File No: STD/1551

May 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

2-Butene, 1,1,1,4,4,4-hexafluoro-, (2*Z*)-

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (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/1551	The Chemours Company (Australia) Pty Ltd	2-Butene, 1,1,1,4,4,4-hexafluoro-, (2*Z*)-	No	< 350 tonnes per annum	Foam expansion agent, fire extinguishant, refrigerant, cleaning solvent and heat transfer fluid

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	402 – Harmful to aquatic life

Human health risk assessment
Provided that the recommended controls are being adhered to, 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 considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Local exhaust ventilation for non-enclosed processes, when possible

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Avoid using the notified chemical in small rooms with limited ventilation
  - Avoid breathing vapours or mists
  - Avoid skin and eye contact with the notified chemical in liquid form
  - Maintain and monitor equipment for leaks and take immediate corrective action where leaks are detected
  - Follow all applicable industry standards and regulations for use of the notified chemical

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Suitable respiratory equipment in case of insufficient ventilation, such as a positive-pressure supplied-air respirator
  - 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.

- This assessment will be referred to Safe Work Australia for consideration of the Workplace Environmental Exposure Level (WEEL) Guide of 500 ppm: 8 h time weighted average (TWA) for the notified chemical (OARS, 2014) in the Australian context.

Public Health

- The following measures should be taken by manufacturers, distributors or unit owners to minimise public exposure to the notified chemical:
  - Equipment should be maintained and monitored for leaks, with immediate corrective action taken where leaks are detected.

Disposal

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

Storage

- The following precautions should be taken 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.

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

- The notified chemical is proposed to exceed 20% concentration in polyurethane foams (including spray polyurethane foams) for use in residential or commercial buildings.

(2) Under Section 64(2) of the Act; if

- the function or use of the chemical has changed from foam expansion agent, fire extinguishant, refrigerant, cleaning solvent and heat transfer fluid, 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.

(Material) Safety Data Sheet

The (M)SDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
The Chemours Company (Australia) Pty Ltd (ABN: 90 169 142 750)
7 Eden Park Drive
MACQUARIE PARK NSW 2113

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: other names, analytical data, degree of purity, impurities, other physical and chemical properties, and import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: dissociation constant, autoignition temperature, acute oral toxicity, acute dermal toxicity, eye irritation and skin sensitisation.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA
EU
Switzerland

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Formacel® 1100

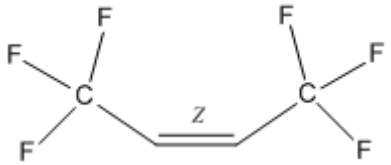
CAS NUMBER
692-49-9

CHEMICAL NAME
2-Butene, 1,1,1,4,4,4-hexafluoro-, (2*Z*)-

OTHER NAMES
FEA-1100
Formacel FEA-1100
HFO 1336mzz(Z)
cis-1,1,1,4,4,4-Hexafluoro-2-butene

MOLECULAR FORMULA
$C_4H_2F_6$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
164.05 Da

ANALYTICAL DATA
Reference GC-FID, NMR, FTIR, MS, UV-Vis spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 99%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless, transparent liquid

Property	Value	Data Source/Justification
Freezing Point	- 90.5 °C	Published (Henne *et. al.,* 1947)
Boiling Point	33 - 33.5 °C at 101.3 kPa	Measured
	33.2 °C at 101.3 kPa	Published (Henne *et. al.,* 1947)
Density	1,377 kg/m^3 at 20 °C	Measured
Vapour Pressure	60.4 kPa at 20 °C	Measured
Water Solubility	0.7633 g/L at 25 °C	Measured
Hydrolysis as a Function of pH	t0.5$_{25\ °C}$ > 1 year at pH 4, 7, and 9	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.3 at 30 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.48 (soil) log K_{oc} = 2.51 (sewage sludge)	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities
Flash Point	Does not flash	Measured
Flammability	Not flammable	Measured
Autoignition Temperature	Not determined	Not expected to undergo autoignition
Explosive Properties	Not determined	Contains no functional groups that imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that imply explosive properties

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

Reactivity
The notified chemical is expected to be stable under normal conditions of use. Hazardous decomposition products may include carbon monoxide and hydrogen fluoride.

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia neat (> 99% purity) as a liquid.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 50	< 100	< 200	< 300	< 350

PORT OF ENTRY
Sydney and Melbourne

IDENTITY OF RECIPIENTS
The Chemours Company (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported in 200 L drums and then transported from the port to distributors' warehouses for storage until delivery to end users.

USE
The notified chemical is proposed for the following uses:

- foam expansion agent at 5-20% concentration;
- fire extinguishant at 50-100% concentration;
- refrigerant for centrifugal chiller at 40-100% concentration;
- cleaning solvent at 4-100% concentration; and
- heat transfer fluid at 40-100% concentration.

OPERATION DESCRIPTION
The notified chemical will not be manufactured in Australia, but may be reformulated after importation.

Reformulation
The notified chemical will be pumped from drums into a mixing tank where it will be blended with other materials to form formulated products containing the notified chemical at required concentrations.

End use as a foam expansion agent
The notified chemical will be used as a foam expansion agent in the manufacture of polyurethane foams, including spray polyurethane foams.

At foam manufacturing sites, the notified chemical at 100% concentration or formulated products containing the notified chemical at 10-40% concentration will be pumped from the receiving drums directly into a closed blending vessel, where it may be mixed with other materials to produce the blended product. The blended product containing the notified chemical will then be transferred to the foaming machine where it will be blended with isocyanate to make the polyurethane foam. 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. The concentration of the notified chemical in finished foam products will be 5-20% concentration which will be trapped within the closed cells of the foam.

Spray polyurethane foams containing the notified chemical at 5-20% concentration will be applied by professional spray foam applicators. The spray foam will be applied using a spray rig for high pressure delivery or a portable spray gun for low pressure delivery.

End use as a fire extinguishant
The notified chemical at 50-100% concentration will be pre-charged by original equipment manufacturers within Australia into special hazard fire extinguishing systems or portable extinguishers which will be ready for installation on site. Alternatively, installing technicians will refill discharged fire extinguishing units off-site with the notified chemical by transfer from drums. These special fire extinguishing systems and portables are not used in general public applications but specifically to protect high value commercial and industrial equipment and operations. The fire extinguishing units will be handled by trained personnel only.

End use as a refrigerant in centrifugal chillers
The notified chemical at 40-100% concentration will be pumped from the receiving drums into centrifugal chillers to be charged or serviced. At the end of the lifecycle of a chiller (expected lifecycle is 10-30 years) the unit will be sent to Refrigerant Reclaim Australia for disposal.

End use as a cleaning solvent
At industrial sites, the notified chemical at 4-100% concentration will be pumped from the receiving drums into a storage/cleaning tank where substrates will be dipped for cleaning. The cleaning operation will occur in a closed system. Used notified chemical will be distilled and recycled. When recycling is no longer viable, or the notified chemical is no longer required for this purpose, the remainder will be disposed of by a licensed waste disposal operator.

End use as a heat transfer fluid
At industrial sites, the notified chemical or formulated products containing the notified chemical at 40-100% concentration will be pumped from the receiving drums into equipment and sealed. The notified chemical will be removed by trained technicians typically every five years and sent off for recovery by filtration and distillation. At least 90% of the notified chemical will be recovered and returned.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

EXPOSURE DETAILS
Potential routes of occupational exposure are dermal, ocular and inhalation. However as the notified chemical is a volatile liquid (boiling point = 33 °C), inhalation is the main anticipated route of exposure. Dermal and ocular exposure to liquid material may occur during transfer operations or accidental leakage.

Transport and Storage
Transport and storage workers are not expected to be exposed to the notified chemical, except in the unlikely event of an accidental leakage.

Reformulation
The blending process is expected to be automated in a closed system; however, plant operators may be exposed to the notified chemical at up to 100% concentration during connection and disconnection of transfer hoses, equipment maintenance and cleaning, and sampling. Engineering controls, such as local exhaust ventilation (LEV), and the expected use of personal protective equipment (PPE) by workers should minimise exposure.

End use as a foam expansion agent
Foam manufacturing is expected to be automated in a closed system; however, operators may be exposed to the notified chemical at up to 100% concentration during connection and disconnection of transfer hoses, equipment maintenance and cleaning, and sampling. Engineering controls, such as LEV, and the expected use of PPE by workers should minimise exposure.

Workers may be exposed to the notified chemical during installation of the foam insulation products through migration from the foam. However, worker exposure is expected to be very low given the closed-cell nature of the foam and the common encapsulation of the foam insulation within the insulating systems, such as inside refrigerated doors.

During spray foam application, applicators may be exposed to the notified chemical at up to 100% concentration during connection and disconnections of transfer hoses, equipment maintenance and cleaning, and during spray application. The expected use of PPE, including respiratory protection during spray application, should minimize exposure.

End use as a fire extinguishant
Worker exposure to the notified chemical at up to 100% concentration may occur during filling and maintenance of extinguishing systems, and during the release into a workspace to extinguish a fire. In addition, exposure to the combustion products of the notified chemical (including carbon monoxide and hydrogen fluoride) may occur during fire-fighting and after re-entry to an area in which the notified chemical has been used as a fire extinguishant.

End use as a refrigerant in centrifugal chillers, cleaning solvent or heat transfer liquid
Worker exposure to the notified chemical at up to 100% concentration may occur during installation, refilling, and emptying the units containing the notified chemical, particularly when connecting and disconnecting transfer hoses. Engineering controls, such as LEV, and the expected use of PPE by workers should minimise exposure.

6.1.2. Public Exposure
When used as a cleaning solvent, refrigerant or heat transfer fluid, the notified chemical will be used in industrial/commercial settings only and handled by professional technicians. Therefore, the public is not expected to be exposed to the notified chemical except in the unlikely event of an accidental leakage from units containing the notified chemical in the vicinity of the public.

Similarly, for use as a fire extinguishant, the general public will not be exposed to the notified chemical as it will be used in industrial/commercial settings only and handled by trained personnel. However, the public may be exposed as a bystander for a brief period of time in the event of a fire.

