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June 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1-Propene, 1-chloro-3,3,3-trifluoro-, (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 conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment.

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 CHEMICAL	INTRODUCTION VOLUME	USE
STD/1499	Honeywell Polymers Australia Pty Ltd	1-Propene, 1-chloro-3,3,3-trifluoro-, (1E)-	No	≤ 300 tonnes per annum	Foam blowing agent, solvent for cleaning, degreasing or lubricating, 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).

The environmental hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute Category 3	H402 - Harmful to aquatic life
Chronic Category 3	H412 - Harmful to aquatic life with long lasting effects

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 products:
  - Local exhaust ventilation for non-enclosed processes, when possible.

- 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 (M)SDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should 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 cardiotoxicity or carcinogenicity 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, solvent for cleaning, degreasing or lubricating, propellant for industrial aerosol cans, refrigerant, or is likely to change significantly;
- the amount of chemical being introduced has increased, 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.

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

NOTIFICATION IN OTHER COUNTRIES
APPLICANT(S)
Honeywell Polymers Australia Pty Ltd (ABN: 35 008 423 096)
OMIT, Ground Level, 71 Queens Rd, Melbourne VIC 3004

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
Japan and Europe

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)

Solstice 1233zd

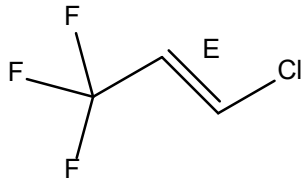
CAS NUMBER
102687-65-0

CHEMICAL NAME
1-Propene, 1-chloro-3,3,3-trifluoro-, (1E)-

OTHER NAME(S)
1233zd, Solstice PF, Solstice LBA

MOLECULAR FORMULA
$C_3H_2ClF_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
130.5 Da

ANALYTICAL DATA
Reference ^{1}H-NMR, ^{19}F-NMR, IR, GC and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
99.95%

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 °C AND 101.3 kPa: clear gas

Property	Value	Data Source/Justification
Melting Point	< -90 °C	Measured
Boiling Point	19 °C at 102.1 kPa	Measured
Saturated Liquid Density	1273 kg/m^3 at 20 °C	Calculated
Saturated Vapour Density	5.845 kg/m^3 at 20 °C	Calculated
Vapour Pressure	106.52 kPa at 20 °C	Measured
Water Solubility	1.9 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Not expected as the notified chemical does not contain readily hydrolysable functionalities
Partition Coefficient (n-octanol/water)	log Pow = 2.2 at 25 °C	Measured
Adsorption/Desorption	Log K_{oc} = 1.9	Calculated (from log Kow = 2.2 - user

		entered, KOCWIN v2.00; US EPA, 2011)
Dissociation Constant	Not Determined	Not expected to dissociate based on the structure of the notified chemical
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	380 °C	Measured
Explosive Properties	Not explosive	Based on the chemical structure.
Oxidising Properties	Not oxidising	Based on the chemical structure.

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties, refer to Appendix A.

Reactivity
Stable under normal conditions of use.

At higher temperatures (> 250°C), decomposition products may include hydrochloric acid (HCl), hydrofluoric acid (HF) and carbonyl halides.

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.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported in ISO tanks and pressurised cylinders at 100% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	100	100	250	250	300

PORT OF ENTRY
Melbourne

IDENTITY OF RECIPIENTS
A-Gas (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be stored in ISO tanks and pressurised cylinders and transported by road.

USE
The notified chemical is proposed for the following uses:

- Blowing agent for polyurethane or polystyrene closed cell foam (70% total import volume);
- A solvent for cleaning, degreasing, or lubricating (25% total import volume);
- Refrigerant for commercial refrigerators or air conditioning (< 5% total import volume);
- Refrigerant for waste heat recovery systems employing the organic rankine cycles (< 1% total import volume).

OPERATION DESCRIPTION
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 will then be discharged at low pressure through a pouring tube into a mould, where it will be left to partially cure and solidify, and then put out onto a pallet to complete the curing process. The foam will then be cut to size. The foam will be used for insulation in commercial and residential structures such as roofs, walls, foundations, storage tanks, insulated panels, refrigerated truck bodies, etc.

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

The notified chemical will also be used for the cleaning/degreasing of electronics parts, avionics parts, or similar. This typically takes place in a vapour degreaser consisting of one or more sumps containing liquid solvent with a dense layer of solvent vapour above. The vessel containing the notified chemical will be directly connected to the vapour degreaser in a closed loop. Cleaning of the part will involve it being immersed in the liquid solvent and then suspended in the vapour zone.

Refrigerant for commercial air conditioning and refrigeration systems or refrigerant for organic rankine cycles
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, refrigeration units and organic rankine cycles 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, refrigeration units and organic rankine cycles 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.

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
Blowing agent		
Storemen	8	260
Blending / foam production workers	8	260
Refrigerant		
Storemen	0.2	50
Repackaging workers	0.2	50
Refrigeration technicians	0.2	10
Aerosol		
Aerosol fillers	8	260
Users of industrial aerosols	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 Safety Data Sheet (SDS) provided by the notifier, local exhaust ventilation is recommended, together with 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 SDS also recommends that workers avoid breathing vapours, mist or gas and avoid contact with skin, eyes and clothing.

Blowing agent
Due to the 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 local exhaust ventilation (LEV) during foaming, and personal protective equipment (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, the expected low diffusion rate and the installation of the foam in exterior locations only. Worker exposure from this use is expected to be low.

Refrigerant or cleaning/degreasing use
When used as a refrigerant for commercial air conditioning, refrigeration systems, organic rankine cycles, or vapour cleaning/degreasing worker exposure may occur during installation, filling, topping-up and emptying air conditioning units, refrigeration systems, organic rankine cycles, and vapour degreasers particularly when connecting and disconnecting transfer hoses. Engineering controls such as use of closed systems for transfer of the chemical, LEV, and 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.

Aerosols
For aerosol can uses, the notified chemical will be released as an inherent part of the end-use spray product and largely volatilised. Workers are likely to be exposed to the notified chemical primarily via inhalation, when the product containing the notified chemical at 10-75% 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.

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) to estimate potential exposure concentrations of notified chemical from use as a propellant. The vapour generation rate is assumed to be constant throughout the day; this accounts for the aggregate exposure scenario of multiple workers using propellant 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

For the use of sprays for specialised industrial applications where worker exposure to the notified chemical is expected to occur, 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, 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, air conditioners, or organic rankine cycle through accidental leakage; however, it is expected that this would not generally result in public exposure, due to the commercial nature of these units. In addition, such commercial equipment is typically fitted with detectors designed to detect small leaks and any leaks are required to be fixed prior to system start-up. Public exposure to the notified chemical through its migration from foam insulation is expected to be very low.

