File No: STD/1415

February 2013

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1-Propene, 1,3,3,3-tetrafluoro-, (1E)-

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health and Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of Sustainability, Environment, Water, Population and Communities.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This Public Report is also available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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SUMMARY

The following details will be published in the NICNAS *Chemical Gazette:*

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS SUBSTANCE	INTRODUCTION VOLUME	USE
STD/1415	A-Gas (Australia) Pty Ltd	1-Propene, 1,3,3,3-tetrafluoro-, (1E)-	No	≤ 100 tonnes per annum	Foam blowing agent, propellant for aerosols and refrigerant

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS), as adopted for industrial chemicals in Australia, or the Approved Criteria for Classifying Hazardous Substances (NOHSC, 2004).

Human health risk assessment
Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment
On the basis of its low hazard to the environment and assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- The notified chemical should be classified as follows under the ADG Code:
  - Class 2, Division 2.2 (non-flammable, non-toxic gases)

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced and in the end use product:
  - Local exhaust ventilation in any non-enclosed processes during foam processing

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced and in the end use product:
  - Avoid using the notified chemical in small rooms with limited ventilation;
  - Follow all standard safety precautions for handling and use of compressed gas cylinders;
  - Avoid breathing vapours, mist or gas;
  - Avoid skin or eye contact with the notified chemical in liquid form;
  - Do not overheat or spray the notified chemical into a flame, to avoid formation of hazardous degradation products;
  - Maintain and monitor equipment for leaks and take immediate corrective action where leaks are detected.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:

- Suitable respiratory equipment in case of insufficient ventilation, such as a positive-pressure supplied-air respirator
- Goggles and impervious clothing
- Face shield and eye protection
- Protective/cold insulating gloves

Guidance in selection of personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

- A copy of the MSDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Public Health

- The following measures should be taken by distributors and equipment owners to minimise public exposure to the notified chemical when used in commercial settings:
  - Equipment must be maintained and monitored for leaks, with immediate corrective action taken where leaks are detected.

Disposal

- The notified chemical should be disposed via an appropriate product stewardship scheme where practicable.

Storage

- The following precautions should be taken by the notifier regarding storage of the notified chemical:
  - Keep containers tightly closed in a cool, well-ventilated place and away from direct sunlight.

Emergency procedures

- Spills or accidental release of the notified chemical should be allowed to evaporate; ventilate enclosed areas until safe for re-entry.

Transport and Packaging

- As the notified chemical has been classified under the ADG Code, appropriate transportation and packing requirements should be followed.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
  - further information on the carcinogenicity or cardiotoxicity of the notified chemical becomes available.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from foam blowing agent, propellant for industrial and consumer aerosol cans, and refrigerant, or is likely to change significantly;
- the amount of chemical being introduced has increased from 100 tonne per annum, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

Material Safety Data Sheet
The MSDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

This notification has been conducted under the cooperative arrangement with the United States Environmental Protection Agency (US EPA). Information pertaining to the assessment of the notified chemical by the US EPA was provided to NICNAS and, where appropriate, used in this assessment report. The other elements of the risk assessment, including the recommendations on safe use of the notified chemical, were carried out by NICNAS.

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
A-Gas (Australia) Pty Ltd (ABN 18 066 273 247)
9-11 Oxford Road, Laverton North VIC 3026

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Belgium, 07-02-0488-00
USA PMN number P-08-550/551
Japan
EU REACH registration number 01-0000019758-54-0000
China

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
HFO-1234ze

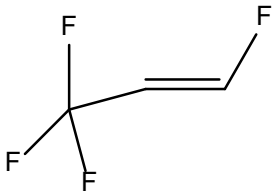
CAS NUMBER
29118-24-9

CHEMICAL NAME
1-Propene, 1,3,3,3-tetrafluoro-, (1E)-

OTHER NAME(S)
HBA-1
HFO-1234ze(E)
Solstice 1234ze
Solstice Propellant
Solstice GBA

MOLECULAR FORMULA
$C_3H_2F_4$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
114.04 Da

ANALYTICAL DATA
Reference GC, MS, NMR, IR spectra were provided.

3. COMPOSITION

DEGREE OF PURITY 99.9 %

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight) None

ADDITIVES/ADJUVANTS None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 ºC AND 101.3 kPa: clear gas

Property	Value	Data Source/Justification
Melting Point	-136.48 ºC	Estimated (mean of several estimate methods)
Boiling Point	-19 ºC at 99.4 kPa	Measured
Density	1180 kg/m^3 at 25ºC	Measured
Vapour Pressure	496 kPa at 25.4 ºC	Measured
Water Solubility	0.373g/L at 24.5 ºC	Measured (Method A.6 of EC Directive of 92/69/EEC)
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionality
Partition Coefficient (n-octanol/water)	log Pow = 1.6 at 25 ºC	Measured
Adsorption/Desorption	log K_{oc} = 1.4	Calculated (from log Kow = 1.6 - user entered, KOCWIN v2.00; US EPA, 2011)
Dissociation Constant	Not determined	Does not contain dissociable functionality
Particle Size	Not determined	The notified chemical is a liquefied gas.

Flash Point	Not determined	The notified chemical is a liquefied gas.
Flammability Limits	Not flammable	Measured
Autoignition Temperature	368 ºC	Measured
Explosive Properties	Not explosive	Based on the chemical structure.
Oxidising Properties	Not oxidising	Based on the chemical structure.
Surface Tension	8.95 mN/m at 20 ºC	Measured

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties not assessed by the US EPA, refer to Appendix A.

Reactivity
Stable under normal conditions of use. Due to the low boiling point of the notified chemical (-19 ºC), it has the potential to cause frostbite burns to human tissue when released from the pressurised form, as it changes from a liquefied gas to a gas.

Decomposition products after heating include hydrogen fluoride and other fluorine-containing compounds.

Dangerous Goods classification
Based on the submitted physico-chemical data in the above table, the notified chemical is classified according to the Australian Dangerous Goods Code (NTC, 2007) as Class 2, Division 2.2 (non-flammable, non-toxic gases). The data above do not address all Dangerous Goods endpoints. Therefore, consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

Although the notified chemical is not classified as flammable according to the Australian Dangerous Goods Code, it exhibits flammability at temperatures above 28 ºC. It is reported that at 30 ºC the lower explosive limit (LEL) and upper explosive limit (UEL) are 7.0% and 9.5% volume percent in air respectively (Honeywell, 2008).

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported at 100% concentration in tanks of approximately one tonne capacity in a 20 ft shipping container. It may also be imported at up to 100% concentration in aerosol cans where the filling is done overseas.

MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	100	100	100	100	100

PORT OF ENTRY
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
A-Gas (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The imported chemical will be repacked from bulk tanks to smaller cylinders of 4.5 to 820 kg capacity, 15 tonne ISO containers or customer facility bulk storage tanks > 15 tonne and will be delivered to customers by road. The imported aerosol cans will be delivered to customers by road.

USE

The notified chemical is proposed for the following uses:

- Refrigerant for commercial air conditioning (excluding cars) and refrigeration systems (35% total import volume);
- Blowing agent for polyurethane or polystyrene closed cell foam (25% total import volume);
- Aerosols for 'down – hole' bag inflation, used in conjunction with explosives in mining applications (25% total import volume);
- Aerosol cans for specialised industrial use or consumer use (15% total import volume).

OPERATION DESCRIPTION

Use as a refrigerant for commercial air conditioning and refrigeration systems

At the notifier's site, the notified chemical will be transferred from the import containers into 5-20 kg cylinders via hoses and interlock valves. The transfer will take place in an open shed with good ventilation.

At the sites where commercial air conditioning and refrigeration units are situated, technicians will top-up or fill these units with the notified chemical by transfer from the 5-20 kg cylinders, using interlock valves and hoses. Technicians will also empty the air conditioning and refrigeration units during maintenance and end-of-service life of the units. In these instances, the notified chemical will be captured and returned to a licensed company for destruction or recycling.

Use as a blowing agent for polyurethane or polystyrene foam

Two stages are involved in the formulation of polyurethane or polystyrene foam: blending and foam production.

During the blending process, the notified chemical will be pumped from cylinders directly into a closed 1000 L stainless steel blending vessel, where it may be mixed with polyols and other materials to produce the blend, which is then decanted from the blending vessel. The area immediately above the cylinders will be ventilated with an extractor.

During the foaming process, the polyol blend containing the notified chemical will be transferred to the foaming machine where it will be combined with the resin in controlled portions. The foam, which contains between 5 and 12% of the notified chemical, results from trapping the notified chemical in gaseous form in the foam (closed cell). The viscous foam is then discharged at low pressure through a pouring tube into a mould, where it is left to partially cure and solidify, and then put out onto a pallet to complete the curing process. The foam is then cut to sizes. The foam is used for thermal insulation in commercial and residential structures. It is used on exterior surfaces such as roofs, walls and foundations.

Use as aerosols for 'down – hole' bag inflation, in conjunction with explosives in mining applications

Aerosol cylinders for this application will be imported or filled in Australia. If the filling is carried out in Australia, the cylinder of the notified chemical will be hooked up to a filling machine via a pressure rated hose and the filling and sealing of the aerosol cans with a pre-set amount of gas (containing the notified chemical at up to 100%) will be done automatically in a closed loop.

At the end use site, bags containing the aerosol cans will be lowered on cords into blast holes in the ground, where they will inflate the bag and form a "plug" in the hole. Explosives will also be placed in the hole and detonated. The notified chemical in the gas bags is expected to be consumed during the explosion process. If the bag needs to be removed from the blast hole this can be done by lancing the bag in situ, waiting for deflation and then retrieving the bag with the drop cord.

Aerosol cans for specialised industrial use or consumer use

The notified chemical will be used as an ingredient (propellant) in aerosol can products for specialised industrial use. Aerosols for these applications may be imported as the ready-to-use cans or be packaged in Australia. Depending on whether they will be used in workplaces or by the public, they will be distributed through retail or wholesale channels to the end-users. Applications for the aerosol cans include contact cleaners, dusters, mould release agents, spray lubricants and personal care (cosmetic) products.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport workers	4	50
Refrigerant		
Storemen	0.2	50
Repackaging workers	0.2	50
Refrigeration technicians	0.2	10
Blowing agent		
Storemen	8	260
Blending / foam production workers	8	260
Aerosol		
Aerosol fillers	8	260
Users of industrial aerosols	8	260
Mining workers	8	260
Beauty salon workers	8	260

EXPOSURE DETAILS

Transport workers and storemen are not expected to be exposed to the notified chemical except in the unlikely event of an accident.

Potential routes of occupational exposure are dermal, ocular and inhalation. However as the notified chemical is a gas at room temperature, inhalation is the main expected route of exposure. Dermal and ocular exposure to the liquefied gas or gaseous material may occur during transfer operations or accidental leakage.

