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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Fire Retardant in Foam Sealants

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 and Energy.

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANTS	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2070	Soudal Pty Ltd Wurth Australia Pty Ltd	Fire Retardant in Foam Sealants	No	≤ 1 tonne per annum	Component of fire retardant foam for construction

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 of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

The environmental hazard classification according to the Globally Harmonised System of 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*
Chronic Aquatic Toxicity Category 1	H410 – Very toxic to aquatic life with long lasting effects

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

There could be uncertainties regarding the potential long-term effects of the notified chemical, based on the characteristics of other brominated flame retardants (BFR). The notified chemical is not expected to be bioaccumulative, but is expected to be persistent in the environment, which could lead to secondary human exposure to the chemical or its degradants. The proposed pattern of use in Australia is not expected to lead to high build-up of indoor dust containing the notified chemical. Therefore secondary exposure and consequent risk to the public are expected to be low.

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 the reported 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 isolation and engineering controls to minimise occupational exposure to the notified chemical in the final products:
  - Use in a well ventilated area.

- 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 in the final products:

- Avoid skin and eye contact
- Clean up spills and waste material promptly
- Avoid inhaling dust when sanding applied surfaces

- 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 in the final products:
  - Protective clothing, including gloves
  - Respiratory protection if dust is generated

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

- A copy of the 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 of 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.

Disposal

- Where reuse or recycling is not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by physical containment, collection and subsequent safe disposal.

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 importation volume exceeds one tonne per annum notified chemical.
  - The notified chemical is imported other than as a component of ready-to-use fire retardant foam at a concentration < 5%.
  - Additional information has become available on reproductive or developmental toxicity of the chemical.
  - If studies become available indicating levels of the notified chemical have been detected in any environmental compartment (including water, air, soil or biota) above any relevant Australian guideline values, including those from the Australian and New Zealand Environment and Conservation Council (ANZECC) or the National Environment Protection Council (NEPC).

or

(2) Under Section 64(2) of the Act; if
  - The function or use of the chemical has changed from component of fire retardant foam for construction or is likely to change significantly.

- The amount of chemical being introduced has increased, or is likely to increase, significantly.
- The chemical has begun to be manufactured in Australia.
- Additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

Safety Data Sheet

The safety data sheet of a product containing the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Soudal Pty Ltd (ABN: 50 159 124 053)
1 Tollis Place
SEVEN HILLS NSW 2147

Wurth Australia Pty Ltd (ABN: 48 002 487 096)
2/1 Healey Road
DANDENONG SOUTH VIC 3175

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year)

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, use details, manufacture/import volume, site of manufacture/reformulation and identity of manufacturer/recipients.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
EU REACH

2. IDENTITY OF CHEMICAL

MARKETING NAMES
The products containing the notified chemical will be marketed as:

- Soudafoam FR
- Wurth Fire Resistant Foam

MOLECULAR WEIGHT
500–1000 g/mol

ANALYTICAL DATA
Reference NMR, FTIR, GC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	-27 °C (Pour point)	Measured
Boiling Point	> 300 °C at 101.3 kPa	Measured
Density	1.541 kg/m^3 at 20 °C	Measured
Dynamic Viscosity	2036 mPa.s at 20 °C	Measured

Property	Value	Data Source/Justification
Vapour Pressure	0.4 kPa at 20 °C 1.2 kPa at 50 °C 1.2 kPa at 55 °C	Measured
Water Solubility	7.94 x 10^{-4} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{1/2}$ = 30.29 h at pH 4, 50°C $t_{1/2}$ = 44.08 h at pH 7, 50°C $t_{1/2}$ = 77.52 h at pH 9, 50°C	Measured
Partition Coefficient (n-octanol/water)	log P_{ow} = 10.2	Measured
Adsorption/Desorption	log K_{oc} = 7.3	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities.
Flash Point	207 °C at 101.3 kPa	Measured
Autoignition Temperature	370°C	Measured
Explosive Properties	Not expected to be explosive	The notified chemical contains no chemical moiety suggesting explosive properties.
Oxidising Properties	Not expected to have oxidising properties.	The notified chemical contains no chemical moiety suggesting oxidising properties.

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

Vapour pressure
The results from vapour pressure determination are expected to contain large margin of errors for values below 1 kPa, according to the study authors. Considering the high molecular weight of the chemical and the boiling point above 300°C, the chemical is expected to have a low vapour pressure.

Reactivity
The notified chemical is expected to be stable under normal conditions of use.