The notifier states that the diffusion rate of the notified chemical through the walls of foam cells such as residential foam insulation or a refrigerator/freezer is very low, in the order of $10 – 150 \times 10^{-4}$ m^2/sec (based on data for a related chemical), compared with the diffusion rate of CO_2 being 9800×10^{-4} m^2/sec. This low diffusion rate indicates very low level of release of the notified chemical over the life of the foam.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute inhalation toxicity	LC50 = 640 mg/L/4 hour; low toxicity (120,000 ppm)
Rabbit, skin irritation	non-irritating
Human, skin sensitisation – RIPT	no evidence of sensitisation
Rat, repeat dose inhalation toxicity – 14 days.	NOAEC = 11 mg/L (2,000 ppm)
Rat, repeat dose inhalation toxicity – 28 days, with unscheduled DNA synthesis test and mammalian erythrocyte micronucleus test	NOAEC = 24 mg/L (4,500 ppm); non-genotoxic
Rat, repeat dose inhalation toxicity – 90 days.	NOAEC = 21 mg/L (4,000 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 (Mice) Erythrocyte Micronucleus Test	non genotoxic
Rabbit, prenatal developmental toxicity	Foetal NOEC = 80 mg/L (15,000 ppm) Maternal NOEC = 80 mg/L (15,000 ppm)
Rat, prenatal developmental toxicity	Foetal NOAEC = 53 mg/L (10,000 ppm) Maternal NOEC = 80 mg/L (15,000 ppm)
Rat, two generation reproduction toxicity	Parental toxicity NOEL = 27 mg/L (5,000 ppm) Fertility and development toxicity NOEL = 80 mg/L (15,000 ppm)

Toxicokinetics, metabolism and distribution

In studies on the biotransformation of the notified chemical (Schmidt et al., 2013), male Sprague-Dawley rats and female albino New Zealand rabbits were exposed by inhalation to levels of 2,000, 5,000, and 10,000 ppm for 6 hours. Urine was collected for 48 hours after the end of the exposure time and urinary metabolites were identified by ^{19}F-NMR, LC-MS/MS and GC/MS.

The major metabolites identified in rat urine were 3,3,3-trifluorolactic acid (32%) and *N*-acetyl-S-(3,3,3-trifluoro-*trans*-propenyl)-*L*-cysteine (40%). Other metabolites included S-(3,3,3-trifluoro-*trans*-propenyl)-mercaptolactic acid; trifluoroacetic acid; 3,3,3-trifuoro-1,2-dihydroxypropane; and 3,3,3-trifluoropropionic acid. In rabbit urine, *N*-acetyl-S-(3,3,3-trifluoro-*trans*-propenyl)-*L*-cysteine (46% of the total) was identified. Other metabolites included S-(3,3,3-trifluoro-*trans*-propenyl)-mercaptolactic acid; trifluoroacetic acid; 3,3,3-trifluoro-1,2-dihydroxypropane, S-(3,3,3-trifluoro-trans-propenyl)-*L*-cysteine and 3,3,3-trifluoro-1-propanol. These metabolites suggest that the notified chemical is metabolised via glutathione conjugation and by oxidative metabolism by cytochrome P-450. *In vitro* studies were also carried out in the presence of liver microsomes from

rats, rabbits and humans in the presence or absence of glutathione and/or a NADPH regenerating system. S-(3,3,3-trifluoro-*trans*-propenyl)-glutathione was the major metabolite in the liver microsomes when glutathione was present.

The quantified amounts of the metabolites excreted with urine in both mice and rabbits, suggest only a low extent and rate of biotransformation of the notified chemical (~ 0.01% of dose received in rabbits, and ~0.002% of dose received in rats); the major metabolites were excreted rapidly after the end of the exposures ($t_{1/2}$ < 6 h).

Breath by breath (BBB) and constant flow (CF) models were developed for adult female humans under acute and chronic exposure scenarios and compared to equivalent scenarios for rats and pregnant rabbits using experimentally derived NOELs of 4,000 ppm and 15,000 ppm, respectively for these species. As the only route for uptake and elimination in the model is via inhalation and exhalation, the most sensitive parameter in the model is the blood:air partition coefficient, which was determined to be lower for humans than for rats or rabbits (refer table below). Therefore, equivalent exposure concentrations result in a delivered dose to the systemic circulation of a female human that is less than half as much as a rat.

Tissue type	*Blood:air partition coefficient (n = 10) (mean ± standard deviation)*
Human whole blood, female	0.586 ± 0.085
Rabbit whole blood	0.897 ± 0.076
Rat whole blood	1.49 ± 0.218

To provide an evaluation of the relative risk of human exposure to the notified chemical, comparisons were made between human and animals based on the total dose received in blood (Area Under the Curve (AUC) values) and the peak concentration in arterial blood (Cmax). The AUC for potential human exposure at the occupational exposure limit (OEL = 400 ppm), was compared with the AUC values at the experimentally derived NOELs for the two animal species, to determine a corresponding margin of safety. Monte Carlo (MC) PBPK was used to address uncertainty in the predicted margins of safety, by considering the 95th percentile, rather than the mean model parameter values. With this conservative approach, the safety margins were 36.2 for the rabbit (6 hr – 14 day exposure in rabbit, compared to 8 hr – 14 day exposure in human), and 11.4 for the rat (same exposure comparison).

The model also estimated concentrations at which the human blood dosimetric matches that of the rabbit and rat at their respective NOELs. The results indicate that higher exposure is required for the human to reach the animal dosimetric, for both the rabbit and rat scenarios.

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 investigated for acute inhalation toxicity in rats. The LC50 was found to be 640 mg/L/4 hour, indicating low acute inhalation toxicity. However, several animals died during exposure at the mid and high dose levels and showed effects in the lungs at necropsy.

Irritation and sensitisation
The notified chemical was non-irritating to the skin of rabbits. An eye irritation study was not performed. Histopathological results of repeated dose inhalation studies suggest that the notified chemical is not irritating to the respiratory system.

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 20,000 ppm in a pilot 14-day study, and up to 10,000 ppm and 15,000 ppm in 28-day and 90-studies, respectively. No test substance related mortalities were observed in any of the groups. The heart was the organ most affected and males tended to be more susceptible to the notified chemical than females. In the 14-day and 90-day studies, test substance related increases in multifocal mononuclear cell infiltrates in the heart were seen (in both males and females at high doses, and only males at some lower doses). In the 28 day study mononuclear cell infiltrates were observed in

the hearts of all dose groups and also in control animals at a similar frequency to the dose groups and was thus not considered to be treatment related. Changes in some clinical chemistry parameters were seen, mainly in high dose animals. It is noted that in the 28-day study, which is the only one to have included a post-exposure recovery period (of 14 days), the clinical chemistry changes were not observed at the completion of this recovery period. In the 90-day study, the NOAEC could not be established due to the multifocal mononuclear cell infiltrates in the heart of males at all dose levels. Thus the LOAEC in this study was determined to be 4,000 ppm. According to a subsequent review by an external expert, the cardiac lesion that was observed in a single male at the 4,000 ppm dose level was not considered to be adverse because of its particular location within the heart and its similarity to normal lesions seen in this strain of rat. On the basis of this later review, 4,000 ppm may instead be considered to be the NOAEC for the notified chemical in the 90-day study (Environmental Pathology Laboratories 2013).

Mutagenicity
When administered as a gas, 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*, or mouse micronucleus erythrocytes *in vivo*. Genotoxicity (unscheduled DNA synthesis and examination of micronuclei in bone marrow) of the notified chemical was also investigated as part of a 28 day repeated inhalation study. It was found to be non-genotoxic. Based on these results, the notified chemical is not suspected to be genotoxic.

Cardiac sensitisation
There was no evidence of cardiac sensitisation to the notified chemical in beagle dogs at all doses tested. However, it is noted that at the mid and high dose levels (35,000 and 50,000 ppm, respectively), cardiac sensitisation could not be definitively evaluated due to the presence of tremors during exposure.

Developmental toxicity
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 NOEC for maternal toxicity was set at 15,000 ppm, the highest dose tested. In one of the studies, an increased incidence of dilated urinary bladders was observed in foetuses of the high dose group and thus the NOAEC for foetal toxicity was established as 10,000 ppm.

Reproductive toxicity
Based on a two-generation reproduction toxicity study in rats carried out to OECD TG 416, the No Observed Effect Level (NOEL) for parental toxicity for exposure to the test substance by inhalation was considered to be 5,000 ppm, due to mortality of two P-females and one F1-female of the high-dose (15,000 ppm) at the end of lactation period. The NOEL for fertility and development toxicity for exposure to the test substance by inhalation was considered to be 15,000 ppm, because no adverse effects on fertility parameters or offspring were observed.