In the MSDS provided by the notifier, engineering controls include local exhaust ventilation, personal protective equipment including suitable respiratory equipment such as a positive-pressure supplied-air respirator in case of insufficient ventilation, protective gloves, goggles, impervious clothing, face shield and eye protection. The MSDS also recommends that workers avoid breathing vapours, mist or gas and avoid contact with skin, eyes and clothing.

Refrigerant

When used as a refrigerant for commercial air conditioning and refrigeration systems, worker exposure may occur during installation, filling, topping-up and emptying air conditioning units, particularly when connecting and disconnecting transfer hoses. Engineering controls such as use of closed systems for transfer of the chemical, local exhaust ventilation (LEV), and personal protection equipment (PPE) used by the workers are expected to minimise the exposure. Workers may also be potentially exposed to the notified chemical if leakage occurs. This exposure would be highest in the case of any sudden loss of containment. Awareness of exposure to leakage of the notified chemical may not occur, because as a gas it is odourless and colourless.

Blowing agent

Due to high volatility of the notified chemical and the inherently dispersive nature of this use, inhalation exposure to the notified chemical may occur during blending and foaming production processes, unless significant controls are in place to reduce worker exposure. The use of enclosed systems for mixing and dispensing the gas, engineering controls such as LEV during foaming, and PPE used by the workers would minimise the exposure.

Workers would also install foam articles and sheets on buildings as thermal insulation. While potential low level migration of the notified chemical from the foam could occur, this would be limited by the closed-cell nature of the foam, an expected low diffusion rate and the installation of the foam in exterior locations only. Worker exposure from this use is expected to be low.

Aerosols
During filling of aerosols for use in mining (down-hole) processes, as specialised industrial and consumer spray uses, there is potential exposure of workers to the notified chemical, mainly by inhalation. However, the engineering controls in place during filling such as mainly automatic processes, LEV and PPE used by the workers will minimise the exposure.

During end-use of down-hole aerosols used in conjunction with explosives in mining, inhalation exposure of workers to the notified chemical is not expected as it is likely to be consumed during the explosion, which would also occur some distance from any workers. Workers would also not be in direct contact with the notified chemical when it is released into the gas bag, prior to placement in the holes. There is potential for worker exposure during the disposal of unused gas bags, if correct disposal procedures are not used.

For other aerosol can uses, the notified chemical is released as an inherent part of the end-use spray product and would be largely volatilised. Workers are likely to be exposed to the notified chemical primarily via inhalation, when the product containing the notified chemical at up to 100% is sprayed. The extent of exposure will vary with the concentration of the notified chemical in the aerosol can, the quantity of product sprayed for each use, the frequency of use, the size of the room and the ventilation conditions.

Aerosols use in beauty salons
One application of aerosols where worker exposure to the notified chemical is expected to occur is the use of hairsprays in beauty salons. Although individual applications are generally of short duration, such use is expected to occur frequently, with multiple stylists applying aerosol can products throughout the day. To estimate potential exposure concentrations of notified chemical from use as propellant in hair sprays, the notifier has provided a commercial ventilation model that assumes a constant emission rate (vapour generation rate) of propellant and a constant removal rate (ventilation rate). The vapour generation rate is assumed to be constant throughout the day; this accounts for the aggregate exposure scenario of multiple stylists using hairsprays throughout the day, often simultaneously.

The model equation is:

$$\mathbf{C = (G[1-e^{(-QT/V)}]/Q)*10^6}$$

Where:
C is the concentration in ppm (parts per million)
G is the generation rate in CFM (cubic feet per minute)
Q is the ventilation rate in CFM
V is the volume of the room in cubic feet
T is elapsed time in minutes
e is the natural log, 2.72

The notifier provided survey data of four hair salons, indicating average weekly use rates of just over 2 cans of hairspray (2.15 cans) of 284 g typical size. The average shop size reported is 1000 ft^2 floor space and 10 ft ceiling. The standard for minimum ventilation level in a beauty shop is 0.4 CFM per square foot of floor space (California Energy Commission, 2010). It is acknowledged that this is a conservative figure; actual ventilation rates are likely to be much higher.

Data on the general composition of hairspray aerosol cans (RIVM, 2006) indicates that approximately 50% is propellant. Using the above data and model equation, and assuming that propellant is 100% notified chemical, the estimated air concentration for the notified chemical in commercial hair salons is 13.18 mg/m^3 (or 2.6 ppm).

The notifier has indicated that, due to the comparatively high cost of the notified chemical, its use in consumer products such as hair sprays would require blending it with other propellants. The notified chemical would be the minority component in the blend. Therefore, the assumption that propellant in hair sprays is 100% notified chemical is conservative.

Typical hair salons operate 8 hrs/day, 6 days/week. Assuming 4 weeks/yr annual holiday time, a typical worker in a hair salon would work 48 weeks/yr. Using these data, the adjusted air concentration is 3.47 mg/m^3.

Aerosols use as specialised industrial applications
Another application of aerosols where worker exposure to the notified chemical is expected to occur is the use of sprays for specialised industrial applications, including dusters and markers. For aerosol dusters, the most conservative assumption is that 100% of the can content is propellant, represented by the notified chemical. Using the model and exposure assumptions for aerosol use in beauty salons, the adjusted air concentration for the notified chemical in the atmospheric air of a room of 10,000 ft^3 volume and minimum ventilation level is 6.93 mg/m^3.

6.1.2. Public Exposure

In general, the public is not expected to be exposed to the notified chemical as a result of its use in industrial applications. There is potential for the notified chemical, as a refrigerant gas, to be released from commercial refrigerators or air conditioners through accidental leakage; however, it is expected that this would not generally result in public exposure, due to the commercial nature of these units. Public exposure to the notified chemical through its migration from foam insulation is not expected, as the foam will not be installed in indoor locations.

Consumers using household or cosmetic aerosol sprays containing the notified chemical will have inhalation exposure to the aerosols when they are sprayed. The manner in which aerosol spray products are used will vary depending on the nature of the operation; however, spray use is intermittent and generally of short duration. A typical aerosol spray product has a delivery rate of 0.5 to 1 or 1.5 grams per second, and is usually sprayed for only a few seconds at a time.

Consumer aerosol sprays including cosmetic (personal care) aerosols
The British Aerosol Manufacturers' Association (BAMA) has developed a model (provided by the notifier) for calculating concentrations of volatile aerosol ingredients in room air.

The BAMA equation is:

$$\mathbf{C_t = (P*S*D/100V)*e^{-NT}}$$

Where:

C_t is the concentration remaining after T minutes
P is the percent by weight of an ingredient in the aerosol
D is the delivery rate in grams per second
S is the duration of the spray in seconds
V is the volume of the room in cubic meters
N is the ventilation rate in air changes per minute
e is the natural log (2.72)
T is elapsed time in minutes

The type of cosmetic aerosols used by consumes include deodorant spray and hair styling products.

For **hair styling products**, data on typical use patterns include (RIVM, 2006): 0.47 g/s delivery rate; 15 s event use duration; 10 m^3 the bathroom volume; 2 air exchanges/h ventilation rate (i.e., 0.033air exchanges/min).

Using a general composition for aerosol can of hairspray of 50% propellant (RIVM, 2006), which is conservatively assumed to be 100% notified chemical, a concentration estimate for the notified chemical in bathroom air of 213.73 mg/m^3, 15 minutes after hairspray use, is obtained.

Typical hairspray use data by consumers (RIVM, 2006) include 15 mins spent in the bathroom for each use event, together with typical event frequency of 438 per year. Using these data, the adjusted air concentration is 2.67 mg/m^3.

For **aerosol deodorants**, data on typical use patterns include (RIVM, 2006): 0.4 g/s delivery rate; 10 s event use duration; 10 m^3 the bathroom volume; 2 air exchanges/h ventilation rate (i.e., 0.033air exchanges/min).

Using a general composition for aerosol can of hairspray of 60% propellant (RIVM, 2006), which is conservatively assumed to be 100% notified chemical, a concentration estimate for the notified chemical in bathroom air of 145.52 mg/m^3, 15 minutes after aerosol deodorant use, is obtained.

Typical deodorant use data by consumers (RIVM, 2006) include 15 mins spent in the bathroom for each use event, together with typical event frequency of 730 per year. Using these data, the adjusted air concentration is 3.03 mg/m^3.

The cumulative estimated daily systemic consumer exposure from the combined use of hairsprays and aerosol deodorants is 5.7 mg/m^3.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix B.

Endpoint	*Result and Assessment Conclusion*
Mice, acute inhalation toxicity	LC50 > 475 mg/L/4 hour; low toxicity (101,850 ppm)
Mice, acute inhalation toxicity	LC50 > 480 mg/L/4 hour; low toxicity (103,000 ppm)
Rat, acute inhalation toxicity	LC50 > 965 mg/L/4 hour; low toxicity (207,000 ppm)
Rabbit, skin irritation	non-irritating
Human, skin sensitisation - RIPT	no evidence of sensitisation
Rat, repeat dose inhalation toxicity – 14 days	pilot study
Rat, repeat dose inhalation toxicity – 28 days	NOAEC = 47 mg/L (10,000 ppm)
Rat, repeat dose inhalation toxicity – 90 days	NOAEC = 23 mg/L (5,000 ppm)
Dog, cardiac sensitisation to adrenaline	no evidence of cardiac sensitisation
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* Mammalian Chromosome Aberration Test (cultured human lymphocytes)	non genotoxic
Genotoxicity – *in vivo* Mammalian (Mouse) Erythrocyte Micronucleus Test (2 studies)	non genotoxic
Genotoxicity – *in vivo* Mammalian (Rat) Erythrocyte Micronucleus Test	non genotoxic
Genotoxicity – *in vivo* Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells	non genotoxic
Rabbit, developmental effects	NOEC = 70 mg/L (15,000 ppm)
Rat, developmental effects	NOAEC = 70 mg/L (15,000 ppm)

Toxicokinetics, metabolism and distribution
In studies on the biotransformation of the notified chemical (Schuster et al., 2009), male Sprague-Dawley rats were exposed by inhalation to levels of 2,000, 10,000, and 50,000 ppm and male B6C3F1 mice were exposed to 50,000 ppm, for 6 hours. Urinary metabolites were identified by ^{19}F-NMR (nuclear magnetic resonance). No metabolites were found in urine from animals exposed to 2,000 and 10,000 ppm, probably due to insufficient sensitivity of the NMR and the low rate of metabolic conversion of the notified chemical.

The major metabolite (66%) identified in rat urine after dosing at 50,000 ppm was S-(3,3,3-trifluoro-trans-propenyl)-mercaptolactic acid. Other metabolites included S-(3,3,3-trifluoro-transpropenyl)-L-cysteine, N-acetyl-S-(3,3,3-trifluoro-transpropenyl)-L-cysteine, and 3,3,3-trifluoropropionic acid. In mouse urine, a presumed amino-acid conjugate of 3,3,3-propionic acid (18% of the total) was identified. These metabolites suggest that the major route of metabolism is via glutathione conjugation. *In vitro* studies were also carried out in the presence of liver microsomes. These studies support the existence of a minor pathway of metabolism, which is likely to occur through a CYP mediated epoxidation.