Public exposure to the notified chemical through its migration from foam insulation is expected to be very low given the closed-cell nature of the foam and the common encapsulation of the foam within the insulating systems, such as inside refrigerated doors. There is a potential for slow release of the notified chemical from foam placed in open cavities such as the roofs of residential structures, over time. Concentration build-up of the notified chemical in such structures, given its physico-chemical properties, cannot be discounted. Public exposure under this scenario is expected to be low, given that such structures are not completely closed and residents' access to these spaces is occasional and of low duration. Migration of the notified chemical in indoor living spaces, over time, either via diffusion through wall materials enclosing foam insulation containing the notified chemical or through circulation of air in the roof space potentially containing higher concentrations of the notified chemical, is also possible. Public exposure under this scenario is not expected to be of concern, given the relatively low concentration of the notified chemical (5 – 20%) in polyurethane foams.

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 > 141 mg/L/2 hour; low toxicity (21,000 ppm)
Rat, acute inhalation toxicity	LC50 > 690 mg/L/4 hour; low toxicity (102,878 ppm)
Rabbit, skin irritation	non-irritating
Rat, repeat dose inhalation toxicity – 5 days	NOAEC = 7 mg/L (1,000 ppm)
Rat, repeat dose inhalation toxicity – 28 days	NOAEC = 17 mg/L (2,500 ppm)
Rat, repeat dose inhalation toxicity – 90 days	NOAEC = 10 mg/L (1,500 ppm)
Rat, repeat dose inhalation toxicity – 90 days	NOAEC = 34 mg/L (5,000 ppm); male NOAEC = 50 mg/L (7,500 ppm); female
Dog, cardiac sensitisation to adrenaline	evidence of cardiac sensitisation; NOEC = 84 mg/L (12,500 ppm)
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus test	non genotoxic
Rat, prenatal developmental toxicity	maternal/foetal NOAEC = 10 mg/L (1,500 ppm)
Rabbit, prenatal developmental toxicity	maternal NOAEC = 34 mg/L (5,000 ppm) foetal NOAEC = 50 mg/L (7,500 ppm)
Rat, two generation reproduction toxicity	systemic NOAEC = 10 mg/L (1,500 ppm); male systemic NOAEC = 17 mg/L (2,500 ppm); female developmental/reproductive NOAEC = 17 mg/L (2,500 ppm)

Toxicokinetics, metabolism and distribution.

Absorption, distribution, metabolism and excretion of the notified chemical were examined in rats following single inhalation exposure to 2,500 ppm or 10,000 ppm of the notified chemical for 1 hour, 4 hours, or 6 hours, or a 14-day repeat inhalation exposure to 2,500 ppm of the notified chemical for 6 hours/day. The notified chemical was found to be present in blood and all collected tissue samples (fat, reproductive organs, muscle, spleen, lung, kidney, heart, brain and liver) 30 minutes after a single 6-hour exposure to 10,000 ppm. By 18 hours after the end of the exposure, the concentrations of the test substance in blood, bile and tissues (except fat) were less than the level of detection. Similar pharmacokinetic behaviour was observed following the single 6-hour exposure to 2,500 ppm, the single 6-hour exposure to 10,000 ppm and the 14-day repeated exposure to 2,500 ppm indicating similar kinetic behaviour for distribution and elimination of the test substance from blood at these exposure levels and the absence of accumulation of the test substance following a 14-day exposure. Minimal notified chemical was detected in urine and faeces, likely due to unmeasured loss due to volatility of the test substance and unmeasured elimination via exhalation.

The primary biotransformation steps appeared to be either oxidation or direct conjugation with glutathione. Additional secondary metabolism resulted in phase I and phase II metabolites including oxidation to a ketone,

formation of a second glutathione conjugate, or further hydrolysis to dihydroxyl-test substance and glucuronidation.

The notified chemical is expected to be absorbed by the dermal route based on its low molecular weight (164.05 Da) and partition coefficient (log Kow = 2.3) although this is expected to be limited given the volatility of the notified chemical.

Fluoride release from the notified chemical is suggested in the repeated dose inhalation studies as skeletal changes in the treated rats are most likely due to fluoride binding to bone.

Acute toxicity.
The notified chemical was found to be of low toxicity in acute inhalation studies.

Irritation and sensitisation.
When administered as a liquid, the notified chemical was found to be non-irritating to the skin of rabbits under semi-occlusive conditions. However, given the volatility of the notified chemical the extent of exposure may have been limited. No ocular irritation study report was submitted for the notified chemical. However no signs of ocular irritation were reported in whole body inhalation studies when the notified chemical was administered in vapour form.
No skin sensitisation data was submitted for the notified chemical.

Repeated dose toxicity.
A 5-day repeated dose inhalation range-finding toxicity study was conducted in rats exposed nose-only to 1,000, 10,000 or 50,000 ppm of the notified chemical. The No Observed Adverse Effect Concentration (NOAEC) was established as 1,000 ppm (7 mg/L) in this study, based on lower body weight gains, decreased food consumption, degeneration of the olfactory epithelium and neutrophilic infiltration and luminal cellular debris in the nasal cavity noted in the higher dose groups.

A 28-day repeated dose inhalation toxicity study was conducted in rats exposed nose-only to 2,500, 5,000 or 10,000 ppm of the notified chemical. The NOAEC was established as 2,500 ppm (17 mg/L) in this study, based on lower body weights and lower cumulative body weight gains noted in the higher dose groups (5,000 ppm and 10,000 ppm), as well as increased serum albumin and total protein levels in male animals of the highest dose group (10,000 ppm).

A 90-day repeated dose inhalation toxicity study was conducted in rats exposed whole body to 500, 1,500 or 10,000 ppm of the notified chemical. The NOAEC was established as 1,500 ppm (10 mg/L) in this study, based on test-substance-related reductions in body weight, food consumption and food efficiency in both male and female animals in the 10,000 ppm group.

With the objective to refine the NOAEC, a second 90-day repeated dose inhalation toxicity study was conducted in rats exposed whole body to 3,000, 4,000, 5,000 or 7,500 ppm of the notified chemical. In this study, the NOAEC was established as 5,000 ppm (34 mg/L) in male rats, based on test-substance-related reductions in body weight and food consumption, and 7,500 ppm (50 mg/L) in female rats based on no test-substance related adverse effects at any exposure groups.

Cardiac sensitisation.
In a cardiac sensitisation study conducted in beagle dogs for the notified chemical, there was evidence of cardiac sensitisation at dose levels of 25,000 ppm and 50,000 ppm. The No Observed Effect Concentration (NOEC) was established as 12,500 ppm (84 mg/L).

Mutagenicity/Genotoxicity
The notified chemical was found to be non-mutagenic in a bacterial reverse mutation test. There was no evidence of clastogenicity to human lymphocytes *in vitro*. The genotoxicity (examination of erythrocyte micronuclei) of the notified chemical was also investigated as part of a 90-day repeated dose inhalation study, where it was found to be non-genotoxic.

Developmental/reproductive toxicity
A prenatal developmental toxicity study was conducted in rats exposed whole body to 500, 1,500 or 10,000 ppm of the notified chemical. The NOAEC for maternal and foetal toxicity was established as 1,500 ppm (10 mg/L)

in this study, based on reductions in mean maternal body weight, mean maternal body weight changes and food consumption, and reductions in mean foetal weight at the higher exposure level of 10,000 ppm.

A second prenatal developmental toxicity study was conducted in rabbits exposed whole body to 2,500, 5,000, 7,500 or 15,000 ppm of the notified chemical. The NOAEC for maternal toxicity was established as 5,000 ppm (34 mg/L) in this study, based on moribundity as a result of impaired use of hind limbs, increased respiration, prostration and/or pale body at 7,500 and 15,000 ppm, and reduced mean body weights and food consumption at 15,000 ppm. The NOAEC for foetal toxicity was established as 7,500 ppm (50 mg/L) based on lower foetal weights at 15,000 ppm.

In a two-generation reproduction toxicity study conducted in rats exposed whole body to 500, 1,000, 1,500 or 2,500 ppm of the notified chemical, the NOAEC for systemic toxicity was established as 1,500 ppm (10 mg/L) in male animals, based on reductions in body weight and nutritional parameters in first filial (F1) generation males exposed to the higher dose level of 2,500 ppm, and as 2,500 ppm (17 mg/L) in female animals, the highest exposure dose tested. The NOAEC for developmental and reproductive toxicity were both established as 2,500 ppm (17 mg/L) based on no adverse effects on fertility parameters or offspring were observed at any exposure doses.

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
The notified chemical is a volatile liquid and the main exposure route is expected to be inhalation. Toxicological studies for the notified chemical showed a low potential for acute inhalation toxicity. In repeated inhalation exposure studies, the notified chemical also displayed a low order of toxicity, showing no adverse effects up to 5,000 ppm. In other studies, the notified chemical did not raise a concern for skin irritation, genotoxicity, developmental or reproductive toxicity. Due to the volatility of the notified chemical, eye irritation and skin sensitisation studies were not performed. At high exposure levels, the notified chemical was shown to cause cardiac sensitisation in dogs following exposure to 25,000 ppm and above, while no such effect was observed at 12,500 ppm.

There is at present no Australian occupational exposure limit for the notified chemical. However, a US Workplace Environmental Exposure Level (WEEL) Guide of 500 ppm: 8 h time weighted average (TWA) for the notified chemical has been developed (OARS, 2014).

Overall, based on the available information, the critical health effect of the notified chemical is that it may cause cardiac sensitisation at high exposure levels (i.e. > 12,500 ppm). In addition, rapid evaporation of the notified chemical may cause frostbite upon contact with the skin and eyes. Therefore, the use of protective clothing and eye protection is recommended when using the notified chemical, as well as respiratory protection where significant inhalation exposure is expected. Local exhaust ventilation should also be employed where vapours or mists of the notified chemical may be formed.

Reformulation
The blending process is expected to be automated in a closed system; however, plant operators may be exposed to the notified chemical at up to 100% concentration during connection and disconnection of transfer hoses, equipment maintenance and cleaning, and sampling. Engineering controls including LEV and PPE are expected to be used during these procedures to minimise exposure.