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

NICNAS recently completed the assessment (STD/1479) of 1-Propene, 1,3,3,3-tetrafluoro-, (1E)-, which is structurally similar to the notified chemical. Based on a weight of evidence approach, which also included the evaluation of data from toxicogenomic assays for mouse lung carcinogenicity, NICNAS concluded that the totality of the evidence/data does not support a significant risk for lung tumour induction in humans after inhalation exposures to 1-Propene, 1,3,3,3-tetrafluoro-, (1E)- under realistic exposure conditions. However it was not possible to rule out carcinogenicity potential.

Based on the above considerations, while carcinogenicity concerns for the notified chemical are unlikely, the risk cannot be ruled out.

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. 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, the SDS indicates that it can ignite when mixed with air under pressure and exposed to strong ignition sources. 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. In addition, contact with rapidly evaporating liquid can cause frostbite to skin or damage to the eyes.

Hazardous decomposition products may be formed after heating or combustion, including hydrochloric acid (HCl), hydrofluoric acid (HF) and carbonyl halides.

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, developmental or reproductive toxicity. Eye irritation was not tested. Acute inhalation toxicity was evaluated as low, with LC50 values of 120,000 ppm (640 mg/L) in rats. In a 90-day repeated dose inhalation study in rats, a No Observed Adverse Effect Concentration (NOAEC) could not be established based on changes in the heart of at least one male in all concentration groups. Thus the Lowest Observed Adverse Effect Concentration (LOAEC) was determined to be 4,000 ppm (21 mg/L). Related low level effects on the heart were also seen in shorter term studies (14-day and 28-day) though they were only considered to be adverse in the 14 day study. Overall, uncertainties in the health effects profile relate to the dose level for onset of cardiotoxic effects after repeated exposure.

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 (OARS 2013).

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 SDS.

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 air conditioning, refrigeration units, organic rankine cycles, and vapour cleaning/degreasing, 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.

The risk to workers who regularly use aerosol cans which contain the notified chemical at up to 100% in the absence of PPE in the workplace can be estimated by calculation of the margin of exposure (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 483 mg/m^3. The workplace adjusted NOAEC is estimated on the rat NOAEC of 4,000 ppm (i.e., 21,350 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. The MoE for workers using these aerosol products is estimated at 139, 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

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.

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 for in Australia 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 for air conditioning and refrigeration systems or for organic rankine cycles. The notified chemical in 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 aerosol can products are likely to be disposed of to landfill.

7.1.2. Environmental Fate

The notified chemical is not 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 = 2.2). 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 6% 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, hydrochloric acid (HCl) and hydrofluoric acid (HF) 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. Some of the notified chemical associated with foam articles or aerosol products may be disposed of to landfill. However, as the notified chemical is highly volatile, 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 1.02×10^{-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 ($t_{½}$ = 45.8 days, $k_{O3} = 2.5 \times 10^{-19}$ cm^3/molecule.s; AOP v1.91; US EPA 2011). Further information on the atmospheric chemistry of the notified chemical is reported in the published literature and is summarised below.

Andersen et al. (2008) 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 four weeks.

	Chlorine atoms	Hydroxyl radicals	Ozone
Rate constant (k; cm^3/molecule.s)	5.22×10^{-11}	4.40×10^{-13}	1.46×10^{-21}
Atmospheric concentrations	*	1.0×10^6 molecules/cm^3	35 ppb
Atmospheric lifetime		26 days	25 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 24.3 days. Therefore, as the half-life is greater than 2 days, the notified chemical is considered to be persistent in the atmospheric compartment.

Andersen et al. (undated) 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, hydrochloric acid, hydrofluoric acid and trifluoroacetic acid (TFA). The extent of conversion of the notified chemical to TFA is less than 10%. 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.

Due to the long atmospheric lifetime of the notified chemical (about four 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 (2007) report concludes that cumulative anthropogenic sources of TFA, such as from the degradation of hydrofluorocarbons (HFCs), are smaller than natural sources.

7.1.3. Predicted Environmental Concentration (PEC)

A predicted environmental concentration (PEC) cannot be calculated for the aquatic compartment because the notified chemical is highly volatile 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.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 (96 h) = 38 mg/L	Harmful to fish
Daphnia Toxicity	EC50 (48 h) = 82 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	NOE_rC (72 h) = 115 mg/L	Not harmful to aglae

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is harmful to fish and aquatic invertebrates. Therefore, the notified chemical is formally classified as "Acute Category 3, Harmful to aquatic life" under the GHS.

Based on its lack of rapid degradability and acute endpoints, the notified chemical is formally classified as "Chronic Category 3, Harmful to aquatic life with long lasting effects" under the GHS.

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 four weeks, the GWP relative to carbon dioxide (CO_2) on a 100-year time horizon is 7 (Andersen et al, 2008). 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 2100 tonnes of CO_2 [Total import volume × GWP = 300 T ×7 = 2100 T]. 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 0.00038% to current Australian greenhouse gas emissions.

The notified chemical has a potential to contribute to stratospheric ozone depletion because it contains chlorine atoms. The ODP of the notified chemical was reported as up to 0.00024 (Wang et al, undated). 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. 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

Melting Point/Freezing Point < -90 °C

Method	OECD TG 102 Melting Point/Melting Range. EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks	Differential scanning calorimetry (DSC) was used. Freezing and/or melting of the test substance was not observed at -90 °C.
Test Facility	NOTOX B.V. (2010)

Boiling Point 19 °C at 101.1 ± 0.1 kPa

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	DSC was used.
Test Facility	NOTOX B.V. (2010)

Density 1273.37 kg/m^3 at 20.06 °C (saturated liquid density)
5.845 kg/m^3 at 20 °C (saturated vapour density)

Method	Internal method
Remarks	The saturated liquid density was determined using vibrating tube densitometer (Anton Paar DMA HPM). The saturated vapour density was calculated using an equation of state as outlined by Walas (1985). The Peng-Robinson required only the critical temperature, critical pressure and acentric factor of the fluid in order to calculated the vapour density.

Vapour Pressure 106.52 kPa at 19.93 °C

Method	Internal method
Remarks	It was measured using a vessel fitted with a previously calibrated pressure reducer and immersed in a thermostated bath. A sufficient amount of a degassed sample of notified chemical was introduced into the vessel so that the vessel would be between 10% and 80% liquid filled at all temperatures of interest. The vessel was given sufficient time to reach thermal equilibrium and the pressure and temperature were recoded. The bath temperature was then changed to the next desired temperature and the procedure was repeated. The pressure was measured using a MKS pressure transducer, which was heated to 100 ºC to avoid condensation. The temperature of the bath was measured using a platinum thermometer.