The quantified amounts of the metabolites excreted with urine in both mice and rats, suggest only a low extent (< 1% of dose received) of biotransformation of the notified chemical; 95% of all metabolites were excreted within 18 h after the end of the exposures ($t_{1/2}$ app. 6 h).

Acute toxicity
Acute oral and dermal toxicity studies were not submitted. No signs of systemic toxicity were seen in a dermal irritation study.

The notified chemical was of low acute toxicity through inhalation in rats (LC50 > 965 mg/L/4hour) and mice (two studies, LC50 > 475 mg/L/4 hour and LC50 > 480 mg/L/4 hour). The MSDS for the notified chemical states that exposure to high concentrations may cause central nervous system effects or asphyxiation.

Irritation
The notified chemical was non-irritating to the skin of rabbits in a study in which skin exposure was carried out via a hilltop chamber. An eye irritation study was not performed. Histopathological results of a 90-day repeat dose inhalation study in rats suggests that the notified chemical is not irritating to the respiratory system.

Skin sensitisation
The notified chemical did not cause skin sensitisation in a repeated insult patch test (RIPT). Due to the high volatility of the notified chemical, it is likely that skin exposure would have been reduced for much of the exposure time.

Repeated dose toxicity
Repeated dose inhalation studies were carried out in rats, with concentrations up to 50,000 ppm in a pilot 14-day study, and up to 15,000 ppm in 28-day and 90-studies. No test substance related mortalities were observed in any of the groups. The organs most affected were the heart and, at higher concentrations, the liver. Changes in haematology and clinical chemistry parameters were seen and at higher concentrations there were changes in some organ weights. In the respiratory system, slightly reduced expression of goblet cells in the nasal cavity was seen in all test concentrations in the pilot study, but not in the longer term studies. In the 14-day and 28-day studies, test substance related increases in focal mononuclear cell infiltrates in the heart were seen at all dose levels, however in the longest study (90 days) this effect occurred also in the control animals at a similar frequency. In the 90-day study, the NOAEC was determined to be 5,000 ppm (23 mg/L), based on microscopic examination revealing that the test substance induced multifocal mononuclear cell infiltrates in the heart of the 15,000 ppm group in males and females. The results of the repeated dose studies are discussed in Rusch et al (2012). The authors suggest that the cardiotoxic effects of the notified chemical may occur through both a direct myocardial effect, and also indirectly via vasoactive effects.

Mutagenicity
The notified chemical was found to be non-mutagenic in a bacterial reverse mutation test and also showed no evidence of clastogenicity to human lymphocytes *in vitro*, in mouse erythrocyte micronucleus test *in vivo* (2 studies), in rat erythrocyte micronucleus test *in vivo*, and in unscheduled DNA synthesis (UDS) test with mammalian liver cells *in vivo*. Based on these results, the notified chemical is not suspected to be genotoxic.

Reproductive and Developmental toxicity
Data related to reproductive toxicity was not submitted. No significant treatment-related changes indicative of developmental toxicity were observed in rabbits or rats for most endpoints, in two inhalation studies carried out to OECD TG 414. In both studies the NOAEC was set at 15,000 ppm (70 mg/L), the highest dose tested. Although the level of post-implantation loss at 15,000 ppm was higher than in controls in both studies, the levels were well within historical controls in the rabbit study. In the rat study the high level of post-implantation loss was attributable to the effects in two animals only, and there was considerable inter-litter variation in this parameter (USA 1991). Overall the two studies do not raise a concern for developmental toxicity of the notified chemical.

Cardiac sensitisation
The notified chemical did not induce cardiac sensitisation in beagle dogs at levels up to 120,000 ppm, the highest dose tested.

Carcinogenicity
No animal studies for chronic effects or carcinogenicity to OECD test guidelines were submitted.

In an unpublished study provided for the assessment (Hamner, 2007), gene expression changes following a 90-day inhalation study were used to assess the carcinogenic potential of the notified chemical in the female mouse liver and male rat kidney. No treatment-related histopathological lesions were observed following exposure at 2,000 and 10,000 ppm. Statistical classification analysis predicted the notified chemical to be non-carcinogenic in both female mouse liver and male rat kidney with 98.5 and 97.5% accuracy, respectively. However, treatment with the notified chemical produced large-scale gene expression changes in the female mouse liver that were related to a variety of basic cellular functions such as RNA metabolism and processing. The significance of these changes is unclear.

In another unpublished study (Hamner, 2009), gene expression changes were examined in the lungs of female mice exposed by inhalation in a 13-week study to 2,000 and 10,000 ppm of notified chemical, to predict the carcinogenic potential in that organ. Histopathological effects in the lung were limited to minimal inflammation in one of nine mice in the low dose group only. Statistical classification analysis predicted the notified chemical to be similar to other substances found to be carcinogenic in the female mouse lung only with 77.5% accuracy. Furthermore, only a limited number of genes were altered following animals exposure to the notified chemical, and the pattern did not show an exposure related response.

An expert opinion (Dekant, 2009) discussed the relevance of the above study and the documents were also evaluated by the US EPA. The adequacy of toxicogenomic assays for mouse lung tumours is in question, as it has been acknowledged in the scientific literature that false positives may be as high as 25%. It is considered that in general toxicogenomic assays for mouse lung carcinogenicity are more suitable for use in a weight-of-evidence approach and not as a stand-alone predictive tool. Several weak points in the study itself were also identified by the study author, e.g. adequacy of the training set.

Other available toxicology and metabolism information was considered as part of a weight of evidence approach for carcinogenicity. For the notified chemical, several factors significantly weaken the support for the toxicogenomics-predicted lung carcinogenicity potential: the low rates of metabolism, the absence of positive results in the genotoxicity studies performed, and the absence of rodent lung pathology in the 90-day subchronic inhalation study. The absence of lung toxicity in the subchronic toxicity study in particular is inconsistent with the mode of action delineated for a number of other chemicals inducing mouse lung tumours after inhalation exposures and bioactivation by pulmonary cytochrome P450s.

It was suggested in the expert opinion that even if the prediction of mouse lung carcinogenicity potential (by toxicogenomics assay) is correct, the risk most likely cannot be extrapolated to humans because human lung is relatively deficient in the activating enzymes (CYP2E1 and 2F1) and susceptible lung cells (Clara cells) that are crucial for the induction of mouse lung cancer. However, this assessment is dependent on the assumption that the mode of action of other chemicals is applicable to the notified chemical.

Overall, the totality of the evidence/data does not support a significant risk for lung tumour induction in humans after inhalation exposures to the notified chemical under realistic exposure conditions. However it is not possible to rule out carcinogenicity potential.

Health hazard classification

Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Physico-chemical hazards

The notified chemical is a gas at room temperature, and storage and handling occurs as a liquefied gas of moderate pressure (approximately 500 kPa at 25ºC). It is classified as a Dangerous Good in Class 2, Division 2.2 (non-flammable, non-toxic gases). Although not classifiable as a flammable gas, it can form flammable mixtures in air at temperatures > 28 ºC, and the MSDS indicates that it can ignite when mixed with air under pressure and exposed to strong ignition sources. Contact with rapidly evaporating liquid can cause frostbite to skin or damage to the eyes. Heating of pressurised containers containing the notified chemical may lead to rupture of the container. Vapours are heavier than air and can reduce the amount of oxygen available for respiration.

Hazardous decomposition products may be formed after heating or combustion, including hydrogen fluoride and other fluorine-containing compounds.

Health hazards

Toxicological testing carried out on the notified chemical did not raise a concern for skin or respiratory tract irritation, skin sensitisation, cardiac sensitisation, genotoxicity or developmental toxicity. Eye irritation was not

tested. Acute inhalation toxicity was evaluated as low, with LC50 values of 101,850 to 207,000 ppm (475 to 965 mg/L) in mice and rats. Central nervous system effects or asphyxiation may occur if high concentrations are inhaled. In a 90-day repeated dose inhalation study in rats, a NOAEC of 5,000 ppm (23 mg/L) was set on the basis of adverse effects on the heart at 15,000 ppm (70 mg/L). Related low level effects on the heart were also seen at lower concentrations in shorter term studies (14-day and 28-day). The carcinogenic potential of the notified chemical was explored through non-standard toxicogenomic assays. Although one study predicted possible lung carcinogenicity, it was considered that the toxicogenomic study was not adequate to determine this endpoint, and not supported by the other available data. Overall, uncertainties in the health effects profile relate to the dose level for onset of cardiotoxic effects after repeated exposure, and the potential for lung carcinogenicity.

The extent and nature of potential worker exposure to the notified chemical is expected to be quite diverse, depending on the type of use. For some scenarios there is the possibility of large-scale exposure through accidental discharge of a pressurised container. Some uses are inherently dispersive e.g. foam blowing and dispensing of aerosol products. Other uses are non-dispersive under normal conditions of use, e.g. refrigeration. Scenarios with high potential exposure include those with poor ventilation and those where there is large accidental or deliberate discharge of the notified chemical. Inhalation exposure to airborne concentrations of the notified chemical can be reduced by the use of the notified chemical in well-ventilated areas. However, if significant inhalation exposure is expected, respiratory protection may be required to reduce exposure.

There is at present no Australian occupational exposure limit for the notified chemical. However, a US Workplace Environmental Exposure Level (WEEL) Guide of 800 ppm: 8 h time weighted average (TWA) for the notified chemical has been developed by the American Industrial Hygiene Association (AIHA, 2011).

The notified chemical is imported as 100% pure gas in pressurised containers. In the liquid form, the notified chemical can freeze skin or eyes on contact, causing frostbite. The use of protective clothing and eye protection when using the notified chemical in bulk form is recommended on the MSDS.

In most use scenarios, flammability should not be a concern, however high concentrations of the notified chemical could be generated in rooms with poor ventilation or as a result of large releases, and flammable concentrations in air could be generated at temperatures > 28ºC. Combustion is expected to produce hazardous by-products.

Blowing agent
Due to the high volatility of the notified chemical, there is a potential for inhalation exposure during foam blowing through various processes involving the notified chemical, such as blending and foaming processes. However, if sufficient engineering controls are in place, in conjunction with PPE if needed, the risk to workers presented by the use of notified chemical is not expected to be unreasonable.

Refrigerant
During use in refrigeration and air-conditioning units, the main potential for occupational exposure is during installation, filling, topping-up and emptying refrigerant equipment, particularly when connecting and disconnecting transfer hoses. Engineering controls and PPE are expected to be used during these procedures to minimise exposure. The potential for accidental leakage would be minimised by plant maintenance, detection systems, and emergency plans.