End use as a foam expansion agent
Foam manufacturing is expected to be automated in a closed system; however, operators may be exposed to the notified chemical at up to 100% concentration during connection and disconnection of transfer hoses, equipment maintenance and cleaning, and sampling. Engineering controls including LEV particularly during the foaming process and PPE are expected to be used during these procedures to minimise exposure.

During spray foam application, applicators may be exposed to the notified chemical at up to 100% concentration during connection and disconnections of transfer hoses, equipment maintenance and cleaning, and during spray

application. The expected use of PPE, including respiratory protection during spray application, engineering controls and safe work practices in place to minimize exposure to the other hazardous components of the polyurethane spray foam, such as isocyanates, should minimise exposure to the notified chemical.

End use as a fire extinguishant
During this use the main potential for exposure to the notified chemical at up to 100% concentration is expected during filling and maintenance of extinguishing systems, and during the release into a workspace to extinguish a fire. In addition, exposure to the hazardous combustion products of the notified chemical (including carbon monoxide and hydrogen fluoride) may occur during fire-fighting and after re-entry to an area in which the notified chemical has been used as a fire extinguishant.

During filling operations, engineering controls and PPE are expected to be used to minimise exposure. During use as a fire extinguishant, worker exposure is expected to be minimised through relevant standards and regulations to assure human exposure to the fire extinguishant is minimised. These standards and regulations also require the owner to maintain the equipment and monitor for any leakage and take immediate corrective action if any leakage is detected. In addition, these standards and regulations also contain the required maintenance and inspection procedures to assure the unit is operational.

End use as a refrigerant in centrifugal chillers, cleaning solvent or heat transfer liquid
During these uses, the main potential for worker exposure to the notified chemical at up to 100% concentration is expected during installation, refilling, and emptying the units containing the notified chemical, 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.

Furthermore, it is required in Australia that a person who carries out work in relation to refrigeration and air conditioning equipment must hold a national Refrigerant Handling Licence. In addition, there is the Australia and New Zealand Refrigerant Handling Code of Practice 2007 for fluorocarbon refrigerants and training courses provided under the Refrigerant Handling Licence scheme. Therefore, licenced workers are expected to have the proper equipment and knowledge to minimise their risks from exposure to the notified chemical when used as a refrigerant.

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 under the proposed uses is expected to be low unless there is accidental release in the vicinity of the public. Therefore the risk to public health 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 will not be manufactured or reformulated in Australia. Therefore, there will be no releases due to these activities. The notified chemical may be repackaged in Australia, but no significant release of the notified chemical is expected during transfer.

RELEASE OF CHEMICAL FROM USE
When used as a blowing agent in the manufacture of foams in aerosols and for foam products, the notified chemical is expected to be collected by engineering controls and released into the atmospheric compartment. It is estimated by the notifier that 15% of the notified chemical is released into the atmospheric compartment during the spray foam blowing installation process as overspray, and 7.5% released during the foaming process in non-spray foam applications. The notified chemical may also be released to the atmospheric compartment as a result of accidental leakages when used as a refrigerant, or following diffusion over the life-time of insulation foams. After installation once the foam is blown, an estimated diffusion rate of 0.25-1.5%/yr of the notified chemical has been established over the life-time of foam products (typically 30-50 years).

When used as a cleaning solvent or heat transfer fluid, no significant environmental release of the notified chemical is expected.

RELEASE OF CHEMICAL FROM DISPOSAL
Residual notified chemical in decommissioned foam articles are expected to share the fate of the articles and be disposed of to landfill.

When used as a refrigerant, cleaning solvent, or heat transfer fluid, the notified chemical is expected to be recovered during the maintenance or at end-of-service life for disposal via an approved product stewardship scheme for either recycling or destruction.

7.1.2. Environmental Fate

The notified chemical is not readily biodegradable (< 2.2% in 28 days), and is expected to be hydrolytically stable under environmental conditions (< 10% hydrolysis after 5 days). For details of the environmental fate studies, please refer to Appendix C. The notified chemical is not, however, expected to bioaccumulate based on its low partition coefficient (log P_{OW} = 2.3). Furthermore, 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 described below.

In the atmosphere, the notified chemical is predicted to have an atmospheric lifetime of 22 days based on the rate constant for reaction with hydroxyl radicals (k_{OH}) of 4.91 × 10^{-13} cm^3/molecule/s (Baasandorj *et al*., 2011). Therefore, as the half-life of the notified chemical is > 2 days, the notified chemical is considered to be persistent in the atmospheric compartment. Reaction with ozone is not expected to be a dominant pathway for degradation in the atmosphere (atmospheric lifetime > 3 years, kO_3 < 6 × 10^{-21} cm^3/molecule/s; Baasandorj *et al*., 2011). The notified chemical is expected to degrade in the atmospheric compartment to eventually form water, oxides of carbon and hydrofluoric acid.

7.1.3. Predicted Environmental Concentration (PEC)

The 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 within 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		
Medaka (*Oryzias latipes*)	96 h LC50 = 76.1 mg/L	Harmful to fish (acute)
Rare minnow (*Gobiocypris rarus*)	96 h LC50 > 95.7 mg/L	Harmful to fish (acute)
Rare minnow (*Gobiocypris rarus*)	28 d NOEC = 9.58 mg/L	Not harmful to fish (chronic)
Daphnia Toxicity		
Daphnia magna	48 h EC50 = 22.5 mg/L	Harmful to daphnids (acute)
Daphnia magna	21 d NOEC = 10.2 mg/L	Not harmful to daphnids (chronic)
Algal Toxicity		
Green alga (*Pseudokirchneriella subcapitata*)	72 h EC50 > 23.7 mg/L	Harmful to algae (acute)
Green alga (*Pseudokirchneriella subcapitata*)	72 h NOErC = 6.92 mg/L	Not harmful to algae (chronic)
Inhibition of Bacterial Respiration	0.5 h EC50 > 1,000 mg/L	Not inhibitory to bacterial respiration

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is considered to be harmful to fish, aquatic invertebrates and algae on an acute basis. Therefore, the notified chemical is formally classified under the GHS as "Acute Category 3, Harmful to aquatic life". The notified chemical is not readily biodegradable; however, it is not formally classified for long term hazard under the GHS based on its low chronic toxicity endpoints.

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, ozone depleting potential (ODP), and global warming potential (GWP).

The notified chemical is considered to have long-range transport potential, as its atmospheric lifetime based on the measured reaction rate with hydroxyl radicals is 22 days.

Baasandorj *et al*. (2011) examined the mechanisms and products of atmospheric degradation of the notified chemical. In the atmosphere, the notified chemical is predicted to have an atmospheric lifetime of 22 days based on the rate constant for reaction with hydroxyl radicals (k_{OH}) of 4.91×10^{-13} cm^3/molecule/s (Baasandorj *et al*., 2011). Degradation via UV photolysis is considered to be negligible (absorption cross section at 253.6 nm < 4×10^{-24} cm^2/molecule). Reaction with ozone is not expected to be a dominant pathway for degradation in the atmosphere (atmospheric lifetime > 3 years, $kO_3 < 6 \times 10^{-21}$ cm^3/molecule/s; Baasandorj *et al*., 2011). The notified chemical is not expected to deplete the ozone layer (ozone depleting potential = 0).

Baasandorj *et al*. (2011) measured the OH reactive coefficient and global warming potential (GWP) of the notified chemical. The atmospheric lifetime was determined to be 22 days based solely on OH reactive loss. The GWP was calculated to be 8.9 for the 100-year time horizon.

7.2.1. Predicted No-Effect Concentration

A Predicted No-Effect Concentration (PNEC) for the aquatic compartment has not been calculated as aquatic exposure is not expected.

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has not been calculated since the PEC and PNEC were not calculated based on its reported usage 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 disposed to landfill as part of decommissioned foam products. 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

Boiling Point 33.0 - 33.5 °C at 101.3 kPa

Method OECD TG 103 Boiling Point
Remarks Determined by distillation method
Test Facility DuPont (2014a)

Density 1,377 kg/m^3 at 20 °C

Method In-house method
Remarks Measured using an Anton Paar DMA 512 P density measuring cell and an Anton Paar DMA 60 processing unit
Test Facility DuPont (2013a)

Vapour Pressure 60.4 kPa at 20 °C

Method Kao *et. al.* 2000
Remarks Measured using Paroscientific pressure transducers, with 0.01% accuracy
Test Facility DuPont (2013a)

Water Solubility 0.7633 g/L at 25 °C

Method OECD TG 105 Water Solubility
Remarks Flask Method/Column Elution Method
Test Facility Wiltec (2014)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH
EC Council Regulation No 440/2008 C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

pH	*T (°C)*	*% Hydrolysis after 5 days*
4	50	6.1
7	50	6.2
9	50	6.5

Remarks After 5 days under the accelerated conditions of 50 °C the rate of hydrolysis of was less than 10% at pH 4, 7, and 9. This equates to a half-life at 25 °C of $t0.5_{25\ ^\circ C} > 1$ year. Therefore, it can be concluded that under the conditions of the test, the notified chemical is hydrolytically stable.
Test Facility MEP (2014a)

Partition Coefficient (n-octanol/water) log Pow = 2.3 at 30 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks HPLC Method. The notified chemical eluted after the reference chemical nitrobenzene.
Test Facility Mitsubishi (2011a)

Adsorption/Desorption – screening test log K_{oc} = 2.48 (soil), 2.54 (sewage sludge)

Method OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks The notified chemical eluted after the reference chemical aniline.
Test Facility DuPont (2013b)

Flash Point Does not flash

Method	ASTM D56
Remarks	Does not exhibit a flash point at or below its boiling point under atmospheric pressure.
Test Facility	DuPont (2014b)

Flammability Not flammable

Method	ASTM E681-04 and ASHRAE Standard 34
Remarks	Not flammable at both 60 °C and 100 °C at atmospheric pressure and 50% relative humidity using a 12 L spherical glass flask
Test Facility	DuPont (2011a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Toxicokinetic

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 417 Toxicokinetics
Species/Strain	Rat/Sprague-Dawley, Crl:CD(SD)IGS BR
Route of Administration	Inhalation – nose-only exposure
Exposure Information	Groups 1-3: 1, 4 or 6 h single exposure Group 4: 14-day repeated exposure, 6 h/day
Vehicle	Filtered air
Physical Form	Vapour

STUDY DESIGN AND OBJECTIVE

The study evaluated absorption, distribution, metabolism and elimination of the test substance in blood following a single 6-hour exposure or a 14-day repeat exposure for 6 hours/day, and in tissues and excreta following a single 1-hour, 4-hour or 6-hour exposure.

