Ethane, pentachloro-: Human health tier II assessment

27 November 2014

CAS Number: 76-01-7

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.

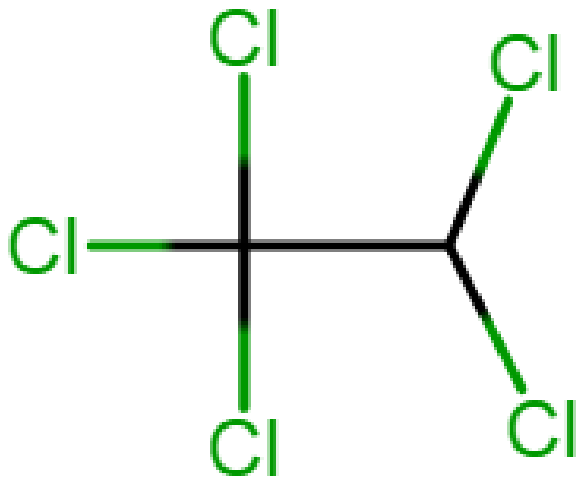
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	Pentalin
Structural Formula	
Molecular Formula	C2HCl5
Molecular Weight (g/mol)	202.29
Appearance and Odour (where available)	Colourless liquid with a sweet, chloroform-like odour.
SMILES	C(Cl)(Cl)(Cl)C(Cl)Cl

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 and the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB).

The chemical has reported site-limited uses including:

- as a solvent for cleaning and degreasing metals;
- as a solvent for cellulose derivatives, rubbers and resins;
- as a drying agent for timber; and
- for separating coal from impurities.

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

The chemical is also listed in Annex XVII to the Registration, Evaluation, Authorization and Restrictions of Chemicals (REACH) Regulation: 'The chemical cannot be used in substances and preparations placed on the market for sale to the general public and/or for diffusive applications such as in surface cleaning and cleaning of fabrics in individual concentration ≥0.1%'.

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):

- Carc. Cat. 3; R40 (carcinogenicity)
- T; R48/23 (repeated dose toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards have been identified (Galleria Chemica):

Time weighted average (TWA):

- 40–42 mg/m^3 (5 ppm) in Denmark, Germany, Iceland, Norway and Switzerland.

Short-term exposure limits (STEL):

- 80 mg/m^3 (10 ppm) in Switzerland.

Health Hazard Information

Toxicokinetics

The chemical was injected subcutaneously into female mice at doses of 1.1–1.8 mg/kg bw. It was excreted unchanged (12–51 %), as trichloroethanol (16–32 %) and as trichloroacetic acid (9–18 %) in urine, and in expired air as trichloroethylene (2–16%) and tetrachloroethylene (3–9 %) within three days (IARC, 1999; HSDB).

The chemical was metabolised in vitro by reductive dechlorination, mediated by cytochrome P450 (CYP450) or by reduced nicotinamide adenine dinucleotide phosphate (NADPH) and rat liver microsomes to form trichloroethylene and 1,1,2,2-tetrachloroethane (IARC, 1999; HSDB). The chemical was also identified as a minor metabolite of hexachloroethane (CAS No. 67-72-1) (NICNAS).

The kinetic constants were determined in male rats following inhalation exposure to the chemical vapour at a concentration of 2895 mg/m^3 for six hours. The maximum metabolic rate (Vmax) was 9.2 mg/kg per hour and the Michaelis constant (Km) was 0.9 mg/L (IARC, 1999).

Acute Toxicity

Oral

The chemical has moderate acute oral toxicity in rats and warrants a hazard classification.

The median lethal dose (LD50) was 920 mg/kg bw in rats (HSDB).

Dermal

No data are available.

Inhalation

Based on the median lethal concentration (LC50) of >35000 mg/m^3 in rats and mice, the chemical has low acute inhalation toxicity. However, the chemical was reported to affect the central nervous system (CNS) causing tremors, muscular cramps and diarrhoea in animals following acute/single inhalation exposure (HSDB). Therefore, a hazard classification is recommended for this effect.

Dogs acutely exposed to 10 mL of the chemical by inhalation displayed symptoms of restlessness and excitement, followed by depression within 20 minutes of exposure (IARC, 1986; HSDB).

Corrosion / Irritation

Respiratory Irritation

Limited information is available.

Although specific studies were not available, the chemical has been reported to be irritating to the respiratory tract during acute or short-term exposure (HSDB; ICSC).

Skin Irritation

No data are available.