Aerosols
Worker exposure during aerosol filling is expected to be controlled by engineering controls and closed processes. Unlike other aerosol uses, workers are not expected to be exposed to the notified chemical during end-use of down-hole bags used in conjunction with explosives. However, incorrect disposal of unused bags could lead to worker exposure unless correct procedures are used.

<u>Aerosols use in beauty salons</u>
Workers in hair and beauty salons may be exposed to cosmetic products containing the notified chemical during spray application of the products to their clients. They are not expected to use PPE during these processes.

The risk to stylists who regularly use hair sprays in the workplace can be estimated by calculation of the margin of exposure (MoE) of the notified chemical, using the exposure estimate of 3.47 mg/m^3 (see Section 6.1.1) and the workplace adjusted NOAEC of 1,055 mg/m^3. The workplace adjusted NOAEC is based on the rat NOAEC of 5,000 ppm (i.e., 23,313 mg/m^3) established in the 90 day repeat-dose inhalation study, adjusted for

occupational exposure conditions and allometrically scaled for body weight differences between rat and human. The use of the workplace adjusted NOAEC in this assessment is justified in the absence of blood:gas ratio data. The acceptable MoE is set at 30, to account for human intraspecies (×10) and interspecies toxicodynamic (×3) factors. Using the abovementioned workplace adjusted NOAEC, a MoE of 304 was estimated, which is acceptable.

Aerosols use in specialised industrial applications

The notified chemical is proposed to be used in a number of aerosol products with specialised industrial application, including dusters, dyes, contact cleaners and spray lubricants. Among these aerosol can products, spray dusters have the potential to contain the notified chemical at up to 100% concentration. Their use results in the notified chemical being released into the atmosphere through spraying, and there is potential for worker inhalation exposure, through repeated and prolonged use of these products in the workplace, in the absence of PPE.

The risk to dusting workers can be estimated by calculation of the MoE of the notified chemical, using the exposure estimate of 6.93 mg/m^3 (see Section 6.1.1) and the workplace adjusted NOAEC of 1,055 mg/m^3. Setting the acceptable MoE at 30, the MoE for dusting workers is estimated at 152, which is acceptable.

Overall, in the context of the proposed industrial applications, controls in place, and the PPE specific to individual uses of the notified chemical, the risk to workers is not considered to be unreasonable.

6.3.2. Public Health

Industrial applications

Public exposure to the notified chemical through its industrial use as a blowing agent, refrigerant or industrial aerosol is expected to be low unless there is accidental release in the vicinity of the public, and the risk to public health from these uses is not considered to be unreasonable.

Consumer aerosol use of hair spray and deodorant

The repeat dose toxicity potential to consumers from simultaneous use of both aerosol hair spray and deodorant was estimated by calculation of the margin of exposure (MoE) of the notified chemical assuming the adjusted concentration of 5.7 mg/m^3 (see Section 6.1.2) and the human adjusted NOAEC of 231 mg/m^3. The NOAEC adjustment principles are those described in Section 6.3.1, except that the rat NOAEC of 5,000 ppm (i.e., 23,313 mg/m^3) established in the 90 day repeat-dose inhalation study was adjusted for consumer, rather than occupational exposure conditions. The allometric scaling has been maintained. The acceptable MoE for consumers is 30 (see Section 6.3.1). The calculated MoE is 41, which is acceptable. It is expected that the MOE for use of other consumer products would also be acceptable.

In the context of the proposed uses, the risk to the public from exposure to the notified chemical is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical is not manufactured or reformulated in Australia: therefore, there will be no releases due to these activities. The notified chemical may be repackaged but no significant release of the notified chemical is expected during transfer of the notified chemical.

RELEASE OF CHEMICAL FROM USE

When used as an aerosol in industrial applications or as a blowing agent in the manufacture of foams, the notified chemical is expected to be collected by engineering controls and released into the atmospheric compartment. The notified chemical may be released to the atmospheric component as a result of accidental leakages when used as a refrigerant or following diffusion over the life-time of insulation foams. When used as an aerosol for the inflation of down-hole bags in conjunction with explosives for mining applications, the notified chemical and/or a combination of its thermal decomposition products are expected to be released to the atmospheric compartment. The notified chemical in consumer aerosol products is expected to be released directly into the atmospheric compartment during use.

RELEASE OF CHEMICAL FROM DISPOSAL

When used as a refrigerant, the notified chemical is expected to be recovered during maintenance or at end-of-service life for disposal via an approved product stewardship scheme for either recycling or destruction. Residual notified chemical in decommissioned foam articles are expected to share the fate of the articles and be disposed of to landfill. Notified chemical in unused gas bag aerosols and consumer products are likely to be disposed of to landfill.

7.1.2. Environmental Fate

The notified chemical is not considered readily biodegradable (refer to Appendix C) and is expected to be stable to hydrolysis under environmental conditions based on its structure. However, the notified chemical is not expected to bioaccumulate based on its low partition coefficient (log Pow = 1.6). Further, the notified chemical is considered unlikely to be released into or partition to the aquatic compartment in significant quantities based on its reported use pattern and atmospheric fate as elaborated below.

Up to 35% of the annual introduction volume of the notified chemical may be recovered when used as refrigerant, and is expected to be mineralised to water, oxides of carbon and hydrofluoric acid during destruction. The rest of the introduction volume of the notified chemical is likely to be released to the atmospheric compartment as a result of its use as a blowing agent and in aerosols. The portion of notified chemical used in conjunction with explosives in mining applications may be thermally decomposed during explosions. However, the extent and completeness of combustion of the notified chemical under these conditions has not been demonstrated. Thus, it is assumed that notified chemical, and any of its thermal decomposition products, are released into the atmospheric compartment following its use in mining applications. Some of the notified chemical associated with foam articles or aerosol products may be disposed of to landfill. However, as the notified chemical is a gas, it is likely that it will be released to the atmospheric compartment as a component in landfill gas emissions.

In the atmosphere, the notified chemical is predicted to have a half-life ($t_{½}$) of 1.05 days based on the rate constant for reaction with hydroxyl radicals (k_{OH}) of 1.021×10^{-11} cm^3/molecule.s (AOP v1.92; US EPA 2011). Reaction with ozone is not expected to be a dominant pathway for degradation in the atmosphere ($t_{½}$ = 16.4 days, $k_{O3} = 7.00 \times 10^{-19}$ cm^3/molecule.s; AOP v1.92; US EPA 2011). Further information on the atmospheric chemistry of the notified chemical is reported in the published literature and is summarised below.

Sondergaard et al. (2007) examined the kinetics of the notified chemical gas-phase reactions with chlorine atoms, hydroxyl radicals and ozone. The measured rate constants are tabulated below together with the global atmospheric concentrations of each reactant and the atmospheric lifetimes for each degradation pathway. The study concluded that the atmospheric lifetime of the notified chemical is determined by the reaction with hydroxyl radicals and is approximately two weeks.

	Chlorine atoms	Hydroxyl radicals	Ozone
Rate constant (k; cm^3/molecule.s)	4.64×10^{-11}	9.25×10^{-13}	2.81×10^{-21}
Atmospheric concentrations	*	1.0×10^6 molecules/cm^3	35 ppb
Atmospheric lifetime		2 weeks	13 years

*Not present in sufficient quantity to impact the atmospheric lifetime of the notified chemical

It is noted that the measured rate constants for the reaction with hydroxyl radicals and ozone are lower than the predicted values. Therefore, the half-life of the notified chemical has been recalculated using the measured rate

constant for the reaction with hydroxyl radicals, and assuming exponential decay, a 12-hour day and atmospheric hydroxyl radical concentration of 1.5×10^6 molecules/cm^3 (US EPA, 2011). The calculated atmospheric half-life of the notified chemical based on the measured rate constant is 11.6 days. Therefore, as the half-life is greater than 2 days, the notified chemical is considered to be persistent in the atmospheric compartment.

Javadi et al. (2008) examined the mechanisms and products of atmospheric degradation of the notified chemical. The study indicates that the notified chemical is expected to degrade in the atmospheric compartment to eventually form water, oxides of carbon, hydrofluoric acid and trifluoroacetic acid (TFA). The extent of conversion of the notified chemical to TFA has not been established. Almost all TFA formed from precursors in the atmosphere is expected to be rained-out into the aquatic compartment (Young & Mabury, 2010). Like other perfluorinated acids, TFA is expected to be resistant to biotic and abiotic degradation and thus is considered very persistent in the aquatic environment.

7.1.3. Predicted Environmental Concentration (PEC)

A predicted environmental concentration (PEC) cannot be calculated for the aquatic compartment because the notified chemical is a volatile gas and no aquatic exposure is anticipated. A PEC for the atmospheric compartment has not been calculated as there are no available environmental effects endpoints for a PEC to be compared with in a quantitative risk characterisation.

The atmospheric degradation of the notified chemical is expected to result in rainout of the persistent degradant, TFA, into the aquatic compartment. Due to the long atmospheric lifetime of the notified chemical (about two weeks), TFA may be deposited in precipitation away from the site of release. TFA is ubiquitous in the aquatic environment and has been found at up to 0.2 µg/L in precipitation and 40 µg/L in enclosed lakes, although surface water concentrations are more typically less than 0.6 µg/L (Boutonnet, 1999). TFA has been reported to be present in ocean water at 0.2 µg/L at Noosa Heads, Queensland (Frank et al., 1996 and Frank & Klein, 1997 cited in Boutennet, 1999). Environmental concentrations are likely to include natural sources of TFA, such as volcanic emissions, as well as direct and indirect anthropogenic sources of TFA. The IPCC/TEAP (2005) report concludes that cumulative anthropogenic sources of TFA, such as from the degradation of hydrofluorocarbons (HFCs), are smaller than natural sources.

7.2. Environmental Effects Assessment

Aquatic Compartment

The results from the submitted ecotoxicological investigations conducted on the notified chemical, as assessed by the US EPA, are summarised in the table below.

Endpoint	*Test Method*	*Result*	*Assessment Conclusion*
Fish Toxicity Carp (*Cyprinus carpio*)	OECD TG 203	96 h LC50 > 117 mg/L	Not harmful to fish
Daphnia Toxicity *Daphnia magna*	OECD TG 202	48 h EC50 > 160 mg/L	Not harmful to aquatic invertebrates
Algal toxicity Green algae (*Selenastrum capricornutum*)	OECD TG 201	72 h E_rC50 >170 mg/L	Not harmful to algae

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is not harmful to fish, aquatic invertebrates and algae. Based on its lack of rapid degradability and acute endpoints, the notified chemical is considered to be not harmful with long lasting effects to fish, aquatic invertebrates and algae. Therefore, the notified chemical is not formally classified for short-term or long-term hazard under the GHS.

The lowest reported endpoint for the persistent degradant, TFA, is an algae no-observed effect concentration (NOEC) of 0.12 mg/L for *Selenastrum capricornutum* (Boutonnet et al., 1999). No other chronic endpoints were available. The median effect concentrations (EC50) for 10 other tested algae species were greater than 100 mg/L, while no effects were observed for fish and daphnia at concentrations of up to 1000 mg/L (ibid.).