A pilot study was performed on a group of rats (8 per sex) exposed to 10,000 ppm of the test substance for 6 hours to help determine appropriate collection times for blood and tissues for the definitive studies.

Vapour of the test substance was generated by heating a flask containing the test substance to approximately 175 °C. The generated vapour was mixed with air to produce the test atmosphere.

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Exposure Duration (hours)*
		Target	*Actual*	
1 (pilot)	8 per sex	10,000	10,100 ± 632	6 h single
2	4 per sex	2,500	2,550 ± 284	6 h single
3	24 per sex	10,000	9,870 ± 732	6 h single
3	4 per sex	10,000	10,500 ± 1810	1 h single
3	4 per sex	10,000	10,500 ± 1810	4 h single
4 (repeated dose)	4 per sex	2,500	2,500 ± 236	14-day, 6 h/day

RESULTS

Body weight

No significant effects were noted in any exposure groups.

Absorption, Distribution and Excretion

Systemic uptake was rapid with blood reaching steady-state (appropriately 19,100 ± 3,070 ng/g) within 2 hours after a single 6-hour exposure to 10,000 ppm (Group 1). The test substance was present in blood samples and all collected tissues (fat, reproductive organs, muscle, spleen, lung, kidney, heart, brain and liver) 30 minutes after a single 6-hour exposure to 10,000 ppm. By 18 hours after the end of the exposure, the concentrations of the test substance in blood, bile and tissues (except fat) were less than the level of detection and were 3,100 ± 3,133 ng/g and 2,266 ± 2,262 ng/g respectively in fat of male and female animals.

The mean terminal elimination half-life values were 2.28 and 2.27 hours with area-under-the-curve (AUC) values of 2,480,000 and 2,210,000 hr × ng/g in male and female animals, respectively.

Similar pharmacokinetic behaviour was noted between male and female animals following the single 6-hour exposure to 2,500 ppm (Group 2), the single 6-hour exposure to 10,000 ppm (Group 3a) and the 14-day repeated exposure to 2,500 ppm (Group 4) indicating similar kinetic behaviour for distribution and elimination of the test substance from blood at these exposure levels and the absence of accumulation of the test substance following a 14-day exposure. Minimal test substance was detected in urine and faeces although some of the test substance may have been lost during collection due to volatility. Elimination of the test substance via inhalation could not be determined under the conditions of the study.

Metabolism
Nine metabolites were tentatively identified in blood, tissues, bile, urine and faeces samples based on accurate mass and parent ion fragmentation spectra. The primary biotransformation steps appeared to be either oxidation or direct conjugation with glutathione. Additional secondary metabolism resulted in phase I and phase II metabolites including oxidation to a ketone, formation of a second glutathione conjugate, or further hydrolysis to dihydroxyl-test substance and glucuronidation. The glutathione conjugates were degraded to cysteine conjugates and N-acetylated cysteine conjugates. The metabolic profile appeared to be quantitatively similar between male and female animals.

TEST FACILITY DuPont (2014c)

B.2. Acute toxicity – inhalation

TEST SUBSTANCE Notified Chemical

METHOD In-house
Species/Strain Rat/Crl:CD(SD)
Vehicle Filtered air
Method of Exposure Whole-body exposure
Exposure Period 2 h
Physical Form Vapour
Remarks - Method A flask containing the test substance was heated to approximately 110 °C to generate vapour of the test substance. The generated vapour was mixed with metered air and oxygen to produce the test atmosphere.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <ppm>*		*Mortality*
		Target	*Actual*	
1	4M	20,000	21000 ± 1400	0/4

LC50 > 21,000 ppm/2 h
Signs of Toxicity Irregular respiration during exposure was noted.
Remarks - Results Slight weight loss was noted on the day after exposure and the animals resumed normal weight gains and gained weight during the recovery period.

CONCLUSION The notified chemical is of low toxicity via inhalation.

TEST FACILITY DuPont (2007a)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 403 Acute Inhalation Toxicity – Limit Test
Species/Strain Rat/ Crl:CD(SD)
Vehicle Filtered air
Method of Exposure Nose-only exposure
Exposure Period 4 h
Physical Form Vapour
Remarks - Method No significant protocol deviations.

Vapours of the test substance were produced through contact of the liquid test substance with heated glass beads (126-135 °C) in a vaporisation column. The generated vapour was mixed with metered air and oxygen to produce the test atmosphere.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <ppm>*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	100,279	102,878	0/10

LC50	> 102,878 ppm/4 h
Signs of Toxicity	Tremors were noted in 2 male animals and 1 female animal, and rales was noted in 2 female animals immediately following exposure. Other clinical signs noted immediately following exposure were typical for animals restrained in nose-only exposure holding tubes for 4 hours. No toxicologically significant clinical signs were noted during the 14-day post exposure observation period.
Effects in Organs	The only macroscopic finding was clear fluid contents in the uterus of 1 female animal, which was considered by the study authors not to be test substance-related.
Remarks - Results	All animals showed normal bodyweight gains.

CONCLUSION The notified chemical is of low toxicity via inhalation.

TEST FACILITY WIL (2009a)

B.4. Irritation – skin

TEST SUBSTANCE Notified Chemical

METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	None
Observation Period	72 h
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Remarks - Results	The scores for erythema and oedema were zero at all observations.

CONCLUSION The notified chemical is non-irritating to the skin.

TEST FACILITY DuPont (2007b)

B.5. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD	In-house
Species/Strain	Rat/Crl:CD(SD)
Route of Administration	Inhalation – nose-only exposure
Exposure Information	Total exposure days: 5 days Duration of exposure: 6 h/day Post-exposure observation period: none
Vehicle	Filtered air
Physical Form	Vapour
Remarks - Method	This was a range-finding, non-GLP study. Vapours of the test substance were produced through contact of the liquid test substance with heated glass beads in a vaporisation column. The generated vapour was carried by air flowing through the column to the

exposure chamber

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Target	*Actual*	
control	5 per sex	0	0	0/10
low dose	5 per sex	1,000	1,160 ± 107.7	0/10
mid dose	5 per sex	10,000	9,999 ± 900.6	0/10
high dose	5 per sex	50,000	48,547 ±1598.7	1/10

Mortality and Time to Death

One male animal in the 10,000 ppm group died on study day 5 during blood collection for clinical pathology evaluations and cause of death was undetermined. No test substance-related clinical signs were noted in the animal prior to death and only red matting of the nasal and buccal skin was noted at gross necropsy. Test substance related histologic lesions included mild degeneration of the olfactory epithelium at nasal levels II, III and IV and minimal neutrophil infiltration at nasal level II which were of a lower severity than those noted in other animals. In addition, there were no animal deaths in the higher dose group of 50,000 ppm. Therefore, the death of this animal was not considered to be test substance-related by the study authors.

Clinical Observations

No test substance-related clinical signs were noted. Yellow material on various aspects of the body and red material around the facial area were noted in several animals. These findings are common with the nose-only method of restraint.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No test material-related changes were noted in coagulation parameters.

Statistically significant differences in haematology parameters including reductions in absolute reticulocyte counts noted in the 10,000 and 50,000 ppm group males, lower MCHC and absolute neutrophil counts in the 10,000 ppm group males, lower absolute basophil and leukocyte counts in the 50,000 ppm group and percentage reticulocyte or leukocyte differential counts were not considered to be test substance-related by the study authors, based on either the findings were not repeated in a 28-day repeated inhalation exposure study (WIL 2009b), did not occur in a dose-related manner, or were not toxicologically important.

No changes in serum chemistry parameters were considered to be directly test material-related. Statistically significant differences including higher albumin, total protein and globulin levels in the 10,000 and 50,000 ppm group males, slightly higher creatinine and sodium levels in the 10,000 ppm group males, higher calcium levels in the 10,000 ppm group males and higher potassium and phosphorus levels in the 10,000 ppm group males were either considered to be secondary or not test substance-related based on the findings did not occur in a dose-related manner or were not toxicologically important.

Effects in Organs

No test substance-related findings were noted at gross necropsy.

Statistically significant differences in organ weights including higher mean liver weight relative to final body weight (↑ 14.0%) in the 50,000 ppm group males, a higher mean kidneys weight relative to final body weight (↑ 15.5%), a higher mean kidneys weight relative to brain weight (↑ 14.9%) in the 50,000 ppm group females were considered by the study authors to be a result of test substance-related lower body weights.

Liver weight changes including higher liver weights (mean absolute, relative to body weight, and relative to brain weight) in the 10,000 and 50,000 ppm group females, higher mean absolute liver weights in the 10,000 (↑ 6.4%) and 50,000 (↑ 12.0%) ppm group females, higher mean liver weights relative to final body weight in the 10,000 (↑ 13.9%) and 50,000 (↑ 19.8%) ppm group females and a higher mean liver weight relative to brain weight (↑ 19.1%) in the 50,000 ppm group females were considered by the study authors to have an uncertain relationship to the test material as there were no gross observations or histologic changes to correlate with the slightly higher liver weights in the 10,000 and 50,000 ppm group females and higher mean absolute liver weights were not observed in the 10,000 and 50,000 ppm group males.

Test substance-related histologic changes included degeneration of the olfactory epithelium, neutrophilic infiltration and luminal cellular debris in the nasal cavity of the 10,000 ppm group males and the 50,000 ppm group males and females, which were considered by the study authors to be a transient effect based on that there were no histopathological changes in the nasal cavity or respiratory tract of either male or female rats in a 28-day repeated inhalation exposure study (WIL 2009b).

Remarks – Results

Lower body weights and lower body weight gains were noted in the 10,000 and 50,000 ppm group males and females when compared to the control group on study day 4, which correlated with a decrease in food consumption for these groups on study day 4. This effect was considered to be test substance-related by the study authors.