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 of 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 as a component of fire retardant polyurethane foam, packed and imported in aerosol cans. The notified chemical will not be manufactured or formulated in Australia.

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

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

PORT OF ENTRY
Sydney

TRANSPORTATION, PACKAGING AND STORAGE
The notified chemical will be transported in 750 mL aerosol cans. The polyurethane foam cans containing the notified chemical will be stored upright in dry and cool conditions (5–25 ºC).

USE
The notified chemical is a component of fire retardant products used in construction. It will be imported and marketed at a concentration < 5% in polyurethane foam, packed in aerosol cans, respectively:

- Soudafoam FR;

- Soudafoam FR Gun; and
- Wurth Fire-Resistant Foam.

These products will be predominantly sold to professional users, namely professional construction workers. Their use ensures passive fire protection in buildings. The polyurethane foam is dispensed into joints and cavities when installing door and window frames, creating a fire retardant effect. The products may have limited availability to the public for DIY use.

OPERATION DESCRIPTION

The notified chemical will not be manufactured, repackaged or reformulated in Australia. At the construction sites, the polyurethane foam containing the notified chemical is extruded from the can as a froth into a joint or cavity. Application can be done by using "gun foam" (for large quantities) or "straw foam" (for small quantities). When dispensed, the foam expands to fill the joint or cavity (1L of product can produce up to 40L of foam) and cures in contact with moisture. Excess cured foam can be easily removed by cutting the foam with a sharp knife. Uncured foam can be removed with a special cleaning product before it hardens. The concentration of the notified chemical in the cured foam is expected to be slightly higher than in the aerosol can, as the propellants in the aerosol can disappear once the foam is dispensed. However, it will remain part of the polyurethane mixture at < 5%. Once cured, the polyurethane foam is expected to be covered with plaster or other construction material such as a doorframe.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Professional building workers	Up to 8	Up to 365

EXPOSURE DETAILS

Transport and warehouse employees

No details are available on transportation and warehouse employees, but contact with the notified chemical for these workers is unlikely, except in the case of accidental rupture of the aerosol cans.

Professional workers

Incidental dermal and ocular exposure to the foam containing the notified chemical may occur when workers apply the polyurethane foam. The notified chemical is not considered to be volatile, and therefore is not expected to be released from the foam. Aerosols are not expected to be generated during the application process as the foam is a froth rather than spray. Therefore inhalation exposure is not expected during these processes. Workers are expected to wear protective equipment including gloves and glasses, based on other hazardous components of the foam. The foam is intended to be used indoors, but outdoor use is not excluded.

Workers may have dermal contact with the cured polyurethane matrix containing the notified chemical, for example while covering the matrix with plaster. However the notified chemical is expected to be incorporated in the matrix and not available for exposure.

6.1.2. Public Exposure

Direct exposure

Although the notified chemical is used in products sold primarily to professional users in the construction sector, there is a possibility that it may be accessed and used by DIY users. The notified chemical is not expected to be released from the foam while using it, however incidental dermal and ocular exposure may occur.

It is also possible that the general public may have direct contact with the cured material, but the foam is expected to be covered by other layers. Direct exposure of the public from the proposed use of the notified chemical is therefore expected to be very low.

Indirect exposure
Dust ingestion is considered to be a major route of human exposure to the class of flame retardants the notified chemical belongs to (confidential, 2016a; confidential, 2017a; confidential, 2018; NICNAS, 2012). The notified chemical could be released into the general environment from its industrial use and disposal, leaching and emissions from landfill and from end-of-life scenarios in buildings. The distribution of the notified chemical into the different environmental compartments (air, water, soil and sediment) is described in Section 7.

The notified chemical has been identified among other flame retardants in samples of indoor dusts from Australian homes, coming from homes, offices and cars or vehicles (confidential, 2018). Compared with other flame retardants, the notified chemical was detected at very low levels only. However, the study indicates that there is a possibility of public exposure to the notified chemical, from the use of formulations or finished articles containing the chemical. In the USA, the notified chemical was detected in air samples collected in public buildings containing polyurethane foams (confidential, 2017a).

The potential for exposure via ingestion could be greater for toddlers and young children, as a result of behavioural patterns during childhood (mouthing of objects or hands contaminated with dust). In Canada, the notified chemical was also detected in breast milk of nursing women. About a third of the samples tested contained the chemical, at very low concentrations (confidential, 2014).