Atmospheric Compartment
There are no standard ecotoxicological endpoints for evaluating effects in the atmospheric compartment. Generally the effects assessment for this compartment involves the evaluation of the long-range transport potential, global warming potential (GWP) and ozone depleting potential (ODP).

The notified chemical is considered to have long-range transport potential as its half-life in the atmosphere, based on the measured reaction rate with hydroxyl radicals, is greater than two days.

Based on the reported atmospheric lifetime of two weeks, the GWP relative to carbon dioxide (CO_2) on a 100-year time horizon is 6 (Sondergaard et al., 2007). Therefore, assuming the entire introduction volume of notified chemical is released into the atmospheric compartment, the introduction of the notified chemical may result in annual greenhouse gas emissions equivalent to 600 tonnes of CO_2. This compares with Australia's annual greenhouse gas emissions of 5.5×10^8 metric tonnes of CO_2 (DCCEE, 2012). Thus, the reported use of the notified chemical represents a very small additional contribution of approximately 0.0001% to current Australian greenhouse gas emissions.

The notified chemical is not expected to contribute to stratospheric ozone depletion because it does not contain chlorine or bromine. The ODP of the notified chemical is reported as 0 (US EPA, 2010). The notified chemical is not a controlled substance listed in Annexes to the Montreal Protocol. Therefore, the notified chemical is not classified as hazardous to the ozone layer under the GHS.

7.2.1. Predicted No-Effect Concentration
A predicted no-effect concentration (PNEC) was not calculated for the aquatic compartment as aquatic exposure is not expected.

7.3. Environmental Risk Assessment
The risk quotient (Q = PEC/PNEC) could not be calculated for the notified chemical as no aquatic exposure is expected based on the reported use pattern. The notified chemical is a gas at environmentally relevant temperature and pressure and is expected to be released into the atmospheric compartment following its use or disposal. The notified chemical is of low hazard to aquatic organisms and is not expected to be released to the aquatic compartment.

In the atmosphere, the notified chemical may undergo long range transport but is not expected to be a significant contributor to global warming or ozone depletion. The notified chemical is a potential precursor of TFA, a persistent degradant that will rainout into the aquatic compartment. TFA is ubiquitous in the environment and is generally of low hazard to the environment. The introduction and use of the notified chemical is not expected to significantly increase background concentrations of TFA in the aquatic compartment from natural and anthropogenic sources.

Therefore, on the basis of the global warming potential and the assessed use pattern the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Boiling Point -19ºC at 99.4 kPa

Remarks Method 1 from the vapour pressure measurement (see below) was used.
Test Facility Grebenkov et al. (2009)

Density 1179.7 kg/m^3 at 25ºC

Remarks Using the constant volume piezometer in a version of "adiabatic constant volume calorimeter", the measurements of the density of notified chemical in the temperature range from -23 to 117ºC were completed along 11 isochors ranging from 27 through 1200 kg.m^{-3} with a total experimental uncertainty of about 1 kg.m^{-3}. The saturated liquid density was measure over a temperature range of -21.7 to 107.7ºC.
Test Facility Grebenkov et al. (2009)

Vapour Pressure 496 kPa at 25.4ºC

Method Method 1: a cylinder of degassed notified chemical was placed in a constant temperature bath. The process was measured using a MKS pressure transducer, which was heated to 100ºC to avoid condensation.
Method 2: the constant volume piezometer in the version of "adiabatic constant volume calorimeter" was used.
Remarks The saturated vapour pressure has been correlated using the extended Antonite equation.
Test Facility Grebenkov et al. (2009)

Partition Coefficient (n-octanol/water) log Pow = 1.6 at 25ºC

Method OECD TG 117 Partition Coefficient (n-octanol/water) (2004).
Remarks HPLC Method. Preliminary estimate for log Kow was 2.01 (KOWWIN v1.67; US EPA)
Test Facility CERI (2008a)

Flammability Limits Not flammable

Method EC Directive 92/69/EEC A.11 Flammability (Gases).
Remarks When tested according to the protocol at 20ºC, no ignition was seen. At some gas concentrations, a small blue or orange glow was seen. Ignition was obtained at electrode gap of ca. 8 mm, which was beyond the gap stipulated in the standard. Therefore this result could not be consideration for classification.
The apparatus was tested using a known flammable gas (propane).
Test Facility Chilworth Technology Limited (2006)

Autoignition Temperature 368ºC

Method EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks No cool flames were observed. Ignition produced an orange flame and black smoke. An exothermic reaction of 1 ºC magnitude was detected at 344 ºC, but no ignition observed.
Test Facility Chilworth Technology Limited (2007)

Explosive Properties Not explosive

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks Examination of the structural formula concluded that the chemical will not possess explosive properties.
Test Facility Chilworth Technology Limited (2006)

Oxidizing Properties Not oxidising

Method EC Council Regulation No 440/2008 A.17 Oxidizing Properties.

Remarks	Through examination of the structural formula it has been concluded that the chemical will not possess oxidising properties.
Test Facility	Chilworth Technology Limited (2006)

Surface Tension 8.95 mN/m at 20ºC

Remarks	Capillary rise method (Liu et al., 1994 cited in Grebenkov et al., 2009).
Test Facility	Grebenkov et al. (2009)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – inhalation

TEST SUBSTANCE	Notified Chemical
METHOD	Similar to OECD TG 403 Acute Inhalation Toxicity.
Species/Strain	Mice/CD-1
Vehicle	Air
Method of Exposure	Whole-body exposure
Exposure Period	4 hours
Physical Form	Gas
Remarks - Method	A minor protocol deviation occurring during the study was not considered to have compromised the validity or integrity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <ppm>*		*Mortality*	
		Target	*Nominal*	*Actual*	
1	2 per sex	20,000	20,500	20,550	0
2	2 per sex	100,000	131,000	101,850	0

LC50	> 101,850 ppm/4 hours
Signs of Toxicity	Laboured breathing was noted in at least half of the animals during the latter 2 hours of both exposures. Upon removal from exposure chamber, all animals were within normal limits immediately following both exposures. Other than a few occurrences of yellow ano-genital staining in the male mice, all animals were within normal limits during the week following both exposures.
Effects in Organs	Other than a single female mouse in the 100,000 ppm group with an ovarian cyst, all animals were within normal limits when sacrificed and macroscopically examined.
Remarks - Results	All animals showed little body weight change during the week after exposure.
CONCLUSION	The notified chemical is of low toxicity via inhalation.
TEST FACILITY	Huntingdon Life Sciences (2004a)

B.2. Acute toxicity – inhalation

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity.
Species/Strain	Albino mice (outbred) VAF/Plus Crl:CD-1 (ICR) BR Albino rats (outbred) VAF/Plus Sprague-Dawley – Derived (CD) Crl:CD (SD) IGS BR
Vehicle	Air
Method of Exposure	Nose only exposure.
Exposure Period	4 hours
Physical Form	Gas
Remarks - Method	Information on feed consumption, macroscopic examinations and organ weights was only obtained for rats. This protocol deviation was not considered to have compromised the validity or integrity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <ppm>*			*Mortality*
		Target	*Nominal*	*Actual*	
1 (mouse)	10 per sex	100,000	80,500	103,300	0
2 (rat)	5 per sex	100,000	75,200	100,000	0
3 (rat)	5 per sex	200,000	198,000	207,000	0

LC50 > 103,300 ppm/4 hours (mice)
> 207,000 ppm/4 hours (rat)

Signs of Toxicity *Mice*
No remarkable observations were noted in the test animals other than wet fur during the exposure and during the 1 or 2 days prior to sacrifice. Body weight for test animals was comparable with control animals.

Rats
No remarkable observations were noted in the test animals except one animal was noted with laboured breathing during the 200,000 ppm exposure. During the 2 hour period immediately after exposure, the test substance exposed animals were comparable to the air control animals with low incidences of red/clear nasal discharge in all groups. All of the 200,000 ppm exposed animals were noted with wet fur but this is frequently seen as a result of the nose-only exposure regimen. During the 14 days prior to sacrifice, red nasal discharge was seen in a few animals for 2 days after exposure in both air control and test substance exposed animals.

There were no treatment related differences in body weights, body weight gains or feed consumption.

Effects in Organs *Rats*
At the terminal sacrifice, there were no treatment related or statistically significant differences in organ weights (kidneys, liver and lungs) or organ to body weight ratios or post-mortem observations.

CONCLUSION The notified chemical is of low toxicity via inhalation.

TEST FACILITY Huntingdon Life Sciences (2004b)

B.3. Irritation – skin

TEST SUBSTANCE Notified Chemical

METHOD Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 1 M, 2 F
Vehicle None
Observation Period 72 hours
Type of Dressing Occlusive
Remarks - Method Due to the physico-chemical properties of the test substance, a dosing method was developed to deliver and apply the test substance. The test substance was supplied (as a liquid) in a cylinder capable of holding 400 psi. The cylinder was fitted with a swagelock tee and septum. The test substance was removed from the cylinder by first connecting a vacuum line to the tee and evacuating the tee. The test substance was then allowed to flow into the tee. A gastight syringe, with valve closed, was inserted through the septum. The syringe valve was then opened allowing the liquid to flow into the syringe. The valve was then closed. The syringe was removed from the septum and the contents were immediately

injected directly onto the pad, near the bottom, of a hilltop chamber that had already been placed on the appropriate site of the test animal. A piece of porous dressing secured with non-irritating tape was immediately placed over the hilltop chamber on the dose site for the exposure period.

A single rabbit was initially treated at separate sites for 3 minute and 4-hour exposure periods. Based on the results of this preliminary study, all 3 animals (including the initial single rabbit, which was treated at a separate site) were treated with 0.4 mL test substance for the 4 hour exposure period.

RESULTS

Remarks - Results

Preliminary study (single animal) – 3 minute and 4 hour exposure
No erythema, oedema or frostbite was observed immediately following or at 60 minutes after the 3 minute exposure or at 60 minutes after patch removal following the 4 hour exposure.

Main study (all three animals) – 4 hour exposure
No erythema or oedema was observed in any animal at 60 minutes, 24, 48 and 72 hours following the 4 hour exposure.

Systemic observations
There were no abnormal physical signs noted during the observation period.

Body weight
No reductions in body weight were noted.

CONCLUSION The notified chemical was non-irritating to the skin, under the conditions of the test.

TEST FACLITY MB Research Laboratories (2010)

B.4. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified Chemical

METHOD Repeated insult patch test with challenge

Study Design
Induction Procedure: it consisted of 9 applications of the test substance (0.3 mL) on Mondays, Wednesdays and Fridays for 3 consecutive weeks and subsequent evaluation of the patch sites 48 hours (or 72 hours for application on Fridays) after the application. The subjects were required to remove the patches approximately 24 hours after application.