Water Solubility 1.9 g/L at 20 °C

Method	OECD TG 105 Water Solubility.
Remarks	Flask Method. Three aliquots of the liquid test substance were added into three separate glass vessels. The vessels were completely filled with water to avoid head space and evaporation loss. After stirring for 1, 3 and 5 hours, excess liquid test substance was observed in each sample which separates from water phase at the bottom of the vessels. The clear aqueous phase was sampled for water solubility determination. The pH of the aqueous samples was 7.5-7.6.
Test Facility	NOTOX B.V. (2010)

Partition Coefficient (n-octanol/water) log Pow = 2.2 at 25 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method.
Test Facility	CERI (2009a)

Flammability Not flammable

Method	EC 440/2008 incorporating EC's "Classification, Packaging & Labelling of Dangerous Substances in the European Union" Part 2, Testing methods, Jan 97. Directive 92/69, Annex V to Council Directive 67/548/EC.
Remarks	When tested according to the protocol, small, localised ignitions were observed but the flame did not detach from the ignition source or propagate. At some gas concentrations, a small blue or orange flame was seen.
Test Facility	Chilworth Technology Limited (2010)

Autoignition Temperature 380 °C at 98.68-103.59 kPa

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	A commercially available auto-ignition temperature apparatus was used.
Test Facility	NOTOX B.V. (2010)

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	NOTOX B.V. (2010)

Oxidizing Properties Not oxidising

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).
Remarks	Through examination of the structural formula it has been concluded that the chemical will not possess oxidising properties.
Test Facility	NOTOX B.V. (2010)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity.
Species/Strain	Rats/SPF-reared, Sprague Dawley
Vehicle	Air
Method of Exposure	Nose-only exposure.
Exposure Period	4 hours
Physical Form	Vapour
Remarks - Method	Two pilot studies were conducted, with the first using one male and female rat exposed to 200,000 ppm and the second using one male and female rat exposed to 50,000 ppm. Minor protocol deviations occurring during the study were 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	5 per sex	96,000	102,896	95,971 ±6,940	1 F
2	5 per sex	120,000	123,032	120,256 ± 699	3 M, 1 F
3	5 per sex	156,000	161,398	131,148 ± 3,551*	5M, 5F

*The authors indicate that this concentration is likely to be an underestimation due to a deviation in the measuring equipment.

LC50	For males 118,200 ppm/4 hours (95% confidence interval of 102,300 - 137,500 ppm) For females 121,700 ppm/4 hours (95% confidence interval of 105,400 - 141,800 ppm) Combined 120,000 ppm/ 4 hours (95% confidence interval of 108,500 - 133,800 ppm)
Signs of Toxicity	The animals in group 1 exhibited slight tremors in tail and body and were restless during exposure. The tremors in the tail and body were also observed in group 2. These tremors might be a sign of neurotoxicity of the test substance. Shortly after exposure in group 1, lethargy, hunched appearance, piloerection, blepharospasm, exophthalmus and restlessness were noted among the females, while restlessness and a red/brown discolouration of the head were observed in one male animal. Shortly after exposure, the surviving animals of group 2 demonstrated hunched appearance, irregular breathing at a decreased rate and in some cases mouth breathing and piloerection. Clinical signs observed during the 14-day observation period among the surviving animals of groups 1 and 3 included ataxia, lethargy, hunched posture, restlessness, blepharospasm, exophthalmus, red eyes and piloerection. These signs were only observed during the first few days of the observation period.
Effects in Organs	Red discolouration of the lungs was the main macroscopic finding of animals that died during exposure, with some lungs also enlarged. Red spots on the thymus were found in two female animals of group 3. Three animals of group 2 had a black discoloured tail. No abnormalities were found at necropsy of the animals that survived the exposure and 14-day observation period apart from grey discoloured lungs in some animals of group 1, in some cases accompanied by petechiae.

Remarks - Results	The male and female animal in the first pilot experiment died after 30 and 12 minutes of exposure to the test substance, respectively. Both animals in the second pilot demonstrated shallow breathing at an increased rate during exposure, but survived the treatment and exhibited no abnormalities shortly after exposure or during the observation period. The two animals of pilot 1 displayed haemorrhagic discharge from the mouth and nose.
CONCLUSION	The notified chemical is of low toxicity via inhalation.
TEST FACILITY	TNO (2009)

B.2. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	1 M, 2F
Vehicle	None
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	The notified chemical as a liquefied gas was extracted from a cylinder and chilled on ice prior to dosing. 0.5mL per site was placed on a patch and secured to the test site.

RESULTS

Remarks - Results	No erythema or oedema was observed in any animal at 60 minutes, 24, 48 and 72 hours following the 4 hour exposure. There were no abnormal physical signs noted during the observation period. No reductions in body weight were noted.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	MB Research Laboratories (2012)

B.3. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	*Induction Procedure:* 9 applications of the test substance (0.2 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:* during the sixth week of the study, 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	94 F, 29 M; age range 18-68 years
Vehicle	None
Remarks - Method	Semi-occluded. The test substance was spread on a 2 cm × 2 cm patch.

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: 123 subjects were enrolled and 106 subjects completed the study. Fourteen subjects were lost to follow-up, 2 subjects voluntarily withdrew and one had protocol violation due to hepatitis C.

There were no adverse responses reported during the study.

CONCLUSION: The notified chemical was non-sensitising under the conditions of the test.

TEST FACILITY: TKL Research INC (2012)

B.4. 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 – whole body 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: 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	2000	1994 ± 1	0
mid dose	5 per sex	7500	7496 ± 5	0
high dose	5 per sex	20000	19955 ± 6	0

Clinical Observations

At the start of the generation of the test atmosphere the test animals were more restless than the control animals. This effect only lasted about 15 minutes. Daily observations did not reveal any other exposure related clinical abnormalities.

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

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

An increase in prothrombin time was found in females of the high dose group. Males of the high dose group showed an increase in absolute number of neutrophils and an increase in absolute and relative number of monocytes.

An increase in ALAT (alanine aminotransferase activity) and ASAT (aspartate aminotransferase activity) was found in males of the high dose group. This was not found for females, but a slight trend was found for increasing ASAT levels. Females of the mid and high dose groups showed an increase in glucose

concentrations. Males and females of the high dose group showed an increase in urea concentrations.

Effects in Organs
Male animals of the higher dose group showed a decreased absolute spleen weight while the relative weight was not significantly decreased.

Remarks – Results
Three females from the high dose group had livers with (focal) pale appearance.

Treatment-related histopathological changes in the heart of the animals of the high dose group, characterised by multifocal mononuclear cell infiltrates, were observed. Based on the observations, it appeared that the males were slightly more susceptible to the test substance than the females. Mononuclear cell infiltrates were present in 3/5 mid-dose males but not in the low-dose males and in none of the low- or mid dose females. Whilst these changes are considered treatment-related, it is noted that the minimal focal mononuclear cell infiltrate observed in the heart of several animals are common findings and they were considered part of background pathology.

The livers showed some variation in hepatocellular vacuolation but it was not considered to be related to the treatment.

CONCLUSION
The No Observed Adverse Effect Concentration (NOAEC) was established as 2000 ppm in this study, based on the histopathological effects.

TEST FACILITY TNO Quality of Life (2008)

B.5. Repeat dose toxicity, including genotoxicity investigations

TEST SUBSTANCE Notified chemical

METHOD Based on OECD TG 412 Repeated Dose Inhalation Toxicity: 28-day Study;
OECD TG 486 Genetic Toxicology: Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in Vivo;
OECD TG 474 Genetic Toxicology: Mammalian Erythrocyte Micronucleus Test.

Species/Strain	Rats/Sprague Dawley
Route of Administration	Inhalation – nose-only exposure
Exposure Information	Total exposure days: 28 days (20 or 21 exposure days in total) Dose regimen: 5 days per week Duration of exposure (inhalation): 6 hours/day Post-exposure observation period: 14 days
Vehicle	Air
Physical Form	Gas
Remarks - Method	Five or six males per group of the control, high-mid, high and positive control groups were used for the unscheduled DNA synthesis (UDS) test in liver hepatocytes. The positive control substance was 2-acetylaminofluorene (2-AAF) and was administered to the animals by gavage 12-16 hours prior to sacrifice. Five males per group of the control, low, low-mid, high, and positive control groups were used for examination of micronuclei in the bone marrow. The positive control group was mitomycin C and it was administered by intraperitoneal injection.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
control	5 per sex	0	0	0

low dose	5 per sex	2000	1994 (± 9)	0
low mid dose	5 per sex	4500	4485 (± 2)	0
high mid dose	5 per sex	7500	7492 (± 9)	0
high dose	5 per sex	10000	9966 (± 26)	0
control recovery	5 per sex	0	-	0
high dose recovery	5 per sex	10000	-	0

Clinical Observations
No exposure related clinical abnormalities.