Based on the available information, it is therefore not excluded that the notified chemical may be released from the foam over time and found in indoor dust, being potentially available for ingestion and/or inhalation.

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 oral toxicity	LD50 > 5000 mg/kg bw. Low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw. Low toxicity
Rabbit, skin irritation	Slightly irritating
Rabbit, eye irritation	Slightly irritating
Guinea pig, skin sensitisation – non-adjuvant test.	Not sensitising
Rat, repeat dose oral toxicity – 28 days	NOAEL = 2210/2450 mg/kg bw/day for M/F
Rat, repeat dose oral toxicity – 90 days	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	Non mutagenic
Mutagenicity – bacterial reverse mutation	Non mutagenic
Genotoxicity – *in vitro* mammalian gene mutation assay	Non genotoxic
Genotoxicity – *in vitro* mammalian chromosomal aberration test	Weakly genotoxic
Genotoxicity – *in vivo* micronucleus test	Negative
Rat, developmental toxicity (GD 5–19)	NOEL = 1000 mg/kg bw/day for maternal toxicity NOAEL* = 1000 mg/kg bw/day for developmental toxicity

*determined by the study authors (see B.13 Appendix B)

Toxicokinetics, metabolism and distribution
No toxicokinetic data were submitted for the notified chemical, but there is information available from literature showing that the notified chemical is expected to have limited absorption via oral and dermal routes.

The notified chemical with radioactive labelling was poorly absorbed following oral administration in rats and mice (confidential, 2017b). Most (> 90%) of a single dose administered to rats and mice was excreted unchanged in the faeces within 72 hours, and less than 1% excreted in the urine. About 1% of the oral dose was detected in tissues within 72 hours. Similarly, repeated oral administration of the notified chemical to rats showed that most of the dose was recovered in the faeces; however increased levels of radioactivity were retained in tissues such as the liver and adrenals after repeated dosing.

When the notified chemical was made systemically available by intravenous (i.v.) administration to rats in the same study, the radioactivity was slowly eliminated in the faeces as a mixture of parent and metabolite(s). Up to 78% of the dose was recovered in the faeces within 72 hours. Biliary excretion was identified as a method of

excretion. Approximately 20% of the radioactivity of the i.v. dose was detected in tissues within 24 hours, with the highest levels in liver, muscle, skin and fat.

Based on a study in *ex-vivo* human skin models, the notified chemical is expected to have poor percutaneous absorption, with only 0.04% of the dose detected in the receptor fluid. Significant amounts were found in the viable epidermis (9.5%) and dermis (0.5%). The results were considered to be the result of high lipophilicity (confidential, 2016b). In a separate study using rat and human skin *in vitro* and rat skin *in vivo*, the systemic exposure for humans was estimated to be < 1% of the dose when applied at 100 nmol/cm^2 in toluene (confidential, 2016c).

Acute toxicity
The notified chemical has low acute oral and dermal toxicity based on the results of studies on rats. Information on acute inhalation toxicity is not available.

Irritation and sensitisation
The notified chemical was slightly irritating to skin and eyes in studies on rabbits. The notified chemical showed no sensitising properties in a delayed contact hypersensitivity test (Buehler) in guinea pigs.

Repeated dose toxicity
In a repeated dose oral toxicity study similar to OECD TG 407, groups of CD rats (n = 10/sex/dose) were given the notified chemical in the diet at concentrations of 200, 2000 or 20000 ppm for 28 days. At mid dose, one male rat died during the study. No other mortality was observed. The notified chemical did not have similar effects to those of the positive control used in the study. There was no clear evidence of toxicity at concentrations up to the highest dose of 2210 mg/kg bw/day and 2450 mg/kg bw/day in males and females respectively. These concentrations are therefore considered to be the NOAELs. A lower NOAEL (2000 ppm) was cited in other international assessments, based on the body weight and clinical chemistry changes in females at the highest dose (confidential, 2015).

In a subchronic oral toxicity study following OECD TG 408, groups of Wistar rats (n = 10/sex/dose) were given the notified chemical by gavage at doses of 0, 100, 300 or 1000 mg/kg bw/day for 90 days. No mortalities were observed throughout the study. No clinical signs were observed. Some statistically significant haematological and clinical chemistry variations were observed in mid and high dose groups, compared with controls. A statistically significant decrease in the absolute and relative heart weight in all treated male rats compared with controls was reported to be attributed to high control values in the study. There were no clear adverse effects reported up to the highest dose tested. The no observed adverse effect level (NOAEL) is considered to be 1000 mg/kg bw/day.