Rest Period: 10-15 days

Challenge Procedure: Identical patches were applied to sites previously unexposed to the test substance. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (i.e., 48 and 72 hours after application).

Study Group 82 F, 30 M; age range 19-71 years

Vehicle None

Remarks - Method
Occluded. The test substance was spread on a 2 cm × 2 cm patch.
The test substance was one of two substances tested.

The test substance was taken from a canister via high pressure syringe and was immediately applied to a patch (hilltop chamber) that was immediately applied to the skin.

	Due to the physico-chemical properties of the test substance and the method of application, the actual amount of test substance to which the subjects were exposed is unclear.
RESULTS	
Remarks - Results	112 subjects were enrolled and 100 subjects completed the study. Seven subjects were lost to follow-up (0-9 induction observations recorded) and 5 subjects voluntarily withdrew (1-8 induction observations recorded). A minimal or doubtful response was noted for 1 subject at induction observations 5-7. There were no adverse responses noted at challenge.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	TKL Research (2010)

B.5. Repeat dose toxicity

Test Substance	Notified Chemical
Method	OECD TG 412 Repeated Dose Inhalation Toxicity: 14-day Study.
Species/Strain	Rats/Sprague Dawley
Route of Administration	Inhalation – oro-nasal exposure
Exposure Information	Total exposure days: 14 days (10 exposure days in total) Dose regimen: 5 days per week Duration of exposure (inhalation): 6 hours/day Post-exposure observation period: none
Vehicle	Air
Physical Form	Gas
Remarks - Method	For this study, a slight different design of the nose-only exposure units was used, namely, with a cylindrical PVC column (volume of approx. 70 L) surrounded by a transparent hood, test atmosphere inlet at the bottom of the central column, and outlet at the top.

Results

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
control	5 per sex	0	0	0
low dose	5 per sex	4,895	4,961 ± 52	0
mid dose	5 per sex	20,462	20,904 ± 833	0
high dose	5 per sex	49,186	51,770 ± 1,778	0

Clinical Observations
Daily observations did not reveal any exposure related clinical abnormalities.

No treatment related differences in body weight gain, food consumption and food conversion efficiency were seen.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
The concentration of red blood cells, thrombocytes and monocyte count increased and the mean corpuscular haemoglobin (MCH) concentration decreased in males of the high concentration group. Prothrombin time increased in female animals of the mid- and high concentration group.

The study authors did not consider the increased white blood cell count in males of the low and high concentration groups to be of toxicological relevance due to the absence of a dose-response relationship.

The levels of plasma of glucose, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT),

albumin and urea increased and levels of cholesterol and phospholipids and sodium decreased in male animals of the high concentration group. The levels of ASAT and urea increased in the male animals of the mid-concentration group. In female animals of the high concentration group, the levels of alkaline phosphatase (ALP), ALAT and urea increased and cholesterol decreased. In the female animals of the mid concentration group the level of cholesterol decreased and the level of ASAT increased. Although the level of ASAT was higher in female animals of the high concentration group, it did not reach statistical significance.

Effects in Organs
Absolute and relative lung weight decreased only in male animals of the high concentration group. Absolute and relative liver weights increased in male and female animals of the high concentration group, although statistical significance was not reached for the absolute liver weight in the male animals.

Macroscopic examination at necropsy revealed an exposure-related pale appearance of the livers of almost all animals of the high concentration group. The other two findings, a flabby kidney in a control female and an abdominal cyst in a high concentration male were not considered by the study authors to be toxicologically relevant.

Microscopic examination revealed histopathological changes in the liver of the mid- and high concentration male animals, in the nasal passages of the high concentration male and female animals, and in the heart of the mid- and high concentration male and female animals, all at statistically significant levels. Effects were also seen at lower dose levels that were not statistically significant. The effects in the heart included mononuclear cell infiltrates, which were most prominent in the animals of the mid-concentration group, and therefore, did not show a concentration related increase in the response. Effects were observed in at least one female animal of the low concentration group, however, they were not statistically significant.

The more pronounced histopathological changes in the liver of exposed males of the mid- and high concentration groups compared to those in exposed females were consistent with the more pronounced changes in liver related clinical chemistry parameters. Compared to controls, goblet cell expression locally decreased in the nasal passage of high concentration males and females and this was also found in a few mid- and low concentration males and females. In the latter groups, as no clear concentration response relationship in incidence and degree was noted, the study authors concluded that decreased goblet cell expression in the intermediate concentration animals was not related to exposure.

Remarks – Results
As a treatment-related effect to the heart in low dose animals could not be ruled out, a NOAEC was not established.

Test Facility	TNO Quality of Life (2005)

B.6. Repeat dose toxicity

Test Substance	Notified Chemical
Method	OECD TG 412 Repeated Dose Inhalation Toxicity: 28-day Study.
Species/Strain	Rats/Sprague Dawley
Route of Administration	Inhalation –oro-nasal exposure
Exposure Information	Total exposure days: 28 days Dose regimen: 5 days per week Duration of exposure: 6 hours/day Post-exposure observation period: none
Vehicle	Air
Physical Form	Gas
Remarks - Method	The concentration levels used were established on the basis of a previous 14-day pilot study. No deviations from the protocol.

Results

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
control	5 per sex	0	0	0
low dose	5 per sex	1,000	972 ± 41	0
low mid dose	5 per sex	5,000	5,000 ± 96	0
high mid dose	5 per sex	10,000	9,979 ± 39	0
high dose	5 per sex	15,000	14,895 ± 474	0

Clinical Observations
Daily observations did not reveal treatment related clinical abnormalities.

Treatment related differences in body weight gain, food consumption or food conversion efficiency were not seen.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Mean corpuscular volume of red blood cells was slightly, but significantly increased in low and low mid dose females. Because a relation with the concentration was absent, the study authors considered the findings not related to the exposure. Other significant differences in red cell or white blood cell parameters were not found.

Treatment related statistically significant differences in clinical chemistry consisted of a decrease of cholesterol concentration in plasma of male animals of the high mid and high dose groups, a decrease of the potassium concentration in plasma of high dose male animals, a decrease of the triglyceride concentration in plasma of all test group females, and an increase of the concentration of urea in plasma in high dose females. The decrease in cholesterol and triglycerides, however, was not concentration related.

These changes were not considered to be toxicologically significant by the study authors as they were sex specific and the fluctuation was small.

Effects in Organs
Treatment related changes in absolute or relative organ weight were not detected except that in low dose male animals absolute weights of the spleen and testes were significantly decreased. The study authors attributed these observations to body weight differences since such significant decreases were not seen in the relative organ weights.

Macroscopic examination at necropsy did not reveal any treatment related findings.

Microscopic examination at necropsy revealed exposure related very slight to moderate inflammation in the heart of high dose males. Moreover, in two of these male animals muscle fibre vacuolation was seen. In the heart of one low mid dose female animal, myocardial vacuolation was observed. Since the finding was only observed focally, only occurred incidentally and was not seen in the heart of female rats of the higher dose groups, this finding was not considered to be exposure-related.

An increased incidence of hepatocellular vacuolation in the liver of female rats was seen in the exposure groups. Since this finding is particularly common in female rats of this strain and age with rather large variation in incidence (it was found in two female rats of the control group), the study authors did not consider this finding to be exposure-related. In addition, hepatocellular vacuolation was not seen in the exposed males.

Conclusion
The No Observed Adverse Effect Concentration (NOAEC) was established as 10,000 ppm in this study, based on exposure related effects in the heart of male animals of the 15,000 ppm group.

Test Facility TNO Quality of Life (2006)

B.7. Repeat dose toxicity

Test Substance Notified Chemical

Method OECD TG 413 Subchronic Inhalation Toxicity: 90-day Study.
Species/Strain Rats/Sprague Dawley

Route of Administration	Inhalation –oro-nasal exposure
Exposure Information	Total exposure days: 90 days Dose regimen: 5 days per week Duration of exposure: 6 hours/day Post-exposure observation period: none
Vehicle	Air
Physical Form	Gas
Remarks - Method	The concentration levels used were established on the basis of a previous 28-day inhalation study. No deviations from the protocol were reported.

Results

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
control	10 per sex	0	0	1 F
low dose	10 per sex	1,500	1,504 ± 4	0
mid dose	10 per sex	5,000	4,999 ± 18	0
high dose	10 per sex	15,000	15,002 ± 57	0

Mortality and Time to Death
One female control animal was found dead on the 75th day of the study (nominal day 77); the cause of death was most probably due to suffocation when trying to turn around in the restraining tube.

Clinical Observations
Daily observation of the animals did not reveal treatment-related clinical abnormalities.

Treatment-related differences in body weight gain, food consumption and food conversion efficiency were not seen. Ophthalmoscopic examination near the end of the exposure period did not reveal treatment related abnormalities.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
It was considered that the statistically significant differences seen in haematology parameters at the high dose, i.e. increases in thrombocytes and monocytes in males and increases in haemoglobin concentration, packed cell volume, and monocytes in females, may be treatment related.

Similarly, the increases seen in clinical chemistry parameters at the high dose, i.e. in ASAT, ALAT, Ca and urea in males, and in glucose, urea, inorganic phosphate, and potassium in female animals of the high concentration group, were considered to be potentially treatment related.

Effects in Organs
The absolute and relative weight of the uterus decreased in female animals of the high concentration group. This finding was considered due to uterus weight variations related to the oestrous cycle rather than exposure related. Relative heart weight was reduced in high dose females and relative adrenal weight reduced in high and mid dose females, however a dose response relationship was not seen and absolute weights were not affected.

Macroscopic examination did not show exposure related gross pathology. One animal in the low dose group and one in the high dose group showed unilateral small epididymis and testes, with corresponding histopathology. These changes were not dose-related and were not considered to be treatment related.

Microscopic examination revealed that the test substance induced multifocal mononuclear cell infiltrates in the heart of the high-concentration males and females. The study authors commented in their summary that this was accompanied by indications of myocardial degeneration. Fibrosis was not observed (a silver impregnation stain did not provide evidence for fibrosis). No other histopathological results were considered treatment related.

Remarks – Results
Haematology and clinical chemistry changes were seen in animals of the high concentration group. Although several of these changes were slight and most of these changes occurred in one sex only, it cannot be excluded that these were exposure-related.

Conclusion
The No Observed Adverse Effect Concentration (NOAEC) was established as 5,000 ppm in this study, based on adverse histopathological changes in the heart in the 15,000 ppm group.

Test Facility TNO Quality of Life (2008)

B.8. Cardiac sensitisation to adrenaline

TEST SUBSTANCE Notified Chemical

METHOD In house method.