CONCLUSION

The No Observed Adverse Effect Concentration (NOAEC) was established as 1,000 ppm in this study, based on lower body weight gains, decreased food consumption, and degeneration of the olfactory epithelium, neutrophilic infiltration and luminal cellular debris in the nasal cavity in the 10,000 ppm and 50,000 ppm groups.

TEST FACILITY WIL (2008a)

B.6. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 412 Subchronic Inhalation Toxicity: 28-day Study

Species/Strain	Rat/Sprague Dawley
Route of Administration	Inhalation – nose-only exposure
Exposure Information	Total treated days: 28 days (20 exposure days in total) Dose regimen: 5 days per week Duration of exposure (inhalation): 6 h/day Post-exposure observation period: 15 days
Vehicle	Filtered air
Physical Form	Vapour
Remarks - Method	Compressed air metred to a 3-neck flask (containing the test substance and a gas dispersion tube) bubbled through the fritted dispersion tube and the liquid test substance to produce vapour of the test substance. The test vapour was mixed with humidified air prior to entering a nose-only exposure system. Exposure doses were selected based on the results of a 5-day repeated dose inhalation toxicity study (WIL 2008a).

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Target	*Actual*	
control	20 per sex	0	0	0/20
low dose	10 per sex	2,500	2,494 ± 111.4	0/10
mid dose	10 per sex	5,000	4,976 ± 183.3	0/10
high dose	20 per sex	10,000	10,281 ± 919.1	0/20
control recovery	10 per sex	0	0	0/10
high dose recovery	10 per sex	0	0	0/10

Clinical Observations

Yellow material on various aspects of the body was noted during the detailed physical examinations period and prior to test substance exposure in the 5,000 and 10,000 ppm groups. These findings are common with the nose-only method of restraint.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Test substance-related findings included increased serum albumin and total protein levels in male animals of the 10,000 ppm group at study week 3. At the recovery period (study week 5), serum albumin levels in male animals of the 10,000 ppm group were slightly lower and total protein levels were statistically significantly lower when compared to the control group.

No test substance-related effects on coagulation or urinalysis parameters were noted.

Effects in Organs

No test substance-related findings were noted at gross necropsy. There were no histopathological changes in any organs examined including the respiratory tract.

Differences in heart and brain weights were observed however the differences were not considered by the study authors as biologically relevant as they were within the historical reference range. There were no test substance-related effects on respiratory tract tissues, nor were there macroscopic or microscopic findings.

Remarks – Results

Lower body weights and lower cumulative body weight gains were noted in the 5,000 and 10,000 ppm groups when compared to the control group throughout the exposure period. This correlated with a decrease in food consumption for these groups throughout the exposure period.

CONCLUSION

The No Observed Adverse Effect Concentration (NOAEC) was established as 2,500 ppm in this study, based on lower body weights and lower cumulative body weight gains noted in the 5,000 and 10,000 ppm groups, as well as increased serum albumin and total protein levels in male animals of the 10,000 ppm group.

TEST FACILITY WIL (2009b)

B.7. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD

Species/Strain	Rat/Crl:CD(SD)
Route of Administration	Inhalation – whole body exposure
Exposure Information	Total exposure days: 90 days (63 exposure days in total) Dose regimen: 5 days per week Duration of exposure (inhalation): 6 h/day Post-exposure observation period: approximately 4 weeks
Vehicle	Filtered air
Physical Form	Vapour
Remarks - Method	Vapour of the test substance was generated by flash evaporation of the liquid test substance with an evaporation flask heated to approximately 175 °C. Air was metered through the heated flask and carried the vaporised test substance into a filtered and conditioned dilutional air stream leading to the exposure chamber.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Target	*Actual (mean ± SEM*)*	
control	20 per sex	0	0 ± 0	0/40
low dose	20 per sex	500	510 ± 2	0/40
mid dose	20 per sex	1,500	1500 ± 4.7	0/40
high dose	20 per sex	10,000	10,000 ± 36	0/40
control recovery	10 per sex	0	0	0/20
high dose recovery	10 per sex	0	0	0/20

* SEM: standard error of the mean

Mortality and Time to Death
There were no test substance-related unscheduled deaths during the study.

Body Weight, Food Consumption and Food Efficiency
Statistically significant reductions in body weight were noted in male and female animals in the 10,000 ppm group, correlated with statistically significant reductions in food consumption and food efficiency. Following the recovery period, body weights of male and female animals exposed to 10,000 ppm were similar to the control animals indicating the test substance induced reduction in body weights is reversible.

Clinical Observations
Clinical signs including abnormal gait, aggressive behaviour, ear twitching, hyperactivity, low posture, tremors, reduced hindlimb strength, hyperreactivity during handling and high arousal were noted in the male animals of the 10,000 ppm group were considered by the study authors to be secondary to the significant reduction in body weight, food consumption and food efficiency in the animals.

No test-substance-related effects were noted in the ophthalmology examinations.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
There were no adverse changes in clinical pathology parameters in male and female animals in all exposure groups.

Effects in Organs
Test substance-related microscopic findings of minimal mucous cell hyperplasia of the respiratory epithelium, incomplete decalcification of enamel and increased lamination of the dentin in the incisor teeth, and incomplete decalcification of bone trabeculae in the femur were consistent with exposure to a fluorine-containing test substance and were not associated with any histopathological changes suggestive of tissue injury or any adverse functional consequences in these tissues. Therefore, these effects were not considered by the study authors to be adverse.

CONCLUSION
The No Observed Adverse Effect Concentration (NOAEC) was established as 1,500 ppm in this study, based on test-substance-related reductions in body weight, food consumption and food efficiency in both male and female animals in the 10,000 ppm group.

TEST FACILITY	DuPont (2010a)

B.8. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 413 Subchronic Inhalation Toxicity: 90-day Study
Species/Strain	Rat/Crl:CD(SD)
Route of Administration	Inhalation – whole body exposure
Exposure Information	Total exposure days: 90 days (65 exposure days in total) Dose regimen: 5 days per week Duration of exposure (inhalation): 6 h/day Post-exposure observation period: none
Vehicle	Filtered air
Physical Form	Vapour
Remarks - Method	A previous inhalation repeated-dose toxicity study (DuPont 2010a) established a No Observed Adverse Effect Concentration (NOAEC) of 1,500 ppm where the next highest exposure level was 10,000 ppm. This study was to assess the potential repeated-dose toxicity at dose levels between 1,500 and 10,000 ppm to establish a more precise NOAEC. No significant protocol deviations between this study and the previous one.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Mortality*
		Target	*Actual (mean ± SEM*)*	
control	10 per sex	0	0 ± 0	0/20
low dose	10 per sex	3,000	3,000 ± 8.4	0/20
mid dose 1	10 per sex	4,000	4,000 ± 12	0/20
mid dose 2	10 per sex	5,000	5,000 ± 10	0/20
high dose	10 per sex	7,500	7,500 ± 8.3	0/20

* SEM: standard error of the mean

Mortality and Time to Death
There were no test substance-related unscheduled deaths during the study.

Body Weight, Food Consumption and Food Efficiency
Statistically significant reductions in mean body weight were noted in male animals exposed to 7,500 ppm, correlated with statistically significant reductions in mean daily food consumption. No change was noted in food efficiency.

Clinical Observations
No test substance-related clinical signs were noted. No adverse changes in ophthalmology evaluation were noted.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
There were no adverse findings in clinical pathology.

Effects in Organs
No adverse findings in organ weight or gross pathological evaluations.

Test substance-related microscopic findings of incomplete decalcification of enamel in the distal region of the upper incisors (in all male and female animals) and incomplete decalcification of bone trabeculae in the femur (in all male animals and the female animals of the 7,500 ppm group) were consistent with exposure to a fluorine-containing test substance and were not associated with any histopathological changes suggestive of tissue injury or any adverse functional consequences in these tissues. Therefore, these effects were not considered by the study authors to be adverse.

CONCLUSION
The No Observed Adverse Effect Concentration (NOAEC) was established as 5,000 ppm in male rats based on test substance-related reductions in body weights and food consumption at the dose level of 7,500 ppm and the NOAEC was established as 7,500 ppm (the highest exposure dose) in female rats, based on no test substance-related adverse effects at any exposure doses.

TEST FACILITY DuPont (2011b)

B.9. Cardiac sensitisation to adrenaline

TEST SUBSTANCE Notified chemical

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, at a minimum of 48 h intervals. Baseline response to the epinephrine challenge doses were collected 3 days prior to exposure to the test substance. The duration of exposure was up to 31 minutes, and the concentrations tested were 1.25, 2.5 and 5% (12,500, 25,000 and 50,000 ppm), respectively. Animals were administered increasing doses of epinephrine as a bolus injection via an appropriate vein approximately 5 minutes following exposure to the test

substance, at approximately 3 minutes apart or until the electrocardiogram of the animal returned to its normal baseline. The animals were monitored twice daily for mortality and moribundity. The ECG recording taken during exposure to the test substance and after administration of the challenge epinephrine doses were compared to the ECG recording taken after administration of the pre-exposure escalating epinephrine doses.

The criteria used to consider unequivocal evidence of cardiac sensitisation include (not exclusively):

- Equivocal but positive evidence: 6 to 10 premature ventricular contractions (PVCs) in a 10 second period that may be multifocal but not uniformly confluent. Typically quickly resolve and not typically life-threatening
- Unequivocal evidence: 11 or more PVCs that are multifocal with periods of confluency take a relatively long time to resolve and may occur in bursts between episodes of normal looking beats; potentially life-threatening
- Unequivocal evidence: serious, life-threatening events such as ventricular tachycardia, fibrillation and flutter

Test substance atmospheres (the target concentration of the test substance vapour and a minimum oxygen content of 19%) were prepared in Tedlar bags and analysed by GC before exposure. At the initiation of the exposure, the three-way valve was turned to the bag position, and during non-exposure periods, it delivered filtered air. Each dog served as its own control, as the same dogs were used for all exposures. After each exposure, the dogs were given at least 48 hours of rest before being given the next exposure.