Mutagenicity/Genotoxicity
Results were negative in two bacterial gene mutation assays using *Salmonella typhimurium* strains. Weakly positive results were observed in an *in vitro* chromosomal aberration test. Negative results were reported in an *in vitro* mammalian cell gene mutation test; however the results were incomplete because of the poor solubility of the test substance at the concentrations tested. Negative results were reported in an *in vivo* micronucleus test with intraperitoneal and dermal doses up to 2000 mg/kg bw. However in the absence of toxicity in the bone marrow and as no clinical signs indicated systemic exposure, it was not demonstrated that the notified chemical reached the bone marrow. Therefore, potential for genotoxicity cannot be excluded.

Toxicity for reproduction
In a prenatal developmental toxicity study following OECD TG 414, the notified chemical was orally administered to pregnant female Sprague Dawley rats (n = 24/dose) at doses of 0, 250, 500 or 1000 mg/kg bw/day during gestation days (GD) 5–19. No maternal toxicity effects were observed up to the highest dose tested. A number of visceral abnormalities were observed in half of the foetuses, affecting mostly stomach tissue, ureter and thymus, but none of the observations was statistically significant. A number of skeletal abnormalities were observed in the other half, but only an increase in unossified areas in frontal and occipital regions at the highest dose was statistically significant and considered to be treatment-related by the study authors. A NOAEL of 1000 mg/kg bw/day was determined in the study for developmental toxicity.

Some variations in foetal skeletal findings were reported from 250 mg/kg bw/day, but most of these were within the historical control ranges for the rat species provided in the study and only a few variations were statistically significant, but with no dose response. At 500 and 250 mg/kg bw/day, there was a statistically significant decreased incidence of incomplete ossification of sacral arch in 9/157 (5.5%) and 11/156 (7.1%) of foetuses

respectively, when compared with 27/149 (17.6%) in controls. As the group mean values were within the historical control data and a decreased incidence was not observed at the highest dose, this observation was considered incidental by the study authors. Although evaluation of skeletal effects is a standard part of a developmental toxicity study, development of the skeleton normally does not complete until well after birth in laboratory species and in humans. Based on published developmental toxicity studies ossification delay is indicated to be a transient finding and not an indication of disrupted development (DeSesso and Scialli, 2018).

Other studies
An expected metabolite of the notified chemical elicited maternal thyrotoxic and hepatotoxic effects in pregnant rats given 500 mg/kg bw orally, and histopathological effects in foetal testes but did not reduce testosterone production up to 500 mg/kg bw (confidential, 2012).

Some *in vitro* testing on the notified chemical has indicated potential for endocrine disruption (confidential, 2013). This study draws attention to a structural analogue of the chemical which has endocrine disruptive properties and developmental and reproductive toxicity.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation
The notified chemical is a brominated flame retardant. The available toxicological information indicates that the notified chemical is not acutely toxic, is slightly irritating to the skin and eyes and is not sensitising to the skin. No clear indications of genotoxicity were seen. Clear evidence of adverse effects was not seen in 28-day and 90-day studies via the oral route. Animal data suggest that the notified chemical is poorly absorbed via the oral and dermal routes.

A developmental toxicity study in rats with doses up to 1000 mg/kg bw/day (Envigo, 2017b) reported no maternal toxicity effects. Some variations in foetal skeletal findings were reported from 250 mg/kg bw/day (lowest dose tested), but most of these were within the historical control ranges for the rat species (according to the data provided by the notifier) and only a few variations were statistically significant, but showed no dose response.

Some *in vitro* investigations on the chemical indicated it to have endocrine disrupting potential (confidential, 2013). If new reproductive or developmental toxicity data or any relevant information on endocrine disrupting potential of this chemical leading to adverse effects becomes available, a further risk assessment may be required.

6.3.1. Occupational Health and Safety
Before it is cured into a matrix, incidental dermal and ocular exposure to the product containing the notified chemical at a concentration < 5% may occur, during application. Dermal contact may also occur with the cured polyurethane matrix containing the notified chemical, for example while applying coatings to the matrix. The notified chemical is expected to be incorporated in the matrix and not directly available for exposure.

Should dermal or ocular contact occur, the workplace controls for the foam as stated in the SDS are considered adequate to minimise exposure. These include personal protective equipment (PPE), precautions for safe handling and recommendations specific to some of the other hazardous ingredients contained in the foam.