Eye Irritation

Limited information is available.

Although specific studies were not available, the chemical has been reported to be irritating to the eyes during short-term exposure (ICSC).

Sensitisation

Skin Sensitisation

The chemical does not have the structural features associated with skin sensitisation, and the Quantitative Structure-Activity Relationship (QSAR) prediction for protein binding was negative.

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause severe health effects following repeated oral exposure. Effects leading to tumour or adenoma formation are discussed under the **Carcinogenicity** section.

The available studies (<13 weeks) do not report specific organ toxicity following repeated oral exposure. The National Toxicology Program (NTP) conducted a 13-week oral study in rats and mice (10/sex/dose). The doses administered (by gavage) were 0, 5, 10, 50, 125 or 250 mg/kg bw/day in rats and 0, 5, 10, 50, 100 or 500 mg/kg bw/day in mice. All rats and male mice survived, but one female mouse at the highest dose died during week 13. At the highest dose, all rats and female mice showed lower mean body weight gains (NTP, 1983).

Short-term studies (10–14 days) have demonstrated neurotoxicity (decreased motor activity and lethargy) in rats at doses ≥500 mg/kg bw/day, and increased renal $a_2\mu$-globulin protein droplet concentrations in male rats at ≥150 mg/kg bw/day. Mortalities have been reported at a very high dose (1000 mg/kg bw/day) in rats and mice (NTP, 1983; IARC, 1999; HSDB).

In a chronic carcinogenicity study, rats were administered the chemical at doses of 0, 75 or 150 mg/kg bw/day for 103 weeks. The male rats showed dose-related, increased incidences of chronic, diffuse inflammation of the kidneys, followed by renal papilla mineralisation. Lower mean body weights were reported for all treated animals during the second year of the study (NTP, 1983; HSDB).

Dermal

No data are available.

Inhalation

The chemical is classified as hazardous with the risk phrase 'Toxic: Danger of serious damage to health by prolonged exposure through inhalation' (T; R48/23) in HSIS. Only limited data are available indicating effects in animals. In the absence of detailed studies to determine the severity of the reported health effects, the existing hazard classification is supported.

In one study, it was reported that cats exposed to the chemical vapour at 1 mg/L (120 ppm), 8–9 hours/day up to 23 days did not show signs of toxicity. However, significant pathological changes in the liver, lungs and kidneys were observed (details not reported). At doses >1 mg/L, symptoms of CNS depression and delayed recovery were reported (details not available). Fatty degeneration of the liver and injury in the kidneys and lungs were observed in dogs exposed to the chemical vapour for three weeks (dose not reported). Decreased antibody formation was observed in rabbits exposed to the chemical vapour at 0.1 mg/L for three hours/day, six times/week, for 8–10 months (IARC, 1986; HSDB).

Genotoxicity

Although the chemical produced positive results for genotoxicity in a range of in vitro assays, the available in vivo data are not sufficient to form a conclusion about the genotoxic potential of the chemical.

The chemical gave mostly positive results in several in vitro assays (NTP, 1983; IARC, 1999; HSDB):

- weakly mutagenic in *Saccharomyces cerevisiae* with metabolic activation;
- generally negative results in bacterial reverse mutation assays with *Salmonella typhimurium* strains up to 333 µg/plate, with or without metabolic activation;
- positive results for sister chromatid exchange (SCE) in Chinese hamster ovary (CHO) cells, but no induction of chromosomal aberrations;
- positive results in Chinese hamster lung (CHL) fibrobrast cells, inducing chromosomal aberrations and aneuploidy; and
- positive results in L5178Y mouse lymphoma cell forward mutation assay.

Only one in vivo study was available. Intraperitoneal (i.p.) injection of the chemical administered to male rats and mice showed the chemical binds to DNA in the liver, stomach and kidneys in the rodents. However, no DNA adducts were observed and the results were reported to be inconclusive (HSDB).

Hepatocellular carcinogenicity observed in mice was postulated to be mediated through a species-specific promoting action, and not directly from the chemical (see **Carcinogenicity**) (NTP, 1983).

Carcinogenicity

The chemical is classified as hazardous—Category 3 carcinogenic substance—with the risk phrase ‘Limited evidence of carcinogenic effect’ (Xn; R40 in HSIS). The available data support this classification.

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘not classifiable as to its carcinogenicity to humans’ (Group 3), based on 'limited evidence in experimental animals for the carcinogenicity of pentachloroethane' and 'no epidemiological data relevant to the carcinogenicity of pentachloroethane were available' in humans (IARC 1999).