Challenge Procedure

Time	*Event*
0 min	Start ECG recording (baseline)
2 min	Test gas initiated
7 min	Increasing challenge doses of epinephrine
Up to approx. 33	Termination of exposure/ECG

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

RESULTS

Summary of Cardiac Response

Dog No.	*Epinephrine Dose (µg/kg)*	*Test Substance Concentration <ppm>*	*1st Epinephrine Challenge (baseline)*	*2nd Epinephrine Challenge (exposure)*
1	2	12,500	-	NSCO
	4	12,500	NSCO	NSCO
	6	12,500	PAC 63 seconds post-epinephrine, PAC(2) 68-70 seconds post-epinephrine	NSCO
	2	25,000	-	NSCO
	4	25,000	NSCO	PVC(8) 14-16 seconds post-epinephrine, PVC 17, 19 and 20 seconds post-epinephrine
	6	25,000	PAC 63 seconds post-epinephrine, PAC(2) 68-70 seconds post-epinephrine	PVC 11, 13 and 14 seconds post-epinephrine, PVC(> 11) 14-18 seconds post-epinephrine
	2	50,000	-	NSCO
	4	50,000	NSCO	PVC(2) 16 seconds post-epinephrine, PVC(4) 23-25 seconds

				post-epinephrine
	6	50,000	PAC 63 seconds post-epinephrine, PAC(2) 68-70 seconds post-epinephrine	PVC(7) 13-21 seconds post-epinephrine
2	2	12,500	-	NSCO
	4	12,500	-	NSCO
	6	12,500	NSCO	NSCO
	8	12,500	NSCO	PVC(8) 10-22 seconds post-epinephrine
	2	25,000	-	AVB2 23 seconds post-epinephrine
	4	25,000	-	AVB2(3) 14-18 seconds post-epinephrine
	6	25,000	NSCO	PVC 13 seconds post-epinephrine
	8	25,000	NSCO	NSCO
	2	50,000	-	NSCO
	4	50,000	-	AVB2(3) 19-25 seconds post-epinephrine
	6	50,000	NSCO	AVB2(3) 22-30 seconds post-epinephrine
	8	50,000	NSCO	PVC(5) 16-22 seconds post-epinephrine, AVB2(2) 25-30 seconds post-epinephrine
3	2	12,500	NSCO	-
	4	12,500	NSCO	-
	6	12,500	NSCO	-
	8	12,500	-	-
	2	25,000	NSCO	-
	4	25,000	NSCO	-
	6	25,000	NSCO	-
	8	25,000	-	-
	2	50,000	NSCO	NSCO
	4	50,000	NSCO	PVC(3) 15-19 seconds post-epinephrine, PVC(6) 20-22 seconds post-epinephrine
	6	50,000	NSCO	PVC 16 seconds post-epinephrine, multiple PVC 17 seconds post-epinephrine, followed by ventricular tachycardia leading into ventricular fibrillation resulting in death
	8	50,000	-	-
4	2	12,500	PVC 4 minutes pre-dose, 3 minutes post-epinephrine	PVC 12 and 190 seconds post-epinephrine
	4	12,500	NSCO	PVC 219 seconds post-epinephrine
	6	12,500	NSCO	PVC 62 seconds post-epinephrine
	8	12,500	NSCO	PVC 11 and 205 seconds post-epinephrine
	2	25,000	PVC 4 minutes pre-dose, 3 minutes post-epinephrine	PVC(5) 15-20 seconds post-epinephrine
	4	25,000	NSCO	PVC(9) 14-16 seconds post-epinephrine
	6	25,000	NSCO	NSCO
	8	25,000	NSCO	PVC(> 11) 16-36 seconds post-epinephrine
	2	50,000	PVC 4 minutes pre-dose, 3 minutes post-epinephrine	PVC pre-exposure, AVB2 16 seconds pre-dose, PVC(2) 125 and 155 seconds post-epinephrine
	4	50,000	NSCO	AVB2 8, 17 and 34 seconds post-epinephrine

	6	50,000	NSCO	AVB2 9 seconds post-epinephrine, PVC(5) 14-18 seconds post-epinephrine, AVB2(2) 16-20 seconds post-epinephrine, PVC 216 seconds post-epinephrine
	8	50,000	NSCO	PVC(> 11) 13-24 seconds post-epinephrine
5	2	12,500	-	NSCO
	4	12,500	-	NSCO
	6	12,500	-	NSCO
	8	12,500	NSCO	NSCO
	2	25,000	-	NSCO
	4	25,000	-	AVB2 18 seconds post-epinephrine
	6	25,000	-	PVC 13 seconds post-epinephrine
	8	25,000	NSCO	PVC(2) 27 seconds post-epinephrine, PVC(> 11) 31-46 seconds post-epinephrine
	2	50,000	-	NSCO
	4	50,000	-	PVC 13 and 16 seconds post-epinephrine
	6	50,000	-	PVC(4) 13-18 seconds post-epinephrine,
	8	50,000	NSCO	PVC(> 11) 14-21 seconds post-epinephrine
6	2	12,500	-	NSCO
	4	12,500	-	PVC 20 seconds post-epinephrine
	6	12,500	-	NSCO
	8	12,500	PAC 9 seconds post-epinephrine	NSCO
	2	25,000	-	NSCO
	4	25,000	-	PVC(> 11) 17-30 seconds post-epinephrine
	6	25,000	-	-
	8	25,000	PAC 9 seconds post-epinephrine	-
	2	50,000	-	NSCO
	4	50,000	-	AVB2 35 seconds post-epinephrine
	6	50,000	-	PVC(> 11) 14-22 seconds pose-epinephrine
	8	50,000	PAC 9 seconds post-epinephrine	-

NSCO: no significant clinical observations; PAC: premature atrial contraction; PVC: premature ventricular contraction; AVB2: atrioventricular block 2nd degree

Note: seconds or minutes are approximate; "-" stands for no data reported; number in ( ) indicates the total number of incidences

Signs of Toxicity	During exposure to 50,000 ppm of the test substance, multiple premature ventricular contractions were noted at 17 seconds post the 6 µg/kg epinephrine dose which was followed by ventricular tachycardia leading into ventricular fibrillation, resulting in death of the animal. Intermittent tremors were noted in 2 animals and pale extremities were noted in 3 animals after exposure to 50,000 ppm and intermittent tremors were noted in 1 animal after exposure to 25,000 ppm.
Myocardial Effects	Cardiac sensitisation was noted in 5 animals post-epinephrine (3 animals at 6 µg/kg and 2 animals at 8 µg/kg) after exposure to 50,000 ppm. Cardiac sensitisation was noted in 4 animals post- epinephrine (1 animal at 4 µg/kg, 1 animal at 6 µg/kg and 2 animals at 8 µg/kg) after exposure to 25,000 ppm.
NOEC	12,500 ppm
Remarks - Results	Body weights were collected but not analysed for test substance effects.

CONCLUSION	There was evidence of cardiac sensitisation at the dose levels of 25,000 ppm and 50,000 ppm, under the conditions of the test.
TEST FACILITY	WIL (2008b)

B.10. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Aroclor 1254-induced rat liver S9
Concentration Range in Main Test	a) With metabolic activation: 15, 50, 150, 500, 1500, 5000 µg/plate b) Without metabolic activation: 15, 50, 150, 500, 1500, 5000 µg/plate
Vehicle	Water
Remarks - Method	Due to the volatile nature of the test substance, test substance dilutions were prepared immediately before use and delivered to the test system at room temperature under yellow light. All test substance dilutions and vehicle were maintained on ice during dilution and use and all dilution vessels were capped. During the preincubation period all tubes receiving the test substance were capped. Concentrations in the main test were selected on the basis of a preliminary test using eight concentrations ranging from 1.5-5000 µg/mL. The negative control was water and positive controls were sodium azide, 9-aminoacridine, 2-nitrofluorene and methyl methanesulfonate in the absence of metabolic activation and 2-aminoanthracene in the presence of metabolic activation.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 1500	≥ 1500	none	negative
Test 2		≥ 1500	none	negative
Present				
Test 1	> 5000	> 5000	none	negative
Test 2		> 5000	none	negative

Remarks - Results	No precipitate was noted. Toxicity was noted at ≥ 1500 µg/plate in the absence of metabolic activation. No positive mutagenic response was noted. The negative and positive controls confirmed the sensitivity of the test.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	BioReliance (2007a)

B.11. Genotoxicity – in vitro

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test

Species/Strain	Human/female adult
Cell Type/Cell Line	Human lymphocytes
Metabolic Activation System	Aroclor 1254-induced rat liver S9
Vehicle	Water
Remarks - Method	Due to the volatile nature of the test substance all dilutions were performed in an ice bath. Test substance dilutions were prepared immediately before use and delivered to the test system at room temperature under yellow light. In addition, to prevent loss during the treatment period the media, S9 and test substance dosing volumes were adjusted so as to fill the tubes completely and the tubes were tightly capped. Concentrations in the main test were selected on the basis of a preliminary study using nine concentrations ranging from 0.164 to 1640 µg/mL. The negative control was water and positive controls were mitomycin C in the absence of metabolic activation and cyclophosphamide in the presence of metabolic activation.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	125, 250*, 500*, 1000*, 1640	4	20
Test 2	125*, 250*, 500*, 1000, 1640	20	20
Present			
Test 1	62.5, 125*, 250*, 500*, 1000, 1200	4	20

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 1640	≥ 1000	none	negative
Test 2	≥ 1640	≥ 500	none	negative
Present				
Test 1	≥ 1640	≥ 500	none	negative

Remarks - Results	Substantial toxicity was noted at 1640 µg/mL in all treatment groups in the preliminary study. In both the absence and presence of metabolic activation, the test substance did not induce a statistically significant increase in the number of aberrant cells at any of the concentrations and time points analysed, when compared to the number of aberrant cells observed in the negative control cultures. The concurrent negative and positive controls gave satisfactory responses confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	BioReliance (2007b)

B.12. Genotoxicity – in vivo

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Rat/Crl:CD(SD)
Route of Administration	Inhalation – whole body exposure
Vehicle	Filtered air
Physical Form	Vapour
Remarks - Method	The study was carried out as a satellite to a 90-day repeated dose inhalation study (DuPont 2011b). Blood collected after the fourth exposure on test day 3 (for all groups), approximately after 4 weeks of exposure on test day 28 (for all groups) and at the time of sacrifice on test day 92 (for control and high dose groups). The samples were analysed and evaluated using the *In Vitro* MicroFlow Plus® Rat Micronucleus assay kit. The positive control provided in the kit was used as the positive control for this study. Toxicity was indicated by the frequency of immature reticulocytes (%RETs) among the total (RETs plus normochromic erythrocytes), and induction of aneugenic or clastogenic alterations was indicated by the frequency of micronucleated reticulocytes (%MN-RETs).

