Ethene, tetrafluoro-: Human health tier II assessment

03 July 2015

CAS Number: 116-14-3

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.

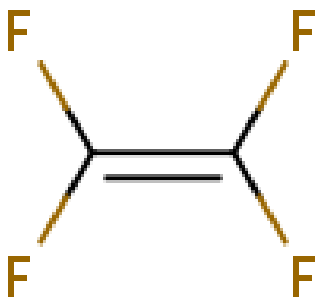
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	tetrafluoroethylene TFE perfluoroethene perfluoroethylene
Structural Formula	
Molecular Formula	C2F4
Molecular Weight (g/mol)	100.0
Appearance and Odour (where available)	colourless, odourless gas
SMILES	C(F)(F)=C(F)F

Import, Manufacture and Use

Australian

The following Australian industrial use was reported under previous mandatory and/or voluntary calls for information.

The chemical has reported site-limited use in resins.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development Screening information data set International Assessment Report (OECD SIAP); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments including the US National Toxicology Program (NTP, 1997) and the International Agency for Research on Cancer (IARC, 1999).

The chemical has reported commercial uses in:

- refrigerants and sterilant gas;
- foam blowing agents; and
- production of fluoropolymers to produce nitroso-rubbers.

The chemical has reported site-limited uses including:

- in synthesis of fluoropolymers;
- in preparation of propellants for food product aerosols;
- in the preparation of polytetrafluoroethylene (Teflon) resins and copolymers; and
- as a monomer for others resins and copolymers.

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

The following exposure standards are identified (Galleria Chemica):

An exposure limit of 2–2.5 mg/m^3 time weighted average (TWA) and 8.2 mg/m^3 occupational exposure limit (OEL) in different countries such as Colombia, Canada, Italy and Switzerland. A short term exposure limit (STEL) of 30 mg/m^3 in Russia.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 2 mg/m^3 TWA.

Health Hazard Information

The chemical ethene, tetrafluoro- (CAS No. 116-14-3) is a colourless, odourless gas with toxicity data available for acute and repeat dose inhalation toxicity, genotoxicity, carcinogenicity and reproductive toxicity. As the chemical is a gas and some of the toxicology studies are not technically feasible, data are not available for other toxicology endpoints (acute toxicity-oral and dermal; repeat dose toxicity-oral and dermal; irritation and sensitisation).

Toxicokinetics

The chemical is rapidly absorbed following inhalation in rats, hamsters and rabbits and is metabolised to *S*-(1,1,2,2-tetrafluoroethyl) glutathione in rat liver fractions, by microsomal and cytosolic glutathione (GSH) S-transferase (GST) catalytic reaction. Cysteine S-conjugate and mercapturic acid conjugates are also excreted in the small intestine and bile, which in turn are reabsorbed into the blood and transported to the kidney. GSH conjugate is further metabolised to ammonia, pyruvate and a reactive thiol by kidney β–lyase (Keller et al, 2000; US EPA, 2008; REACH).

A significant increase in the urinary creatinine and potassium was observed following exposure to the chemical. Following exposure, a significant increase in fluoride excretion was observed on days six, 13 and 14.

A dose and exposure related increase in urinary fluoride was observed in rats and hamsters following inhalational exposure to the chemical in the range of 100–2500 ppm for two or 18 weeks, respectively (NTP, 1997).

Acute Toxicity

Inhalation

The chemical was of low acute toxicity in animal tests following inhalational exposure. The reported median lethal concentration (LC50) was 31000 to 32000 ppm (126.79 to 130.88 mg/L) for rats. Lesions were reported in the liver, kidneys and brain; degeneration and necrosis of the convoluted tubules was noted in the kidney (NTP, 1997; US EPA, 2008).

In another acute inhalational toxicity study, an approximate LC50 value of 40 000 ppm has been reported in rats. Groups of four male CD rats were exposed to the chemical at concentrations of 10000, 20000, 40000, 80000, or 800000 ppm for 4 hours. Mortalities increased with increasing concentrations were reported as 0/4, 0/4, 2/4, 4/4, and 4/4, respectively (NTP, 1997; US EPA, 2008).

In an acute inhalational toxicity study conducted according to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 403, male golden Syrian hamsters (10 animals/dose) were exposed to the chemical as a whole body inhalational exposure at concentrations of 0, 10200, 20700, 25000, 30000, 40100 or 78700 ppm for four-hours. All animals in the 40100 and 78700 ppm dose groups died, with clinical signs of salivation and lethargy at 40100 ppm and clear discharge from the nose and reduced response to sound at 78700 ppm. Although significant (7/10) mortalities were noted in the 30000 ppm group, only 1/10 animal died in the 25000 ppm group. The LC50 was established as 28500 ppm (116500 mg/m^3) (NTP, 1997; IARC, 1999; US EPA, 2008; REACH).

Repeated Dose Toxicity

Inhalation

A number of repeated dose inhalational toxicity studies in animals indicate that the main target organs for toxicity are kidney, liver, and blood cells, leading to carcinogenic effects. These effects are appropriately covered in the **Carcinogenicity** section.