In a carcinogenicity study, groups of B6C3F1 mice (50/sex/dose) were administered the chemical (by gavage) in corn oil at doses of 0, 250 or 500 mg/kg bw/day, five days/week up to 103 weeks. At the high dose, early deaths occurred in males (42/50) by week 41 and all females died by week 74. Only 22/50 males and 9/50 females in the low dose group survived until the end of the exposure period. Significantly increased incidences of hepatocellular carcinoma were observed in low doses administered to males and in females at both doses. The females also displayed significantly elevated incidences of hepatocellular adenomas. The low survival rate of the males was attributed to a lifetime incidence of hepatocellular carcinomas (NTP, 1983; HSDB).

In another carcinogenicity study, groups of Fischer 344/N (F344/N) rats (50/sex/dose) were administered the chemical in corn oil at doses of 0, 75 or 150 mg/kg bw/day, five days/week up to 103 weeks. Survival rates were significantly lower than controls for all high-dose rats. Dose-related increased incidences of tubular-cell adenomas were observed in the male kidneys, but were not statistically significant. The chemical was concluded to be not carcinogenic in rats (NTP, 1983; HSDB).

The chemical used in these studies was contaminated by 4.2 % hexachloroethane, which has been shown to induce hepatocellular carcinomas in mice but not in rats. In addition, the chloroethylene metabolites of the chemical (see **Toxicokinetics**) are known hepatocellular carcinogens in mice but not in rats. Although the contribution of hexachloroethane to observed carcinogenic effects could not be evaluated, an additive mechanism of both the impurity and the metabolites of the chemical has been proposed as a potential mode of action involved in the observed carcinogenesis (NTP, 1983).

Reproductive and Developmental Toxicity

No data are available.

Other Health Effects

Neurotoxicity

Animal studies have indicated potential neurotoxic effects following inhalation exposure to the chemical, warranting hazard classification (see **Acute toxicity: Inhalation**).

The chemical has been reported to produce more potent central nervous system (CNS) effects than chloroform or tetrachloroethane (HSDB).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- systemic acute effects through oral and inhalation exposure;

- harmful effects following repeated inhalation exposure; and
- systemic long-term effects (carcinogenicity).

Data on genotoxicity are inconclusive and no data are available on dermal toxicity, skin and eye irritation, skin sensitisation and reproductive/developmental toxicity of the chemical.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Therefore the risk to the public is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, inhalation exposure of workers to the chemical may occur, particularly where manual or open processes are used. Worker exposure to the chemical at lower concentrations may 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 can pose an unreasonable risk to workers unless adequate control measures to minimise inhalation 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.

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 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 hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Harmful if swallowed (Xn; R22) Vapours may cause drowsiness and dizziness (R67)	Harmful if swallowed - Cat. 4 (H302) May cause drowsiness or dizziness - Specific target organ tox, single exp Cat. 3 (H336)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)*	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
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 may 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.

References

ChemIDPlus Advanced. Accessed October 2014 at http://chem.sis.nlm.nih.gov/chemidplus/

Galleria Chemica. Accessed October 2014. http://jr.chemwatch.net/galleria/

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed on October 2014 at http://toxnet.nlm.nih.gov.

International Agency for Research on Cancer (IARC) 1986. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 41, Some Halogenated Hydrocarbons and Pesticide Exposures, Pentachloroethane, pp. 99-111. Accessed October 2014 at http://monographs.iarc.fr/ENG/Monographs/vol1-42/mono41.pdf

International Agency for Research on Cancer (IARC) 1999. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 71, Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. Pentachloroethane, pp 1519-1523. Accessed October 2014 at http://monographs.iarc.fr/ENG/Monographs/vol71/

International Chemical Safety Cards (ICSC). Accessed October 2014 at http://www.inchem.org/documents/icsc/icsc/eics1394.htm

National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Inventory Multi-Tiered and Prioritisation (IMAP) Human Health Tier II Assessment for Hexachloroethane (CAS No. 67-72-1). Available at http://www.nicnas.gov.au

National Toxicology Program (NTP) 1983. Carcinogenesis Bioassay of Pentachloroethane (CAS No. 76-01-7) in F344/N Rats and B6C3F1 Mice (Gavage Study). Accessed October 2014 at http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr232.pdf

Safe Work Australia (SWA). Hazardous Substances Information System (HSIS). Accessed October 2014 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Last update 27 November 2014

Share this page