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

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
For the haematology parameters tested, elevated basophiles were observed in high dose males. This difference was not seen after the 14-day recovery period.

For the clinical chemistry parameters tested, males of the high mid and high dose groups displayed elevated potassium levels, and females of low and low mid dose groups showed elevated cholesterol. Males of the high dose group showed decreased creatinine. These changes were not observed in recovery animals.

Urinalysis parameters were not different between control and treatment groups.

Effects in Organs
No treatment-related effects were observed on organ weights. No treatment-related macroscopic or microscopic effects were observed.

Genotoxic effects
No significant differences were observed between the controls and treated groups for UDS in net nuclear grain count (NNG) or cells in repair. The positive control (2-AAF) exhibited > 20% “cells in repair” but, for unknown reasons, did not induce a NNG ≥ 5. Historical control values for 2-AAF are NNG of approximately 7.5 with approximately 60% “cells in repair”. The authors did not consider that this affected the conclusions regarding the genotoxicity of the test substance.

No significant differences were observed between the controls and treated groups in induction of micronuclei in polychromatic erythrocytes in the bone marrow. Marginal statistically significant decreases in the mean number of polychromatic erythrocytes in the low mid and high concentration groups were judged not to indicate cytotoxicity because the effect was not concentration-related and the effect of treatment was not consistent at increasing dose levels. Note that there was no increase in the mean numbers of micronucleated polychromatic erythrocytes in any dose group compared to the negative control group. This suggests that the substance did not reach the bone marrow and did not damage the chromosomes and/or spindle apparatus of the bone marrow cells.

Remarks – Results
Mononuclear cell infiltrates were observed in the heart at most dose levels and in controls. Focal infiltrates like this are commonly observed in rats of this strain and age. Note that, in contrast, multifocal infiltrates were observed in a 14 day repeat dose toxicity study (see Section B.4.) and in a 90-day repeat dose study (see section B.6.) and were considered to be treatment-related in these studies..

CONCLUSION
The No Observed Adverse Effect Concentration (NOAEC) was established as 4500 ppm in this study, based on elevated potassium levels in males at 7500 and 10000 ppm being judged to be treatment-related. No genotoxicity was observed as indicated by no treatment-related induction of UDS in liver cells or micronuclei of bone marrow cells.

TEST FACILITY TNO Quality of Life (2009a)

B.6. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 413 Subchronic Inhalation Toxicity: 90-day Study.
Species/Strain	Rat/Sprague Dawley (Crl:CD[SD])
Route of Administration	Inhalation – nose-only exposure
Exposure Information	Total exposure days: 65 days 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	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
control	10/sex	0	0	0
low dose	10/sex	4000	3987 (± 45)	0
mid dose	10/sex	10000	9974 (± 127)	0
high dose	10/sex	15000	14903 (± 217)	0

Clinical Observations

No significant clinical signs, differences in body weights or changes in food consumption were noted in treated animals. No opthalmoscopic abnormalities were noted in control and high dose animals (the only groups examined for this effect) at the end of the observation period.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical Chemistry

The plasma concentrations of ASAT and ALAT were significantly elevated in high dose males. A small decrease in the plasma concentration of ASAT in low dose males was not considered to be treatment related.

Glucose and urea plasma concentrations were significantly elevated in mid and high dose females. Potassium was also elevated in females at the high dose. Triglycerides were slightly but significantly decreased in high dose females.

Haematology

The only red cell parameter affected was a statistically significant decrease in thrombocytes in low and mid dose females. As this was not dose related it was considered not to be biologically significant. The relative concentration of lymphocytes was decreased in high dose males and low dose females and the relative concentration of neutrophils was decreased in low dose females. These changes were not considered to be biologically significant.

Urinalysis

No significant differences between the groups were observed for urinary volume and density or in microscopic observations. For high dose males the amount of occult blood in the urine was elevated.

Effects in Organs

Relative heart weight was significantly decreased in high dose animals. In males the absolute heart weight was also decreased. The relative liver weight was significantly increased in high dose males although the increase was slight. A significant increase in the relative kidney weight of low dose males was considered to be incidental.

Macroscopic observations

No treatment-related gross changes were found.

Microscopic observations

Treatment-related multifocal inflammatory (mononuclear cell) infiltrations (ranging from very slight to moderate) were observed in the ventricular part of the heart muscle with the following frequency:

Concentration	Number of males (/10)	Number of females (/10)

Low	1	0
Mid	7	0
High	9	5

In several cases the inflammatory changes were accompanied by vacuolisation of cardiac muscle cells.

A range of other histopathological changes were equally distributed amongst the groups and were identified as common findings in rats of this strain and age.

Remarks – Results
Haematological and clinical chemistry changes were slight, seen in one sex only and were not correlated with histopathological changes in the liver or kidneys. Nevertheless they may be treatment-related and the ASAT and ALAT changes in high concentration males could be related to an increase in relative liver weight.

Microscopic examination revealed that the notified chemical induced histopathological changes in the heart. These changes were more pronounced in males.

CONCLUSION
A No Observed Adverse Effect Concentration (NOAEC) could not be established based on changes in the heart of at least one male in all concentration groups. Thus the Lowest Observed Adverse Effect Concentration (LOAEC) was determined to be 4000 ppm.

TEST FACILITY TNO Quality of Life (2011a)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Modified plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from Aroclor induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 3, 6, 8, 11, 21, 37 mmol/L b) Without metabolic activation: 3, 6, 8, 11, 21, 37 mmol/L
Vehicle	Air
Physical Form	Gas
Remarks - Method	The desiccator method, a modification of the plate incorporation method, was used. The plates, inverted and uncovered, were placed within 9 L desiccators and then the test substance was introduced by withdrawing an appropriate amount of air and replacing it with the test substance to give the appropriate dose. The desiccators were maintained in an incubator with stirring for 24 hours (preliminary toxicity test) or 48 hours (mutagenicity test) at 37 °C. Following the 24-hour incubation in the preliminary toxicity test, the plates were removed from the dessicators and incubated with the lids replaced at 37 °C for an additional 24 hours. The preliminary toxicity test was conducted at doses of 1, 3, 6, 8, 11, 21 and 37 mmol/L.

RESULTS

Metabolic Activation	*Test Substance Concentration (mmol/L) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 37	≥ 11	> 37	Negative

Present				
Test 1	≥ 11	≥ 11	> 37	Negative

Remarks - Results

In the main test, the test substance did not result in an increase in the number of revertant colonies for any of the bacterial strains, at any dose, either with or without metabolic activation.

Toxicity as evidenced by a reduction in revertant colonies was observed at 11, 21 or 37 mmol/L.