In a chronic/carcinogenicity study conducted according to OECD TG 453, Fischer 344 (F344) rats (60 animals/sex/dose) were administered the chemical by whole body inhalation at concentrations of 0, 156, 312 or 625 ppm (equivalent to 0, 640, 1280 or 2560 mg/m^3) for males and 0, 312, 625 or 1250 ppm (equivalent to 0, 1280, 2560 or 5125 mg/m^3) for females. The exposure duration was six hours/day, five days/week for 104 weeks (see **Carcinogenicity**). A significant reduction in the survival of the highest dose males and reduction in the mean body weights was reported. The incidences of cataracts in females exposed to 1250 ppm were greater than those in the controls. The primary non-neoplastic tissue lesions were dose-related hyperplasia and degeneration of the renal tubules in some or all of the treated male and female groups. The lowest observed adverse effect concentration (LOAEC) for the chemical was reported to be 640 mg/m^3 for both male and female rats based on the increased incidences of renal tubule degeneration (NTP, 1997; US EPA, 2008; HSDB; REACH).

Groups of B6C3F1 mice (58 animals/sex/dose) were administered the chemical by whole body inhalation at concentrations of 0, 312, 625 or 1250 ppm (equivalent to 0, 1280, 2560 or 5125 mg/m^3) for six hours/day, five days/week for 95-96 weeks (see **Carcinogenicity**). At 90 weeks, the survival of mice in all dose groups was severely reduced and this was attributed to exposure-related liver neoplasms. An increased incidence of angiectasis (gross dilation and lengthening of a blood or lymph vessel) was noted in all exposed groups. Multifocal coagulative necrosis of the liver in all exposed groups of males, increased incidences of haematopoietic cell proliferation in the liver in females and the spleen of all exposed groups of both males and females was also noted in the study. Increased incidences of renal tubular dilatation and karyomegaly (enlarged cell nucleus) were also observed in all exposed groups. The LOAEC was judged to be 312 ppm (1275 mg/m^3) (NTP, 1997; IARC, 1999; REACH).

In a 90-day study conducted similarly to OECD TG 413, Syrian golden hamsters (15 animals/sex/day) were exposed to the chemical by inhalation for six hours/day for five days/week at concentrations of 0, 203, 606 or 1989 ppm for 90 days. There were no noted clinical observations related to the treatment. Hamsters exposed to 1989 ppm of the chemical showed an increase in the incidence of testicular atrophy with associated focal hypocellularity of the germinal epithelium of the seminiferous tubules. However, testicular immaturity was not observed in animals of the 605 ppm treatment group. A no observed adverse effect concentration (NOAEC) for male hamsters of 203 ppm (based on the testicular effects) and 1989 ppm for females was reported (NTP, 1997; US EPA, 2008; HSDB; REACH).

In a 2-week study, Sprague Dawley (SD) rats were exposed to the chemical at concentrations of 0, 1099 or 3510 ppm for four hours/day for five days/week for two weeks. Animals from the 1099 ppm treatment group showed reversible kidney damage and animals from the 3510 ppm treatment group showed incomplete recovery of the extensive kidney damage at the end of the 14-day recovery period (NTP, 1997; US EPA, 2008; HSDB; REACH).

In a 12-day study, female B6C3F1 mice (five animals/sex/dose) were exposed to the chemical at concentrations of 0, 30, 300, 600 or 1200 ppm by inhalational exposure for six hours/day over one, five or nine days over a 12 day period. No treatment-related mortality and no significant effects on the body weights were observed. Slight increases in cell proliferation on the kidney in 600 and 1200 ppm groups and microscopic lesions of kidney at 1200 ppm were observed. Kidney function, liver and spleen had no adverse effects. A NOAEC for the chemical was reported to be 30 ppm (NTP, 1997; US EPA, 2008; HSDB; REACH).

Genotoxicity

The available information indicate that the chemical does not have mutagenic or clastogenic potential.

In vitro studies

In an Ames test, the chemical was negative for genotoxicity in *Salmonella typhimurium* strains TA97, TA98, TA100 and TA1535, with and without metabolic activation, at concentration range of 0.5-5 %. Negative results were also reported for the chemical in a gene mutation assay at the HPRT locus in Chinese hamster ovary (CHO) cells, with and without metabolic activation (NTP, 1997; IARC, 1999; US EPA, 2008; HSDB; REACH).

In vivo studies

Negative results were observed for the chemical in several in vivo assays (IARC, 1999; US EPA, 2008; HSDB; REACH):

- chromosomal aberration in C57BL/6jfC-1/Alpk mice;
- micronucleus assays in B6C3F1 mice;
- gene mutation in mice; and
- unscheduled DNA synthesis (UDS) assay in CD-1 mice.

Carcinogenicity

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Possibly carcinogenic to humans’ (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animal testing (IARC, 1999). The available data support this classification for the chemical (refer to **Recommendation** section).

