts et al., 2007). However, current information is inadequate to classify the chemical as a skin sensitiser.

QSAR modelling using OASIS–TIMES resulted in negative predictions, although the prediction was out of the total domain of the model.

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause severe health effects following repeated oral exposure. The tumour-related observations are discussed under **Carcinogenicity**.

In a two-year combined chronic/carcinogenicity study conducted by the National Toxicology Program (NTP), rats and mice (n = 50/sex/dose) were administered the chemical in corn oil at 0, 125 or 250 mg/kg bw/day; and 0, 250 or 500 mg/kg bw/day, respectively. At the highest dose levels, central nervous system (CNS) effects (weakness, inactivity and loss of coordination) were observed in rats from week 44, and in mice from week 34. Cumulative toxicity resulted in a significantly reduced survival rate for male rats and male and female mice, the latter being moribund after 65 weeks. Other effects observed in the high-dosed animals included renal lesions (papillary mineralisation, accumulation of crystals in the tubule lumen) in male rats, and depressed mean body weights in mice. Liver lesions (inflammation, necrosis, fatty metamorphosis) were observed at an increased incidence in mice administered with high doses from week 51 (NTP, 1983; IARC, 2014). The lowest observed adverse effect level (LOAEL) was considered to be 125 mg/kg bw/day in rats (US EPA, 1987).

In a short-term renal toxicity study conducted by the NTP, male F344 rats (n = 5) were administered the chemical in corn oil at doses of 0.62 or 1.24 mmol/kg bw/day (104 or 208 mg/kg bw/day), daily for 21 days. Hyaline droplet nephropathy, consistent with the male rat-specific a2µ–globulin nephropathy was observed at the high dose, and an increase in the renal tubule cell labelling index indicated replicative DNA synthesis (NTP, 1996).

In a repeated dose oral toxicity study, Wistar rats were administered the chemical at 300 mg/kg bw/day, five days/week for 10 months. Hepatotoxic effects (steatosis, increased triglycerides and decreased liver enzyme activities) were only observed in the females (HSDB).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Limited data are available that indicate there are effects on humans following exposure to the chemical.

A high percentage of large mononuclear cells were detected in patients' blood that were suffering from the early stages of poisoning (stated to be from tetrachloroethane). Other effects reported were lethargy, slight nausea, headaches, and gastric symptoms including a lack of appetite (HSDB).

The CNS effects (headaches, vertigo, nervousness, tremors) were reported in factory workers in India (n = 380) exposed to the chemical via inhalation (dose not stated), when using it as a cleaning agent. A dose-related increase in the incidence of tremors was reported (in 14 % of the workers exposed to 9–17 ppm and 50 % exposed to 65–98 ppm) (HSDB).

Genotoxicity

Based on the weight of evidence from the available data, the chemical is not considered to be genotoxic. Limited evidence of in vivo DNA binding is available.

The chemical gave mixed results in several in vitro assays (IARC, 2014; HSDB):

- negative results in most bacterial reverse mutation assays with *Salmonella typhimurium* strains up to 1000 µg/plate, with or without metabolic activation;
- not mutagenic in *Saccharomyces cerevisiae*, but elicited high levels of respiratory deficiency in the assay, indicating anti-mitochondrial activity;
- positive results in L5178Y mouse lymphoma cell forward mutation assay only with metabolic activation;
- no induction of chromosomal aberrations in Chinese hamster ovary (CHO) and Chinese hamster lung (CHL) fibroblast cells, but induced sister chromatid exchanges in CHO cells and aneuploidy in CHL cells with no metabolic activation; and
- negative results in BALB/c-3T3 cell transformation assays.

In one in vivo study, male Wistar rats and BALB/c mice received a single intraperitoneal (i.p.) injection of the chemical at ~1 mg/kg bw. After 22 hours, binding of the chemical to DNA, ribonucleic acid (RNA) and protein in the liver, lungs, kidneys and stomach were observed. The covalent binding index (CBI) for liver DNAs was calculated to be 40 (rat) and 82 (mouse), classifying the chemical as a weak to moderate initiator. When the study was further evaluated in vitro, the microsomal and cytosolic fractions from rat organs were found to bio-activate the chemical (IARC, 2014; HSDB).

The chemical did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (IARC, 2014).

Carcinogenicity

Based on the available animal data, the chemical is considered to be carcinogenic, warranting hazard classification.

IARC (2014) classified the chemical as 'possibly carcinogenic to humans (Group 2B)'. IARC (2014) concluded that 'There is *inadequate evidence* in humans for the carcinogenicity of 1,1,1,2-tetrachloroethane. There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,1,1,2-tetrachloroethane'.

In a carcinogenicity study, groups of B6C3F1 mice (n = 50/sex/dose) were administered (gavage) the chemical in corn oil at doses of 0, 250 or 500 mg/kg bw/day, five days/week for 103 weeks. Mice receiving the highest dose were euthanised after week 65 of exposure due to CNS effects (see **Repeat dose toxicity: Oral**). A statistically significant treatment-related increase in the incidence of hepatocellular adenomas was observed in both sexes, and an increase in hepatocellular carcinoma was seen in female mice (IARC, 2014).

In the same study, groups of Fischer 344 (F344) rats (n = 50/sex/dose) were administered the chemical in corn oil at doses of 0, 125 or 250 mg/kg bw/day, five days/week for 103 weeks. A marginal increase in liver neoplastic nodules or hepatocellular carcinoma (combined) was observed in male rats. A statistically significant increase in the incidence of mammary gland fibroadenomas was observed in female rats at the low dose (125 mg/kg bw/day). At the high dose, rare tumours that included renal tubular cell adenomas (male and female) and transitional cell papilloma of the bladder (males) were observed. Furthermore, six male rats (3/50 at the low dose and 3/48 at the high dose) developed 'uncommon mesotheliomas of the tunica vaginalis or the peritoneum' (IARC, 2014).

In an initiation–promotion assay, the chemical was evaluated for its potential to promote ?-glutamyltranspeptidase-positive foci in rat liver. Male rats (n = 10) were i.p. injected with a single dose of the chemical at 30 mg/kg bw, 24 hours after partial hepatectomy. After one week, the rats were administered the chemical (gavage) at the maximum tolerated dose in corn oil, five days/week for seven weeks. The chemical did not cause any initiating or promoting activity (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
- systemic acute effects through oral and inhalation exposure.

No data are available on dermal toxicity or reproductive and developmental toxicity of the chemical.

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, exposure might occur, particularly where manual or open processes are used. 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 and acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended 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 by inhalation (Xn; R20)	Harmful if swallowed - Cat. 4 (H302) Harmful if inhaled - Cat. 4 (H332)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)	Suspected of causing cancer - Cat. 2 (H351)

[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 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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