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

BioReliance (2008)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Commission Regulation No. 440/2008. Method B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	S9 fraction from phenobarbital/5,6-benzoflavone induced rat liver
Vehicle	Ethanol
Physical Form	Gas
Remarks - Method	No preliminary test was conducted. Given the test substance is a liquefied gas, all cultures were treated in sealed 160 mL glass bottles using a syringe and needle, inserted through the septum cap to prevent any loss of the test substance within the test system. The glass bottles were incubated at 37 °C on their sides in a roller apparatus that rotates the bottles once every eight minutes. The lymphocytes coat the inside of the bottles and were immersed in culture medium once every revolution and exposed directly to the test substance for the rest of the revolution.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	60.89, 101.48, 169.13, 281.88, 469.8*, 783*, 1305*	3	21
Test 2	169.13, 281.88, 469.8*, 783*, 1305*	21	21
Present			
Test 1	60.89, 101.48, 169.13, 281.88, 469.8*, 783*, 1305*	3	21
Test 2	169.13, 281.88, 469.8*, 783*, 1305*	3	21

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 1305	> 1305	Negative
Test 2	> 1305	≥ 169.48	Negative
Present			
Test 1	> 1305	> 1305	Negative
Test 2	> 1305	> 1305	Negative

Remarks - Results	In Test 1, 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 both with and without metabolic activation, when compared to the number of aberrant cells observed in the negative control cultures. In Test 2, in the absence of metabolic activation, the mean values for the solvent control were on the limit of the laboratory historical control range (including gaps) and outside the laboratory historical range (excluding gaps). Increased values were also observed at all doses evaluated but there was no dose response and they were not statistically significant increases. The study authors have therefore considered the result as negative. There were no statistically significant increases in the number of aberrant cells with metabolic activation. The concurrent positive controls gave satisfactory responses confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Huntingdon Life Sciences (2011)

B.9. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mouse/CD-1
Route of Administration	Inhalation - nose-only exposure
Vehicle	Air
Physical Form	Gas
Remarks - Method	Only a single dose level of the test substance was tested. The exposure level of 50,000 ppm is approximately equivalent to an oral dose of 65,800 mg/kg which is substantially above the recommended limit dose of 2000 mg/kg. Exposure duration was 4 h. The positive control was dosed intraperitoneally as a solution in physiological saline.

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Sacrifice Time hours*
		Nominal	*Actual*	
I (vehicle control)	5 males	0		24
	5 males			48
II (test substance)	5 males	51,865	48,719	24
	5 males			48
V (positive control, M)	5 males	0.75 mg/kg bw		24

M=mitomycin C.

RESULTS

Doses Producing Toxicity	No mortalities were observed during the course of the study. Given the mice are restrained clinical observations were restricted. However, in a preliminary experiment to ascertain a tolerable dose, one male mouse exposed for 4 hours to a target concentration of 50,000 ppm did not show any signs of toxicity apart from slight restlessness and a slight increased breathing rate.
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 24 or 48 h.

	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. However, the dose of 50,000 ppm is approximately equivalent to an oral dose of 65,800 mg/kg which is substantially above the recommended limit dose of 2000 mg/kg.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo micronucleus test.
TEST FACILITY	TNO Quality of Life (2009b)

B.10. Developmental toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 414 Prenatal Developmental Toxicity Study. US EPA 870.3700 Prenatal Developmental Toxicity Study.
Species/Strain	Rabbit/New Zealand White
Route of Administration	Inhalation – whole body exposure
Exposure Information	Exposure days: from gestation day (GD) 6 up to and including GD 28 Duration of exposure: 6 hours/day, 7 days/week Post-exposure observation period: none
Vehicle	Air
Physical Form	Vapour (substance volatilised by nitrogen)
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number of Animals*	*Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
control	22	0	0	0
low dose	22	2500	2513	0
mid dose	22	10000	9945	0
high dose	22	15000	14942	0

Mortality and Time to Death

None of the animals died during the study.

Effects on Dams

No clinical findings in any exposed group that were not transient, minor and/or non-adverse. No statistically significant differences in food consumption, body weight or body weight change observed between the test and control groups.

Macroscopic findings were typical of background findings in rabbits of the strain and age. No treatment-related findings were noted.

Reproduction and Litter Data

There were no treatment-related effects on pregnancy status or pregnancy rate, on litter size, gravid uterine weight or placental weight. There were no treatment-related effects on number of corpora lutea, implantations, sex ratio or post-implantation loss.

Effects on Foetus

There were no treatment-related effects on foetal body weight. There was no evidence of treatment-related qualitative or quantitative effects on the external, visceral or skeletal malformations/variations or ossifications.

Remarks - Results

An increase in preimplantation loss was statistically significant at the high concentration but was considered not to be treatment-related as this was established prior to initiation of exposure.

CONCLUSION

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

TEST FACILITY Huntingdon Life Sciences (2010)

B.11. Developmental toxicity

TEST SUBSTANCE Notified chemical

METHOD

	OECD TG 414 Prenatal Developmental Toxicity Study.
	EC Directive 2004/73/EC B.31 Prenatal Developmental Toxicity Study.
Species/Strain	Rat/Wistar Crl:WI(WU)
Route of Administration	Inhalation – nose-only exposure
Exposure Information	Exposure days: from GD 6 up to and including GD 19
	Duration of exposure (inhalation): 6 hours/day
	Post-exposure observation period: to GD 21
Vehicle	Air
Physical Form	Gas
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number of Animals*	*Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
control	24	0	0	0
low dose	24	4000	3988 (± 3)	0
mid dose	24	10000	9981 (± 11)	0
high dose	24	15000	14906 (± 22)	0

Mortality and Time to Death

None of the animals died during the study.

Effects on Dams

No clinical findings in any exposed group. No statistically significant differences in food consumption, body weight or body weight change observed between the test and control groups.

The mean weights of the gravid uterus, carcass (and weight change from day 0), empty uterus and ovaries in the exposed groups were not different from those of the control group.

Macroscopic observations of the kidneys, bladders, ureters and uteri showed incidental and sporadic changes unrelated to treatment. There were no statistically significant differences.

Reproduction and Litter Data

Observations were made on gestation index, female fecundity index, corpora lutea, implantation sites, pre- and post implantation loss, live and dead foetuses, resorptions and sex ratio. No statistically significant differences were observed between the test and control groups. A total of 18, 17, 20 and 18 females of control, low, mid and high dose groups, respectively, appeared to be pregnant. One female of the control group had no viable

foetuses including a late resorption.

Effects on Foetus

There were no treatment-related statistically significant differences in foetal external observations. Malformations in one foetus from the low concentration group were judged to be incidental. No treatment-related findings on the placenta were observed. There were no statistically significant differences in foetal and placenta weights ascribed to treatment.

No visceral malformations were observed.

High concentration foetuses displayed a statistically significant increase in dilated urinary bladder. A single mid concentration foetus displayed diverticulum of the intestines. This was not considered to be treatment-related as it did not occur in the high concentration group.

A range of visceral variations (haemorrhagic areas in the oral and nasal cavities, folded retinas, soft lenses not well-defined, pericard and stomach filled with haemorrhagic fluid, kinked and bent ureters) were observed in all groups. Overall, the total incidence of visceral variations was reduced in the low and high concentration groups compared to the control group. Statistically significant decreases were observed for folded retina in the high concentration group and stomach containing haemorrhagic fluid in the low concentration group.

No skeletal malformations or anomalies were observed.

No statistically significant differences in skeletal variations were observed among the groups. Skeletal variations were seen in parietal and intraparietal (supernumerary) bones, supraoccipital bones (holes), ribs (accessory lumbar ribs) and irregular ossification of one or irregular shape of one or more sternebrae and one or two supernumerary caudal bodies.

A few statistically significant differences in skeletal retardations were observed in the low and mid concentration groups but these were incidental or inconsistent and are classed as normal developmental variability. The differences included decreased incidence of three or more incompletely ossified caudal arches in the low or mid concentration groups and decreased incidence of 1-2 incompletely ossified metacarpals in the low concentration group.

Remarks - Results

The increased incidence of dilated urinary bladders in foetuses of the high concentration group is considered to be treatment-related as it occurred more frequently with increasing concentration of the notified chemical.