Group	*Number and Sex of Animals*	*Dose/Concentration <ppm>*		*Sacrifice Time (day)*
		Target	*Actual (mean ± SEM*)*	
control	5 per sex	0	0 ± 0	92
low dose	5 per sex	3,000	3,000 ± 8.4	92
mid dose 1	5 per sex	4,000	4,000 ± 12	92
mid dose 2	5 per sex	5,000	5,000 ± 10	92
high dose	5 per sex	7,500	7,500 ± 8.3	92

* SEM: standard error of the mean

RESULTS	
Doses Producing Toxicity	No mortality was seen. Statistically significant decreases in the %RETs in male animals of the 3,000, 4,000 and 7,500 ppm groups at test day 3 were considered to be test substance-related but not adverse, based on that there were no changes in red cells mass parameters at test day 92 and the absolute RET count at test day 92 was increased in male animals of the 5000 and 7500 ppm groups. The expected decreases in %RETs at the test day 28 and 92 were attributed to the maturation of the animals and not considered to be adverse.
Genotoxic Effects	There were no statistically significant increases in the %MN-RETs in any treated groups at any testing point.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo mammalian erythrocyte micronucleus test.
TEST FACILITY	DuPont (2011b)

B.13. Developmental toxicity

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 414 Prenatal Development Toxicity Study.
Species/Strain	Rat/Crl:CD(SD)
Route of Administration	Inhalation – whole body exposure
Exposure Information	Exposure days: day 6 through to day 20 of gestation Duration of exposure (inhalation): 6 h/day Post-exposure observation period: none

Vehicle	Filtered air
Physical Form	Vapour
Remarks - Method	Vapour of the test substance was generated by flash evaporation of the liquid test substance with an evaporation flask heated to approximately 175 °C. Air was metered through the heated flask and carried the vaporised test substance into a filtered and conditioned dilutional air stream leading to the exposure chamber.

RESULTS

Group	*Number of Animals*	*Dose/Concentration* <*ppm*>		*Mortality*
		Target	*Actual (mean ± SEM*)*	
1	22	0	0 ± 0	0/22
2	22	500	510 ± 3.6	0/22
3	22	1,500	1,500 ± 9.0	0/22
4	22	10,000	10,000 ± 80	0/22

* SEM: standard error of the mean

Mortality and Time to Death

There was no test substance-related, unscheduled mortality.

Effects on Dams

An increase in the incidence of pallor was noted in dams exposed to 10,000 ppm. Increased incidences of stained and/or wet fur were noted in dams exposed to 1,500 ppm and 10,000 ppm.

Significant reductions in mean maternal body weight and mean maternal body weight changes were noted from day 7 of gestation until the end of the study in the 10,000 ppm group, correlated with significant reductions in food consumption for the duration of the exposure period. Mean maternal body weight, weight changes and food consumption in the 500 ppm and 1,500 ppm groups were comparable to those of the control group.

There were no test substance-related maternal gross postmortem findings at necropsy.

Effects on Foetus

Statistically significant reductions in mean foetal weight were noted in the 10,000 group. Mean foetal weights in the 500ppm and 1,500 ppm groups were comparable to those in the control group.

The mean numbers per litter for implantation sites, resorptions, live foetuses and sex ratio were comparable across all groups tested.

No foetal malformations or test substance-related foetal variations were noted at any dose level tested.

CONCLUSION

The No Observed Adverse Effect Concentration (NOAEC) for maternal and foetal toxicity was established as 1,500 ppm in this study, based on reductions in mean maternal body weights, mean maternal body weight changes and food consumption and reductions in mean foetal weight at the exposure level of 10,000 ppm.

TEST FACILITY DuPont (2010b)

B.14. Developmental toxicity

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 414 Prenatal Development Toxicity Study.

Species/Strain	Rabbit/ New Zealand White
Route of Administration	Inhalation – whole body exposure
Exposure Information	Exposure days: day 7 through to day 28 of gestation Duration of exposure (inhalation): 6 h/day Post-exposure observation period: none
Vehicle	Filtered air

Physical Form	Vapour
Remarks - Method	The study was conducted in 2 phases due to space limitation of the exposure chambers. However, due to excessive toxicity noted in the animals exposed to 15,000ppm in Phase 1, the animals were not exposed to 15,000 ppm in Phase 2. Vapour of the test substance was generated by releasing the test substance in gas form from the original cylinders using a Brisk Heat blanket controlled to be at 60-70 ºC.

RESULTS

Group-Phase	*Number of Animals*	*Dose/Concentration <ppm>*		*Mortality/Moribundity*
		Target	*Actual*	
1-1 (vehicle control)	12F	0	0	0/12
1-2 (vehicle control)	12F	0	0	0/12
2-1	12F	2,500	2,426	0/12
2-2	12F	2,500	2,415	0/12
3-1	12F	5,000	4,934	0/12
3-2	12F	5,000	5,047	0/12
4-1	12F	7,500	7,429	1/12
4-2	12F	7,500	7,305	0/12
5-1	12F	15,000	14,667	7/12

Mortality/Moribundity and Time to Death

Test substance-related moribundity was noted for females in the 7500 ppm and 15000 ppm groups. Seven of 12 females of the 15,000 ppm group were euthanised *in extremis* in Phase 1 during gestation days 18-27 due to impaired use of the hindlimbs (with a dislocation of the lumbar vertebrae at necropsy for some animals), increased respiration, hypoactivity, tonic convulsions, labored respiration, prostration and/or a pale body. One female of the 7,500 ppm group was euthanised *in extremis* on gestation day 25 due to impaired use of the hindlimbs, tonic convulsions, and rapid and shallow respiration. No other test substance-related moribundity or mortality was noted.

Effects on Dams

Test substance-related, adverse effects in body weight included mean body weight losses or reduced mean body weight gains (with corresponding reduced mean food consumption) for female animals in the 15,000 ppm group during gestation days 7-29. Reduced mean body weight gains noted in the 2,500, 5,000, and 7,500 ppm groups, (with corresponding effects on mean food consumption noted in the 5,000 and 7,500 ppm groups during gestation days 13-20) were considered by the study authors to be test substance-related but not adverse, based on mean body weights in these groups were not affected. Mean net body weights, net body weight changes, and gravid uterine weights in the 2,500, 5,000, and 7,500 ppm groups were similar to the control group.

Clinical findings of decreased defecation were noted for the animals in the 7,500 and 15,000 ppm groups.

There were no test substance-related macroscopic findings for any animals at the scheduled gestation day 29 necropsy.

There were no test substance-related microscopic findings noted in the heart at any exposure levels.

Effects on Foetus

Test substance-related lower mean foetal weights were noted in the 15,000 ppm group (only 4 litters available for evaluation). Mean foetal weights in the 2,500, 5,000, and 7,500 ppm groups were unaffected by test substance exposure. The lower mean foetal weights in the 2,500, 5,000, and 7,500 ppm groups were not considered by the study authors to be test substance-related, based on that the results were within the ranges of values in the test facility's historical control data and were influenced by 1-2 litters in each of these groups with mean foetal weights below 30.0 g.

Intrauterine survival and foetal morphology at all exposure levels were unaffected by test substance exposure.

CONCLUSION
The No Observed Adverse Effect Concentration (NOAEC) for maternal toxicity was established as 5,000 ppm in this study, based on adverse clinical findings and moribundity of maternal females at 7,500 and 15,000 ppm and reduced mean body weights and food consumption at 15,000 ppm. The No Observed Adverse Effect Concentration (NOAEC) for foetal toxicity was established as 7,500 ppm in this study, based on lower foetal weights at 15,000 ppm (only 4 litters evaluated).

TEST FACILITY WIL (2013 and 2014)

B.15. Toxicity to reproduction – two generation study

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 416 Two-Generation Reproduction Toxicity
Species/Strain Rat/Crl:CD(SD)
Route of Administration Inhalation – whole body exposure
Exposure Information Exposure period – parental (P) generation and first filial (F1) generation males: at least 10 weeks prior to mating, up to 2 weeks during mating, 3-4 weeks after the end of the mating period
Exposure period – P-generation and F1-generation females: at least 10 weeks prior to mating, up to 2 weeks during mating, followed by:
- for females without evidence of mating or no litter delivered: at least 24 days after the end of mating period
- for females with no evidence mating but assumed pregnant based on weight gain: until up to 6 days following the end of cohabitating period (or sooner based on gestation day 14 weight gain)
- for pregnant females: 20 days during gestation period (GD 0-19) and 14 days during lactation period (LD 7- 20)

Duration of exposure (inhalation/dermal): 6 h/day, 7 days/week
Vehicle Filtered air
Physical Form Vapour
Remarks - Method Vapour of the test substance was generated by heating the flask containing the test substance to approximately 175 °C. The generated vapour was mixed with air to form a filtered and conditioned dilutional air stream leading to the exposure chamber.

Generation	*Group*	*Number and Sex of Animals*	*Dose/Concentration* <*ppm*>	
			Target	*Actual (mean ± SEM*)*
P	1 (control)	30 per sex	0	0 ± 0
	2	30 per sex	500	500 ± 1.3
	3	30 per sex	1,000	1,000 ± 1.8
	4	30 per sex	1,500	1,500 ± 2.1
	5	30 per sex	2,500	2,500 ± 2.5
F1	1 (control)	30 per sex	0	0 ± 0
	2	30 per sex	500	500 ± 1.2
	3	30 per sex	1,000	1,000 ± 1.5
	4	30 per sex	1,500	1,500 ± 2.2
	5	30 per sex	2,500	2,500 ± 2.5

* SEM: standard error of the mean

RESULTS
Mortality and Time to Death
All male animals of P1-generation and F1-generation survived to scheduled euthanasia. Three female animals of P1-generation and 3 female animals of F1-generation were euthanised early due to clinical signs, loss of litter or a fractured nose; however, the deaths were not considered by the study authors to be test substance-related.