STUDY DESIGN

Species/Strain Dog/Beagle

Study Design A group of 6 male dogs was exposed to multiple concentrations of the test substance via muzzle-only inhalation (vapour), at 48 h intervals. The duration of exposure was 10 minutes in each case, and the concentrations tested were 2.0, 6.0 and 12% (20,000, 60,000 and 120,000 ppm, respectively). Animals were administered a pre-exposure dose of epinephrine (adrenaline) as a bolus injection via a cephalic vein approximately 5 minutes prior to exposure to the test substance. Five minutes after exposure to the test substance began, the animals were administered a challenge dose of epinephrine. Dogs were monitored for the development of arrhythmias by means of a continuous electrocardiogram tracing. The response to epinephrine was determined for each animal in a pre-test acclimatisation phase, and used to determine the amount of epinephrine administered in the main study. The epinephrine level used for each animal was the highest level that did not elicit significant ECG findings such as premature ventricular contractions (PVCs).

The criteria used to determine whether cardiac sensitisation has occurred include (not exclusively):

- Eleven or more PVCs in 10 seconds, with episodes of confluency
- Ventricular tachycardia
- Fibrillation

The study also included a cardiac sensitisation study on a different chemical, carried out on the same animals approximately two weeks earlier.

Test substance atmospheres were prepared in Tedlar bags and analysed by GC before exposure. At the initiation of the exposure, the three-way valve was turned to the bag position, and during non-exposure periods, it delivered filtered air. Each dog served as its own control, as the same dogs were used for all exposures. After each exposure, the dogs were given at least 2 days of rest before being given the next exposure.

Challenge Procedure

Time	*Event*
0 min	Start ECG recording.
2 min	Blood sample collected.
	1st adrenaline challenge (iv) (baseline).
7 min	Test substance introduced into air supply line.
12 min	Blood sample collected.
	2nd adrenaline challenge (iv).
17 min	Test substance supply discontinued.

Stop ECG recording.

Remarks - Method: Two protocol deviations occurring during the study were not considered to have compromised the validity or integrity of the study.

RESULTS

Summary of Cardiac Response

Dog Number	*Adrenaline Dose (µg/kg)*	*Test Substance Concentration <ppm>*	*Number of Premature Ventricular Contraction (PVCs):* *1st Adrenaline Challenge (baseline)*	*Number of Premature Ventricular Contraction (PVCs):* *2nd Adrenaline Challenge (exposure)*
1	2	20,000	0	0
		60,000	0	0
		120,000	0	0
2	8	20,000	0	0
		60,000	0	0
		120,000	0	1, occurring 24 seconds after injection
3	4	20,000	0	0
		60,000	0	0
		120,000	4 in 24 seconds, occurring 33 seconds after injection	3 in 6 seconds , occurring 29 seconds after injection
4	8	20,000	5 in 22 seconds, occurring 32 seconds after injection	8 in 33 seconds, occurring 27 seconds after injection
		60,000	10 in 37 seconds, occurring 23 seconds after injection	17 in 45 seconds, occurring 25 seconds after injection
		120,000	14 in 37 seconds, occurring 24 seconds after injection	16 in 57 seconds, occurring 22 seconds after injection
5	6	20,000	0	28 in 49 seconds, occurring 24 seconds after injection
		60,000	0	0
		120,000	0	0
6	2	20,000	0	0
		60,000	0	0
		120,000	0	0

Signs of Toxicity: All animals survived to study termination. There were no test substance-related clinical observations. All clinical findings in the test substance-related groups were limited to single animals, were not observed consistently and/or common findings for laboratory dogs of this age and breed.

Myocardial Effects: Challenge dosing with epinephrine while the animals were under test substance exposure did not result in the occurrence of arrhythmias such as ventricular fibrillation, tachycardia, or of an increased rate of premature ventricular contractions, compared to the pre-exposure challenge values. The results obtained did not meet the study criteria for cardiac sensitisation.

NOEL: 120,000 ppm

Remarks - Results: Body weights were unaffected by test substance administration.

CONCLUSION: There was no evidence of cardiac sensitisation under the conditions of the test.

TEST FACILITY: WIL Research Laboratories LLC (2006)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE: Notified Chemical

METHOD: Similar to OECD TG 471 Bacterial Reverse Mutation Test.

	Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA (pKM101)
Metabolic Activation System	S9 mix was prepared from the livers of phenobarbital/β-naphthoflavone induced male Sprague-Dawley rats.
Concentration Range in Main Test	a) With metabolic activation: 0, 1, 2, 5, 10, 20, 50% b) Without metabolic activation: 0, 1, 2, 5, 10, 20, 50%
Vehicle	Air
Physical Form	Gas
Remarks - Method	A gas exposure method was used. To prepare the target concentrations of the test substance, the substance and air were quantitatively injected into a gas dilution bag and mixed (5 min storage time prior to use). The vessel for the study was a gas exposure bag, which contained the plates (lids removed) and 500 mL of the test substance gas (2 plates/dose for the test substance and positive controls and 4 plates/dose for the negative control, in the presence and absence of metabolic activation). The exposure bags were maintained in an incubator at for 24 hours at 37 °C. The plates were then removed from the bags and left to stand for 20-30 minutes to allow evaporation of the test substance. The lids were then replaced on the plates, the plates turned upside down and transferred to vinyl bags before being incubated for an additional 24 hours and the numbers of revertant colonies counted. A preliminary (dose-determination) test was conducted at 0.05-50% concentration. The study report was translated from Japanese to English.

RESULTS

Metabolic Activation	*Test Substance Concentration (%) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test	> 50%	> 50%	> 50%	negative
Present				
Test	> 50%	> 50%	> 50%	negative

Remarks - Results	In the main test, the test substance did not result in an increase the number of revertant colonies, more than twice that of the negative control in any strain, with or without metabolic activation and did not inhibit bacterial growth under any condition tested. The concurrent positive controls gave satisfactory responses confirming the validity of the test system, although it is noted that these substances were not tested in the gaseous state.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Japan Bioassay Research Centre (2009)

B.10. Genotoxicity – *in vitro*

TEST SUBSTANCE	Notified Chemical
METHOD	Similar to OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test.
Cell Type/Cell Line	Cultured human lymphocytes

Metabolic Activation System	S9 fraction from Wistar rats treated with Aroclor 1254.
Physical Form	Gas
Remarks - Method	No preliminary test was conducted.

Based on the physico-chemical properties of the test substance, the culture flasks containing the human lymphocytes were exposed in modular incubator chambers to various concentrations of the test substance. The atmosphere in the chamber consisted of 19% O_2, 5% CO_2 and the test substance supplemented with N_2 (i.e. the negative control consisted of 76% N_2, 19% O_2 and 5% CO_2). The chambers were flushed with the test atmosphere using at least 5 times the volume of the chamber.

Following the exposure period, the cells were removed from the chambers (and in the case of cells treated in the presence of metabolic activation, the cells were washed with buffer and supplied with complete medium) and incubated for the relevant time period at ~37 °C in humidified air containing 5% CO_2.

A continuous exposure assay in the absence of metabolic activation was not conducted.

Mitomycin C in the absence of S9-mix and cyclophosphamide in the presence of S9-mix were used as positive controls.

Metabolic Activation	*Test Substance Concentration (%)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 10, 20, 40*, 60*, 76*	4	24
Test 2	0*, 10, 20, 40*, 60*, 76*	4	48
Present			
Test 1	0*, 10, 20, 40*, 60*, 76*	4	24
Test 2	0*, 10, 20, 40*, 60*, 76*	4	48

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (%) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 76	> 76	negative
Test 2	≥ 40	> 76	negative
Present			
Test 1	> 76	> 76	negative
Test 2	≥ 76	> 76	negative

Remarks - Results

At the harvesting time of 48 hours, in the absence of metabolic activation, the study authors indicated that the test substance appeared to be cytotoxic to the cells at the two lowest concentrations analysed (mitotic indices 61% and 50% at 60% and 40% concentration, respectively) but not at the highest concentration tested (mitotic index 81% at 76% concentration).

In both the absence and presence of metabolic activation, the test substance did not induce a statistically significant increase in the number of aberrant cells at any of the concentrations and time points analysed, when compared to the number of aberrant cells observed in the negative control cultures.

The concurrent negative and positive controls gave satisfactory responses

confirming the validity of the test system, although it is noted that these substances were not tested in the gaseous state.

CONCLUSION The notified chemical was not clastogenic to human lymphocytes treated *in vitro* under the conditions of the test.

TEST FACILITY TNO (2005)

B.11. Genotoxicity – *in vivo*

Test Substance Notified Chemical

Method Similar to OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain Mouse/CD-1 albino
Route of Administration Inhalation – whole body
Vehicle Air
Physical Form Gas
Remarks - Method Only a single dose level of the test substance was tested. Exposure duration was 4 h. The positive controls were dosed by oral gavage.

The criteria for a positive result was a significant ($p < 0.01$) increase in micronucleated polychromatic erythrocytes.

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Sacrifice Time hours*
		Nominal	*Actual*	
I (control)	5 per sex	0		48
				72
II (test substance)	5 per sex	10,000 ppm	11,497 ppm	48
				72
III (positive control, M)	5 per sex	12 mg/kg		48

M=mitomycin C.

Results
Toxicity No mortality or adverse clinical signs were seen after administration of the test substance.
Genotoxic Effects Mice treated with the test substance did not show a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes over the frequency of the air control at either 48 h or 72 h, although some increase was seen at each sampling time.

There was no significant decrease in the ratio of polychromatic to normochromatic erythrocytes (PCE/NCE ratio) after treatment of the animals with the test substance, suggesting no bone marrow toxicity occurred at this exposure level.
Remarks - Results The concurrent negative and positive controls gave satisfactory responses confirming the validity of the test system, although it is noted that the positive control substance was not administered by inhalation.

It is not clear whether the notified chemical reached the bone marrow as no toxicity was seen.

Conclusion The notified chemical was not clastogenic under the conditions of the test.

Test Facility Huntingdon Life Sciences (1997)

B.12. Genotoxicity – *in vivo*

TEST SUBSTANCE	Notified Chemical
METHOD	Similar to OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Albino mice (outbred) VAF/Plus Crl:CD-1 (ICR) BR
Route of Administration	Inhalation – nose only exposure
Vehicle	Air
Physical Form	Gas
Remarks - Method	The study was carried out as a satellite to an acute inhalation study (Huntingdon Life Sciences, 2004a).Exposure time was 4 h. Only a single dose of the test substance was tested for genotoxicity. The positive control substance was administered by intraperitoneal injection.

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Sacrifice Time hours*
		Nominal	*Actual*	
I (air control)	10 per sex	0		24 (5 per sex) 48 (5 per sex)
II (test substance)	10 per sex	100,000 ppm	103,300 ppm	24 (5 per sex) 48 (5 per sex)
III (positive control, CP)	10 per sex	40 mg/kg		24 (5 per sex) 48 (5 per sex)

CP=cyclophosphamide.