CONCLUSION

The No Observed Adverse Effect Concentration (NOAEC) for foetal toxicity was established as 10000 ppm in this study, based on the increased incidence of dilated urinary bladders in foetuses of the 15000 ppm concentration group. The No Observed Effect Concentration (NOEC) for maternal toxicity was established as 15000 ppm based on the lack of adverse effects in any treated group.

TEST FACILITY TNO Quality of Life (2011b)

B.12. 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 2.5, 3.5 and 5% (25000, 35000 and 50000 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 increasing challenge doses of epinephrine at least three minutes apart, or until the electrocardiogram of the animal returned to its normal baseline rhythm. 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
- Ventricular fibrillation or flutter

Test substance atmospheres were prepared in Tedlar bags and analysed by gas chromatography 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.

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

RESULTS

Adrenaline Dose (μg/kg)	*Test Substance Concentration <ppm>*	*Exposure Findings: After Adrenaline Challenge*
2	0	All dogs NSCO
4		All dogs NSCO
6		5 dogs NSCO; dog 4: ESC(2) ~ 15-20s PC; ESC(6) from 20s post-dose to 47s PC
8		5 dogs NSCO; dog 4: AVB2(4) from 30-40s PC; ESC(2) from 50-55s PC
2	25000	All dogs NSCO
4		All dogs NSCO
6		dogs 1,2,5: NSCO; dog 3: AVB2 from 98s PC; dog 4: ESC(4,2,2) from 29-39s, 40-50s, 50-60s, resp. PC; dog 6 ESC(1,5,3,2,3) 22s and from 30-40s, 40-50s, 50-60s, 60-70s resp. PC; dog 6 AVB(2,2) from 40-50s, 60-70s resp. PC
8		dog 1: NSCO; dog 2: ESC(2) 11 and 12s PC; dog 3: AVB2 72s PC, ESC(8) 28-57s PC; dog 4: ESC(3,4,1) 21-26s, 40-50s, 50-60s resp., PAC(2) 40-50s PC; dog 5: AVB(2) 48-54s PC; dog 6: ESC(1,4,4) 20s, 34-40s, 41-51s resp., AVB(2,1,2) 23-32s, 34-40s, 41-51s PC
	35000	dogs 3 and 5: challenge not completed and not evaluated; dog 3: AVB2 prior to exposure
2		dogs 1,2,4,6: NSCO
4		dogs 1,2,4,6: NSCO

6		dogs 1,2,6: NSCO; dog 4: PVC approx. 39s PC
8		dogs 1,2,4,6: NSCO
	50000	dogs 1-4,6: no challenge performed; dog 5 after challenge with 0.2 and 0.4 µg/kg adrenaline the challenge was discontinued and the ECG waveform was unreadable

NSCO = No Significant Clinical Observation
ESC = Escape complex
AVB2 = Atrioventricular block 2nd degree
PAC = Premature atrial contraction
PC = Post Challenge
() = Number in parentheses indicates the total number of incidences; values separated by "," indicate number of incidences at different time intervals.

Signs of Toxicity	All animals survived to study termination. Inhalation exposure of test substance to beagle dogs resulted in clinical findings of tremors, injected sclera and excessive salivation at exposure levels of 35000 and 50000 ppm. Vocalisation during exposure, reddened gums and convulsions were noted following exposure to 50000 ppm test substance, and evidence of salivation and reddened ears were noted after exposure to 35000 ppm test substance.
NOAEL	25000 ppm
Remarks - Results	Body weights (ranged from 7.4 to 10.1 kg on the days of dosing) were collected for determination of doses only and were not analysed for test article effects.
CONCLUSION	There was no evidence of cardiac sensitisation following exposure to 25000 ppm (2.5%) notified chemical; the cardiac sensitisation potential following exposure to 35000 and 50000 ppm (3.5% and 5.0%, respectively) notified chemical could not be definitively evaluated due to the presence of tremors during exposure.
TEST FACILITY	WIL Research Laboratories LLC (2008)

B.13. Toxicity to reproduction – two generation study

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 416 Two-Generation Reproduction Toxicity.
Species/Strain	Rats/Wistar
Route of Administration	Inhalation – nose only exposure/whole body exposure
Exposure Information	Exposure period – parental males: 6 hours/day and 5 days/week for at least 10 weeks prior to mating (nose only) and daily during mating for 6 hours/day until sacrifice (nose only) Exposure period – parental females: 6 hours/day and 5 days/week for at least 10 weeks prior to mating (nose only) and daily during mating and up to gestation day (GD) 19 for 6 hours/day (nose only). From day 5 of lactation onwards, females were exposed daily for 6 hours/day to the test substance by whole body exposure until the end of the lactation period (postnatal, PN day 21) or the sacrifice of females soon after. From PN day 22 up to approximately 6 weeks of age, the F1-generation male and female pups were exposed by whole body exposure for 6 hours/day and 5 days/week. Subsequently, F1-generation males were exposed by nose-only exposure until the end of premating period for 6 hours/day and 5 days/week, and daily for 6 hours/day during mating and up to sacrifice. F1-generation females were exposed by nose-only exposure until the end of the premating period for 6 hours/day and 5 days/week, and

daily during mating and up to GD 19 for 6 hours/day. From PN day 5 onwards, F1-generation females were exposed daily 6 hours/day to the test substance by whole body exposure until sacrifice on or shortly after PN day 21.

Non-mated females were exposed (nose-only) until the end of the nose-only exposure period. Non-pregnant females were exposed by nose-only exposure until GD 19 of the presumed gestation period; then the exposure was not resumed.

Vehicle: Air
Physical Form: Gas
Remarks - Method: Protocol deviations were considered not to have affected the validity of the study.

Generation	*Group*	*Number and Sex of Animals*	*Dose/Concentration* <*ppm*>	
			Nominal	*Actual*
P	1	28 per sex	0	0
	2	28 per sex	2,000	2,005 (± 7)
	3	28 per sex	5,000	5,003 (± 38)
	4	28 per sex	15,000	14,996 (± 147)
F1	1	28 per sex	0	0
	2	28 per sex	2,000	2,005 (± 7)
	3	28 per sex	5,000	5,003 (± 38)
	4	28 per sex	15,000	14,996 (± 147)

RESULTS

Mortality and Time to Death

Two females of the high-dose group in the P-generation and one female in the high-dose group in the F1-generation were found dead on lactation days 16, 17 and 19, respectively.

Histopathological observation of these animals revealed no obvious cause of death. The first dead female animal from the F0-generation showed red lungs that did not collapse properly and were hyperaemic. The second animal showed red lungs that were hyperaemic, a swollen stomach, a swollen and necrotic caecum, a red thymus that showed microhaemorrhages, and large adrenals that were hyperaemic. Effects observed for the dead female animal in the F1-generation were: the stomach was swollen and its mucosa was brown, the jejunum was red, the caecum was swollen and necrotic, the ovaries were red and hyperaemic, the lungs showed red patches, were hyperaemic and were not collapsed properly, and the uterus had a dark appearance. Microscopic examination of the uterus revealed no explanation for the dark appearance.

Although no treatment-related findings were noted in all surviving high-dose rats, it cannot be excluded that the death of these three high-dose rats was test substance related. The incidence of mortality in the high-dose group was considered to be related to exposure to the test substance.

Effects on Parental (P) animals and 1st Filial Generation (F1)

For either generation, all clinical signs were within the expected range for animals of this strain and age. No treatment-related statistically significant differences were observed on mean body weights, body weight changes and food consumption of the test substance-exposed animals during premating, gestation and lactation. No adverse effects of the test substance were observed on estrus cycle parameters of the P- and F1-female animals and on sperm parameters of the male P- and F1-animals.