Effects on P- and F1-Generation
For either generation, there were no test substance-related clinical observations.

Adverse test substance-related toxicity included reductions in body weight and nutritional parameters in adult male animals of F1-generation exposed to 2,500 ppm.

There were no adverse effects on gross observations, organ weights or microscopic alterations in adult animals of P1- or F1-generation and offspring of F1- or F2-generation.

The data for mating, fertility, precoital interval length, gestation length and implantation site was comparable across all groups tested for each respective generation, indicating no test substance-related effects on reproduction in P1- and F1-generation.

CONCLUSION
Under the conditions of this two-generation reproduction toxicity study in rats, the No Observed Adverse Effect Concentration (NOAEC) for systemic toxicity was established as 1,500 ppm in male animals, based on reductions in body weight and nutritional parameters in F1 males exposed to 2,500 ppm, and as 2,500 ppm in female animals, the highest exposure dose tested. The NOAEC for developmental and reproductive toxicity were both established as 2,500 ppm, the highest exposure dose tested, based on no adverse effects on fertility parameters or offspring were observed.

TEST FACILITY DuPont (2014d)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test
Inoculum	Secondary effluent from a domestic wastewater treatment plant (Machida-shi, Japan).
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biochemical Oxygen Demand (BOD)
Remarks - Method	No significant deviation in protocol

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	0	7	74.5
14	0	14	86.5
21	0	21	82.5
28	0 (-2)	28	84

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate (86.5%), surpassed the threshold level of 60% by 14 days. Therefore, the test indicates the suitability of the inoculums. The degree of degradation of the notified chemical after 28 days was 0%. Therefore, the notified chemical cannot be classified as readily biodegradable according to the OECD (301 D) guideline.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Mitsubishi (2011b)

C.1.2. Inherent biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 302 C Inherent Biodegradability: Modified MITI Test (II)
Inoculum	Activated sludge, surface soil, and surface water samples from ten sites across four districts in Nanjing, China
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biochemical Oxygen Demand (BOD).
Remarks - Method	No significant deviation in protocol

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
4	0 (-1.4)	4	72.4
7	0.42	7	82.6
14	3.05	14	88.5
21	3.06	21	88.6
28	2.18	28	88.5

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation

of the reference compound, sodium benzoate (64.7%), surpassed the threshold level of 60% by 3 days. Therefore, the test indicates the suitability of the inoculums. The toxicity control exceeded 40% biodegradation after 2 days, showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical after 28 days was 2.18%. Therefore, the notified chemical cannot be classified as readily biodegradable according to the OECD (302 C) guideline.

CONCLUSION The notified chemical is not readily biodegradable.

TEST FACILITY MEP (2014b)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD OECD TG 203 Fish, Acute Toxicity Test – Semi-Static
Species *Oryzias latipes* (medaka)
Exposure Period 96 hours
Auxiliary Solvent None
Water Hardness 122.2 mg $CaCO_3$/L
Analytical Monitoring GC-MS
Remarks – Method Following the range finding test (conducted at nominal concentrations of 10, 50, 100, 250, and 500 mg/L of the notified chemical), the definitive test was conducted at nominal concentrations of 25, 44, 79, 140, and 250 mg/L of the notified chemical. No significant deviation in protocol.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	10	0	0	0	0	0
25	13.1	10	0	0	0	0	0
44	20.5	10	0	0	0	0	20
79	34.4	10	0	0	0	0	0
140	55.2	10	0	0	0	0	0
250	105	10	100	100	100	100	100

LC50 76.1 mg/L (95% CL: 13.1-105 mg/L) at 96 hours.
NOEC Not determined
Remarks – Results All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 96 h test period. Abnormal swimming ability was observed among fish exposed to 34.4 mg/L (measured concentration) of the notified chemical at 48 h, and the majority of fish exposed to 55.2 mg/L (measured concentration) of the notified chemical were observed to swim abnormally or were incapable of swimming at 3 h. The 96 h LC50 for fish was determined to be 76.1 mg/L (95% CL: 13.1-105 mg/L), based on calculations from measured concentrations.

CONCLUSION Under the study conditions, the notified chemical is harmful to fish.

TEST FACILITY Mitsubishi (2011c)

C.2.2. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-Static
Species	*Gobiocypris rarus* (Rare minnow)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	122.2 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	Following the range finding test (conducted at nominal concentrations of 1, 10, and 100 mg/L of the notified chemical), the definitive test was conducted at nominal concentrations of 100 mg/L of the notified chemical (measured concentration: 95.7 mg/L). No significant deviation in protocol.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*			
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	10	0	0	0	0
100	95.7	10	0	0	0	0

LC50	> 95.7 mg/L at 96 hours
NOEC	95.7 mg/L at 96 hours
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 96 h test period. No abnormalities in behaviour or appearance were observed. The 96 h LC50 for fish was determined to be > 95.7 mg/L, and correspondingly the NOEC was determined to be 95.7 mg/L, based on measured concentrations.
CONCLUSION	Under the study conditions, the notified chemical is harmful to fish.
TEST FACILITY	MEP (2014c)

C.2.3. Chronic toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 210 Fish, Early-life Stage Toxicity Test – Semi-Static
Species	*Gobiocypris rarus* (Rare minnow)
Exposure Period	28 days (post-hatch)
Auxiliary Solvent	None
Water Hardness	122.2 mg $CaCO_3$/L
Analytical Monitoring	GC-FID
Remarks – Method	No significant deviation in protocol

RESULTS

Concentration mg/L		*Number of Eggs*	*Mortality post-hatch (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	30	0	0	0	0	0
1	0.972	30	0	0	0	0	0
10	9.58	30	3.8	3.8	3.8	3.8	3.8

NOEC	9.58 mg/L at 28 d post-hatch
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the test period. No effects were observed. The 28 d post-hatch NOEC for fish was determined to be 9.58 mg/L, based on measured concentrations.

CONCLUSION	Under the study conditions, the notified chemical is not harmful to fish on a chronic basis.
TEST FACILITY	MEP (2014d)

C.2.4. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test – Semi-Static
Species	*Daphnia magna*.
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	GC-MS
Remarks - Method	Following the range finding test (conducted at nominal concentrations of 0.1-100 mg/L of the notified chemical), the definitive test was conducted at 5, 11, 22, 47, and 100 mg/L of the notified chemical. No significant deviation in protocol.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
5	1.57	20	0	0
11	4.27	20	0	0
22	7.88	20	0	0
47	16.8	20	0	30
110	51.3	20	70	95

EC50	22.5 mg/L (95% CL: 17.9-29.6 mg/L) at 48 hours
NOEC (or LOEC)	Not determined
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the 48 h test period. The 48 h EC50 was determined to be 22.5 mg/L (95% CL: 17.9-29.6 mg/L), calculated based on measured concentrations.
CONCLUSION	Under the study conditions, the notified chemical is harmful to daphnids.
TEST FACILITY	Mitsubishi (2011d)

C.2.5. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 211 *Daphnia magna* Reproduction Test – Semi-Static
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	None
Water Hardness	221-232 mg $CaCO_3$/L
Analytical Monitoring	GC-FID
Remarks - Method	Following the range finding test (conducted at nominal concentrations of 1 and 10 mg/L of the notified chemical), the definitive test was conducted at a nominal concentration of 10 mg/L of the notified chemical. No significant deviation in protocol.

RESULTS

	Test Concentration mg/L	
	Control	*10.2*
Adult mortality (%)	0	0
Total number of offspring released by survived *Daphnia*	67	59
Inhibition rate (%)	-	11.1

NOEC 10.2 mg/L

Remarks - Results All validity criteria for the test were satisfied. The test solutions were renewed every 24 h during the 21 d test period. The measured concentration of the test solution was 10.2 mg/L of the notified chemical. The 21 d NOEC was determined to be 10.2 mg/L, based on measured concentrations.

CONCLUSION Under the study conditions, the notified chemical is not harmful to daphnids on a chronic basis.

TEST FACILITY MEP (2014e)

C.2.6. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test

Species *Pseudokirchneriella subcapitata* (green alga)

Exposure Period 72 hours

Concentration Range Nominal: 50-500 mg/L
Actual: 0.541-7.71 mg/L

Auxiliary Solvent None

Water Hardness Not reported

Analytical Monitoring GC-MS

Remarks - Method Following the range finding test (conducted at nominal concentrations of 50-500 mg/L of the notified chemical), the definitive test was conducted at nominal concentrations of 50, 89, 160, 280, and 500 mg/L of the notified chemical (15.5, 23.3, 47.8, 99.3, and 159 mg/L measured, respectively). No significant deviation in protocol.

RESULTS

Biomass		*Growth*	
E_bC50	*NOE_bC*	*E_rC50*	*NOE_rC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
Not determined	Not determined	> 23.7	6.92

Remarks - Results All validity criteria for the test were satisfied. The actual concentrations of the test substance were measured at 0, 24, 48, and 72 hours within the 72 h test period. The measured concentrations of the notified chemical at the start of the test were 15.5, 23.3, 47.8, 99.3, and 159 mg/L; at the end of the test the respective concentrations were 0.541, 1.15, 2.51, 3.91, and 7.71 mg/L. No significant effects on growth observed.

CONCLUSION Under the study conditions, the notified chemical is harmful to algae.

TEST FACILITY Mitsubishi (2011e)

C.2.7. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test – Carbon and Ammonium Oxidation
Inoculum	Aerated activated sludge from a synthetic sewage feed
Exposure Period	30 minutes
Concentration Range	Nominal: 10-1000 mg/L Actual: Not determined
Remarks – Method	The test was conducted at nominal concentrations of 10, 100, and 1000 mg/L of the notified chemical. No significant deviation in protocol.
RESULTS	
EC50	> 1000 mg/L at 30 minutes
NOEC	Not determined
Remarks – Results	All validity criteria for the test were satisfied. No significant effects were observed. Consequently, the EC50 could not be calculated and was determined to be > 1000 mg/L, the highest concentration in the study. The NOEC was determined to be 1000 mg/L.
CONCLUSION	Under the study conditions, the notified chemical is not inhibitory to microbial activity.
TEST FACILITY	MEP (2014f)

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