The above conclusion was based on the increased incidences of hepatocellular carcinomas, histiocytic sarcomas and haemangiosarcomas in the liver in both sexes of mice and of hepatocellular carcinomas and kidney tubule cell adenomas in both sexes of rats (NTP, 1997; IARC, 1999).

In a carcinogenicity study conducted according to OECD TG 453, F344 rats (60 animals/sex/dose) were administered the chemical by whole body inhalation at concentrations of 0, 156, 312 or 625 ppm (equivalent to 0, 640, 1280 or 2560 mg/m^3) for males and 0, 312, 625 or 1250 ppm (equivalent to 0, 1280, 2560 or 5125 mg/m^3) for females. The exposure duration was six hours/day, five days/week for 104 weeks. A significant reduction in the survival of the highest dose males and reduction in the mean body weights was reported. Increased incidence of liver neoplasms (haemangiosarcomas and hepatocellular adenomas/carcinomas) was noted in all treated groups of males and females. Increased incidence of renal tubule neoplasms (primarily adenomas) was also noted in the high dose males (625 ppm) and females (1250 ppm). Incidences of mononuclear cell leukaemia were increased in a dose-related manner in all treated groups of female rats (NTP, 1997; IARC, 1999; HSDB; REACH).

Groups of B6C3F1 mice (58 animals/sex/dose) were also administered the chemical by whole body inhalation at concentrations of 0, 312, 625 or 1250 ppm (equivalent to 0, 1280, 2560 or 5125 mg/m^3) for six hours/day, five days/week for 95-96 weeks. At 90 weeks, the survival of mice in all dose groups was severely reduced and this was attributed to exposure-related liver neoplasms. A dose-related increase in the incidence of haemangiosarcomas of the liver, hepatocellular adenomas and/or carcinomas and histiocytic sarcomas was noted in both sexes. Kidney neoplasms were not increased in treated mice (NTP, 1997; IARC, 1999; HSDB; REACH).

Reproductive and Developmental Toxicity

No data are available.

However, in repeated dose toxicity studies (see **Repeat Dose Toxicity: inhalation**), the treatment showed some effects on the histology of reproductive organs.

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is the systemic long-term effect of carcinogenicity.

Public Risk Characterisation

Given the uses identified for the chemical, it is unlikely that the public will be exposed. Although the public could come into contact with articles or coated surfaces made using the chemical, it is expected that the chemical will be irreversibly bound within the article or coated surface and hence will not be bioavailable. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

During product formulation, inhalational exposure may 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 health effect, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise inhalational 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]

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Carcinogenicity	Carc. Cat 2 - May cause cancer by inhalation (T; R49)	May cause cancer - Cat. 1B (H350i)

[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 inhalational 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 that 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.

References

Consonni D, Straif K, Symons JM, Tomenson JA, Amelsvoort L, Sleeuwenhoek A, Cherrie JW, Bonnetti P, Colombo I, Farrar DG and Bertazzi PA (2013). Cancer Risk Among Tetrafluoroethylene Synthesis and Polymerisation workers. Americcan journal of Epidemiology, Vol 178;(3): 350-358.

Galleria Chemica. Accessed June 2015 at http://jr.chemwatch.net/galeria/

Hazardous Substances Data Bank (HSDB). National Library of Medicine. Accessed June 2015 at http://toxnet.nlm.nih.gov

International Agency for Research on Cancer (IARC) 1999. Tetrafluroethylene. IARC Monographs Volume 71. Accessed June 2015 at http://www.inchem.org/documents/iarc/vol71/048-tetrafluo.html

Keller DA, Kennedy GL, Ross PE, Kelly Dp and Elliott GS (2000). Toxicity of Tetrafluoroethylene and S-(1,1,2,2-tetrafluoroethyl)-L-cysteine in rats and mice. Toxicological Sciences 56; (2); 414-423.

National Toxicology Program (NTP, 1997). Report on the toxicology and carcinogenesis studies of tetrafluoroethylene in F344/n rats and B6C3F1 mice. Accessed June 2015 at http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr450.pdf

OECD (2003). SIDS Initial Assessment Profile (SIAP) on Chlorotrifluoruethylene (CTFE). Accessed June 2015 at http://webnet.oecd.org/Hpv/ui/handler.axd?id=63dd8882-00b9-49d1-9ebe-99b8d58bdd6e

REACH Dossier (REACH). Tetrafluoroethylene (CAS No. 116-14-3). Accessed June 2015 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

SPIN (Substances in Preparations in Nordic Countries) Database. Accessed May 2015 at http://195.215.202.233/DotNetNuke/default.aspx

US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR). Accessed June 2015 at http://actor.epa.gov/actor/faces/ACToRHome.jsp

US EPA 2008, Acute exposure guidelines levels (AEGLs) for tetrafluoroethylene (CAS Reg. No. 116-14-3) (Interim report), Accessed June 2015 at http://www.epa.gov/opptintr/aegl/pubs/tetrafluoroethylene_interim_ornl_jun_2008c.pdf

Last update 03 July 2015

Share this page