The number of pregnant P-females was 25, 21, 21 and 19 in the control, low-, mid- and high-dose group, respectively. The number of pregnant F1-females was 22, 23, 25 and 26 in the control, low-, mid- and high-dose group, respectively. Although both female and male fertility indices tended to be decreased in the high dose group of the P-generation, this was not considered by study authors to be treatment-related, because no effect on fertility was observed in the test substance-exposed groups of the F1-generation. Precoital time, gestation index and duration of gestation, male and female fertility indices, incidence of dams with live- and stillborn pups were not affected by exposure to the test substance in either generation.

In both generations, the mean number of pups delivered, the incidences of liveborn- and stillborn pups, the

number of live and dead pups at delivery, the number of pups lost during the lactation period, the sex ratio, pup clinical observations, pup organ weight and macroscopic observations were considered by study authors not to be affected by exposure to the test substance. No statistically significant differences were observed among the various groups in timing of balanopreputial separation or vaginal patency.

Pup body weight was statistically significantly increased in F1-generation female pups of the high-dose group on PN days 0, 4 and 7 (about 10%, 10% and 8% compared to the control group, respectively). The increased pup body weight observed in F1-female pups on PN days 0, 4 and 7 were considered not to be an adverse effect of the test substance, based on the absence of a clear dose-response and reduction of the effect on PN days 14 and 21. Mean pup body weight was statistically significantly increased when combining male and female pup weights in the high-dose group at days 4 and 7. No statistically significant differences in pup weight changes were observed between the pups of the test substance-exposed groups and the control group.

At necropsy, some changes in relative organ weights were noted (increase in relative liver weight in P-males at all dose groups, and in F1-females of the high-dose group; increase in relative kidney weight in P-males of the mid- and high-dose groups; and a decrease in thyroid weight in F1 generation females of the high-dose group). These changes were not consistently observed in both generations, not all dose-related and not accompanied by corroborative histopathological effects. Therefore no toxicological significance was attributed to these organ weight changes by the study authors.

CONCLUSION

Under the conditions of this two-generation reproduction toxicity study in rats, the No Observed Effect Level (NOEL) for parental toxicity for exposure to the test substance by inhalation was considered to be 5,000 ppm, due to mortality of two F0-females and one F1-female of the high-dose (15,000 ppm) at the end of lactation period. The NOEL for fertility and development toxicity for exposure to the test substance by inhalation was considered to be 15,000 ppm, because no adverse effects on fertility parameters or offspring were observed.

TEST FACILITY TNO Triskelion (2012)

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	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Gas chromatography
Remarks - Method	The closed bottle test was chosen as the test substance is highly volatile. The test substance was added into vacuum sampling bottles by microsyringe to limit volatilisation. The degradation of the test item was assessed by the determination of biochemical oxygen demand (BOD). The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation (BOD)*	*Day*	*% Degradation (BOD)*
7	-1	7	58
14	-1	14	68
21	-4	21	61
28	-2	28	78

Remarks - Results	All validity criteria for the test were satisfied. The negative biodegradation was considered to be due to the detection limit of the method as the test substance has a low biodegradability. The average degradation of the test substance was considered to be 0% as the measured degradation was negative.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	CERI (2009b)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test - static
Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	53.3 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography
Remarks – Method	A stock solution was prepared by bubbling the test substance (gas) through dilution water for 45 minutes, followed with 30 minutes standing in a sealed vessel. Samples were taken for concentration measurement. In order to get more test substance in the stock, the stock solution was bubbled with test substance for another 15 minutes. The stock solution was determined to contain more test substance and it was clear with

colourless, oily globules of test substance on the bottom of the vessel. All other test solutions were prepared by dilution of this stock solution.

The test solutions were not aerated during the test. The number of mortalities and any sub-lethal effects of exposure in each test and control were monitored at 3, 24, 48, 72 and 96 hours. The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*			
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
Control	< 0.077	7	0	0	0	0
15	12	7	0	0	0	0
30	25	7	0	0	0	0
60	59	7	86	86	100	100
120	140	7	100	100	100	100
240	500	7	100	100	100	100

LC50	38 mg/L at 96 hours (95% confidence limits: 25 - 59 mg/L).
NOEC	25 mg/L at 96 hours.
Remarks – Results	All validity criteria for the test were satisfied.

The results were calculated and reported based on the mean measured concentrations. At the concentration of 25 mg/L, fish was observed to be surfacing after 3 hours exposure. At the measured concentration of 59 mg/L, more than 30% mortality or toxicity symptoms (loss of balance and dark-colouring) were observed. At the measured concentration of 140 and 500 mg/L, the test was terminated after 24 hours exposure time period since all fish were dead.

CONCLUSION The notified chemical is harmful to fish

TEST FACILITY BEL (2009a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 *Daphnia* sp. Acute Immobilisation Test - static

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	244 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography/Mass Spectrometry
Remarks - Method	A stock solution (70% saturated) was prepared by bubbling the test substance (gas) through dilution water for 60 minutes via a sintered glass diffuser to obtain a saturated solution of the gas (100%). This solution was diluted to 70% saturation with media that had been diffused with oxygen for 30 minutes. All other concentrations were prepared by dilution of the 70% stock solution.

Twenty daphnia (five daphnids × 4 replicates) were exposed to an aqueous solution of test substance at 20 °C under static conditions. The test solutions were not aerated and the daphnids were not fed during the test.

The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Concentration		*Number of D. magna*	*Number Immobilised*	
Nominal (% saturation)	*Actual (mg/L)*		*24 h*	*48 h*
Control	< 0.003	20	0	0
4.38	27	20	0	0
8.75	38	20	0	1
17.5	91	20	0	13
35	175	20	17	19
70	405	20	20	20

EC50 82 mg/L at 48 hours (95% confidence limit: 66-100 mg/L)
NOEC 26 mg/L at 48 hours
Remarks - Results All validity criteria for the test were satisfied. The results were calculated and reported based on the mean measured concentrations. No other symptoms of toxicity were observed during the test.

CONCLUSION The notified chemical is harmful to aquatic invertebrates

TEST FACILITY BEL (2010)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.
Species *Pseudokirchneriella subcapitata*
Exposure Period 72 hours
Concentration Range Nominal: 4.38, 8.75, 17.5, 35 and 70% of saturation
Actual: 13.5, 32, 60.5, 115 and 215 mg/L
Auxiliary Solvent None
Water Hardness Not reported
Analytical Monitoring Gas Chromatography/Mass Spectrometry
Remarks - Method A stock solution (70% saturated) was prepared by bubbling the test substance (gas) through dilution water for 60 minutes via a sintered glass diffuser to obtain a saturated solution of the gas (100%). This solution was diluted to 70% saturation with media that had been diffused with oxygen for 30 minutes. All other concentrations were prepared by dilution of the 70% stock solution.

Pseudokirchneriella subcapitata was exposed to an aqueous solution of test substance at 24 °C under constant illumination and shaking. The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 72 h	*NOE_bC mg/L at 72 h*	*E_rC50 mg/L at 72h*	*NOE_rC mg/L at 72 h*
106.7	≥ 215	≥ 215	115
95% confidence limit: 42.1-154 mg/L			

Remarks - Results Based on growth rate over the test period, the lowest observed effect concentration (LOEC) was determined to be 215 mg/L. The E_rC50 is, therefore, concluded to be ≥ 215 mg/L.

The results were calculated and reported based on the mean measured concentrations. All validity criteria for the test were satisfied.

CONCLUSION	The notified chemical is not harmful to algae
TEST FACILITY	BEL (2009b)

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