RESULTS	
Toxicity	No mortality was seen. Clinical signs were limited to wet fur.
Genotoxic Effects	No statistically significant increases in the frequency of micronucleated polychromatic erythrocytes were seen in the test group, compared to concurrent negative control values at either 24 h or 48 h after administration ($P > 0.01$ in each case). No substantial decreases in the proportion of polychromatic erythrocytes were observed in mice exposed the test substance, suggesting that there was no toxicity to the bone marrow.
Remarks - Results	The concurrent negative and positive controls gave satisfactory responses confirming the validity of the test system. It is noted that the positive control substance was not administered by inhalation. It is not clear whether the notified chemical reached the bone marrow as toxicity was not seen.
CONCLUSION	The notified chemical was not clastogenic under the conditions of the test.
TEST FACILITY	Huntingdon Life Sciences (2004b)

B.13. Genotoxicity – *in vivo*

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Rats/Sprague Dawley
Route of Administration	Inhalation –oro-nasal exposure
Vehicle	Air
Physical Form	Gas
Remarks - Method	The study was carried out as a satellite to a 28-day repeated dose inhalation study (TNO Quality of Life, 2006). Examination of the test groups was performed at the end of the 28 day exposure period. The positive control substance was administered by intraperitoneal injection.

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Sacrifice Time hours*
		Nominal	*Actual*	
control	5 M	0	0	24
low mid dose	5 M	5,000	5,000 ± 96	24
high mid dose	5 M	10,000	9,979 ± 39	24
high dose	5 M	15,000	14,895 ± 474	24
positive control, M	5 M*	1.5 mg/kg/bw	not tested	24

*M=mitomycin C (exposed by intraperitoneal injection)

RESULTS

Doses Producing Toxicity	The mean numbers of polychromatic erythrocytes per number of erythrocytes in the rats exposed to the three levels of test substance were not statistically significant different from the numbers of polychromatic erythrocytes per number of erythrocytes found in the controls. Therefore, no treatment related cytotoxicity could be demonstrated in the target cells of the rat bone marrow.
Genotoxic Effects	The treatment with three exposure levels of the test substance did not yield a statistically significant increase in micronucleated polychromatic erythrocytes. It was considered that the treatment did not result in genotoxicity to the bone marrow target cells.
Remarks - Results	The results of two rats in the positive control group were not used for statistical analysis as the level of micronucleated polychromated erythrocytes were unusually low in these animals, possibly due to failed peritoneal injections. The concurrent negative and positive controls (excluding the two rats in the positive control group) gave satisfactory responses, confirming the validity of the test system. The ratio of polychromatic erythrocytes (PCE) to normatochromatic erythrocytes (NCE) did not change significantly in the test groups, compared to the negative controls, indicating that the notified chemical was not toxic to the bone marrow. However, systemic exposure is expected to have occurred, based on changes noted in the concurrent 28-day repeated dose study.

CONCLUSION The notified chemical was not clastogenic under the conditions of this *in vivo* micronucleus test.

TEST FACILITY TNO Quality of Life (2006)

B.14. Genotoxicity – *in vivo*

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 486 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo*.

Species/Strain	Rats/Sprague Dawley
Route of Administration	Inhalation –oro-nasal exposure
Vehicle	Air
+Physical Form	Gas
Remarks - Method	The study was carried out as a satellite to a 28-day repeated dose inhalation study (TNO Quality of Life, 2006). The protocol was altered to decrease the dosing volume from 20 mL/kgbw to 10 mL/kg bw for the positive control.

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Sacrifice Time hours*
		Nominal	*Actual*	
control	5 + 2 M	0	0	24

low mid dose	5 + 2 M	5,000	5,000 ± 96	24
high dose	5 + 2 M	15,000	14,895 ± 474	24
positive control, 2-AAF	5 M	10 mL.kg/bw	not tested	12-16

2-AAF= 2-Acetylaminofluorene (administered by gavage)

RESULTS

Doses Producing Toxicity	One animal of positive control group died within 12 hours after dosing, due to incorrect gavage.
Genotoxic Effects	Both the test substance and the negative control showed NNG (net nucleus grains) ≤ 0. Since exposure to the test substance did not induce NNG ≥ 5, it was considered that the test substance did not induce unscheduled DNS synthesis in rat hepatocytes.
Remarks - Results	The positive control did not induce NNG ≥ 5 with at least 20% of the cells in repair, the criteria for genotoxicity set by the test laboratory. The study author attributed this to the reduction in dosing volume (from 20 to 10 mL.kg/bw), which may have decreased the fraction of the positive control available for absorption, due to the limited solubility. However it was noted the mean net nuclear grains (NNG) determined for the positive control (-6.31) was clearly higher than the mean NNG of the negative control (-9.78) and the test substance (-13.04 and -11.82). The percentage "cells in repair" was also higher for the positive control group (3.25%) versus the negative control group (0.50%) and the test substance groups (both 0.20%). Negative controls and background counts were within historical range. As the study was conducted as part of a 28-day study and effects were seen during the study, it is expected that the liver cells were exposed to the notified chemical.

CONCLUSION The notified chemical was not clastogenic under the conditions of this *in vivo* unscheduled DNA synthesis Test.

TEST FACILITY TNO Quality of Life (2006)

B.15. Developmental toxicity

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 414 Prenatal Development Toxicity Study.

Species/Strain	Rabbits/New Zealand White
Route of Administration	Inhalation – whole body
Exposure Information	Exposure days: day 6 through to day 28 of gestation Duration of exposure (inhalation): 6 hours/day Post-exposure observation period: none
Vehicle	Air
Physical Form	Gas
Remarks - Method	The purpose of this study was to assess gross maternal and/or embryo-foetal toxicity of notified chemical in a non-rodent species, the rabbit. Dose levels were chosen on the basis of a range-finding study. On gestation Day 24, one animal from 10,000 ppm group was exposed to the test substance for approximately 3 hours instead of 6 hours. This and another minor protocol deviation were not considered to have compromised the validity or integrity of the study.

RESULTS

Group	*Number of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
1	22 F	0	0	0
2	22 F	4,000	4,037	0
3	22 F	10,000	10,288	0
4	22 F	15,000	15,058	0

Effects on Dams

No mortality was seen. In-chamber observations were within normal limits on all exposure days for all test groups.

There were no exposure related differences in body weights, body weight gains and feed consumption in the test substance exposed animals during the gestation period as compared with the air control group.

There were no test substance related macroscopic abnormalities. Macroscopic findings were typical of the background findings seen in rabbits of this age.

There were no test substance related effects on pregnancy status. However, a reduced pregnancy rate of 73% and 77% was observed at 4,000 and 10,000 ppm, respectively. This change is not dose related and is unlikely to be affected by treatment as it would have been determined prior to dosing.

There was no difference between the groups pertaining to the number of corpora lutea, number of implantations, or sex ratio (% male). The decrease in pre-implantation loss (%) at ≥ 4,000 ppm was unlikely affected by treatment as these parameters were established prior to initiation of exposure.

However, there were increases in post-implantation losses (%) at ≥ 4,000 ppm. These increases were not considered adverse because they did not occur in an exposure related manner, were not statistically significant and the values were within the historical control values held by the Test Facility.

There were no test substance related effects on gravid uterine or placental weights. Body weight changes (gestation day 6 to 29) were reduced at 4,000 and 10,000 ppm, while adjusted body weight changes were increased when compared with control animals. The study author considered this is due to the exclusions of the non-pregnant animals from group means at the end of the study.

Effects on Foetus

There were no test substance related effects on foetal weights or on foetal external, visceral or skeletal abnormalities.

CONCLUSION

The No Observed Effect Concentration (NOEC) was established as 15,000 ppm in this study, based on that no effects of exposures on survival, clinical signs, body weights, food consumption or maternal or foetal findings at sacrifice.

TEST FACILITY Huntingdon Life Sciences (2010)

B.16. Developmental toxicity

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 414 Prenatal Development Toxicity Study.

Species/Strain	Rats/Wistar
Route of Administration	Inhalation –oro-nasal exposure
Exposure Information	Exposure days: day 6 through to day 20 of gestation Duration of exposure (inhalation): 6 hours/day Post-exposure observation period: none
Vehicle	Air
Physical Form	Gas

Remarks - Method

The study was carried out concurrently with a sub-chronic (13-week) inhalation toxicity study in rats (TNO Quality of Life, 2008).

Three protocol deviations occurring during the study were not considered to have compromised the validity of the study.

RESULTS

Group	*Number of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
control	24 F	0	0	0
low dose	24 F	1,500	1,504 ± 3	0
mid dose	24 F	5,000	5,003 ± 10	0
high dose	24 F	15,000	14,997 ± 15	0

Effects on Dams

Daily clinical observations during the gestation period did not reveal any remarkable findings in the animals' appearance, general condition or behaviour between the dosing and control groups.

No effect was seen on the mean body weight and on food consumption.

In each group, 24 females were mated of which 21, 20, 22 and 19 female of the control and low-, mid- and high-dose group, respectively, appeared to be pregnant and had live foetuses at caesarean section. One female in the high dose group had an early delivery on gestation day 21 just before scheduled necropsy. Ten pups were born with no remarkable gross observations. No statistically significant differences were observed in the female fecundity index, gestation index, number of corpora lutea, the number of implantation sites, number of live foetuses, or the sex ratio. The relative high value for post-implantation loss in the high-dose group was caused by two animals (one with post-implantation loss 50% and another 93.3%).

No effect was seen on the weight of gravis uterus, empty uterus and ovaries. The carcass weight and net weight change from gestation day 6 were not affected. Macroscopic findings at necropsy did not reveal any remarkable or treatment related findings among the dosing and control groups.

Effects on Foetus

No statistically significant differences in the incidences of foetal external observations and/or placental findings were observed. Foetal and placental weights were not affected. No treatment related effects were observed at visceral and skeletal examination.

CONCLUSION

The No Observed Adverse Effect Concentration (NOAEC) was established as 15,000 ppm in this study, based on that the notified chemical did not induce maternal or prenatal developmental toxicity at any dose tested.

TEST FACILITY TNO Quality of Life (2007)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test.
Inoculum	Secondary effluent of municipal sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Dissolved oxygen was determined by iodine titration to calculate the biological oxygen demand (BOD). Test substance concentrations were also determined by gas chromatography (GC) with flame ionisation detector.
Remarks - Method	The test was conducted in accordance with the guideline above and in compliance with OECD principles of Good Laboratory Practice. A test substance saturated solution of 739 mg/L was prepared by bubbling the test substance through purified water. The concentration of the test substance in the test solutions was 7.39 mg/L. The ThOD was determined to be 7.26 mg O_2/L.

RESULTS

Day	*% Degradation*		
	Test Substance		*Sodium Benzoate*
	By BOD	*By GC*	
7	3	-	69
14	0	-	82
21	1	-	76
28	0	0	68

- not determined

Remarks - Results	All validity criteria were satisfied. A toxicity control was not performed.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	CERI (2008b)

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