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

This risk assessment does not cover the exposure of workers to the notified chemical during end-of-life cycle activities, such as removal and disposal of material from building renovation or demolition.

6.3.2. Public Health
The notified chemical is mainly intended for industrial and professional use. Public DIY use is not excluded, but is expected to be infrequent. The notified chemical is not expected to be released from the foam while using it, however incidental dermal and ocular exposure may occur. The general public may have dermal exposure to the cured polyurethane matrix containing the notified chemical; however this is unlikely because the matrix is

expected to be covered by other layers, as part of the construction process. Overall, direct public exposure to the notified chemical from its proposed use is expected to be very low.

Indirect exposure of the public to the notified chemical may occur through the outdoor and indoor environment. A very small amount of the notified chemical contained in dusts is expected to end up in soil from long-term degradation of construction materials from buildings, and may lead to public exposure through inhalation or ingestion. Based on outdoor human exposure estimates of up to 4.8 ng/kg bw/day for another brominated flame retardant, hexabromocyclododecane (NICNAS, 2012), which is used widely in various articles, exposure to this chemical in outdoor dust is expected to be very low. Based on the available literature, the notified chemical can be found in indoor dusts (e.g. from household appliances containing the chemical). However the proposed pattern of use is not expected to generate significant amounts of indoor dust.

Based on the available hazard data indicating no health concerns, and on the likely low public exposure from the proposed use pattern, the notified chemical is not considered to pose an unreasonable risk to public health.

7. ENVIRONMENTAL IMPLICATIONS

The notified chemical is a member of a class of chemicals known as brominated flame retardants (BFRs). This class of chemicals has come under increased international attention because of the potential of these chemicals to cause adverse effects to the environment and human health. The notified chemical is a replacement BFR for PBDE (polybrominated diphenyl ether). The PBDE class of chemicals are of particular concern because they are persistent in the environment and have high potential for bioaccumulation and chronic toxicity and as such, some PBDEs have been classified as Persistent Organic Pollutants (POPs).

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of end-use foam sealants for construction. Accidental spills of the products containing the notified chemical during import, transport or storage will only occur if the packaging is breached. Spillages are expected to be adsorbed onto suitable materials and collected for disposal, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

At construction sites, the foam containing the notified chemical will be extruded from the can into a joint or cavity. The foam expands considerably when dispensed and after it is dispensed, it cures in contact with moisture from the environment to form a solid matrix containing the notified chemical. Once the polyurethane matrix has been formed in the joint, it is expected to be covered with plaster or other construction materials. Excess cured foam can be easily removed by cutting the foam with a sharp knife. Uncured foam can be removed with a special cleaning product before it hardens. These wastes containing the notified chemical are expected to be disposed of, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM DISPOSAL

The notified chemical is expected to share the fate of the construction material to which it has been applied, to be disposed of to landfill at the end of its useful life. Any release of the notified chemical from disposal is expected to be in the form of dust from the solid matrix, containing the notified chemical. Empty containers containing the notified chemical are expected to be disposed of in accordance with local government regulations.

7.1.2. Environmental Fate

Environmental fate studies conducted on the notified chemical show that it is not inherently biodegradable and not bioaccumulative through ingestion in rainbow trout. For the details of the environmental fate studies refer to Appendix C.

Most of the notified chemical will share the fate of the construction material to which it has been applied, and therefore will be disposed of to landfill at the end of its useful life. In landfill, the notified chemical will be present as cured solids and will be neither bioavailable nor mobile. Low water solubility (7.94×10^{-4} g/L), high partition coefficient (log P_{ow}= 10.2) and high adsorption coefficient (log K_{oc} = 7.3) indicate the notified chemical will be immobile in soil. The notified chemical is expected to undergo slow degradation by biotic and abiotic processes and has the potential to degrade to other BFRs. Eventually it is expected to form water and oxides of carbon and simpler compounds of bromine.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has not been calculated as release of the notified chemical to the aquatic environment will be limited based on its reported use pattern.

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*
Acute fish toxicity	96 h EL50 > 1,000 mg/L (nominal concentration)*	Not harmful to fish up to its water solubility limit
Acute daphnia toxicity Study 1[a]	48 h EL50 > 10 mg WAF**/L (nominal concentration)	Not harmful to aquatic invertebrates up to its water solubility limit
Acute daphnia toxicity Study 2	48 h EC50 = 0.27 mg/L (measured concentration)***	Very toxic to aquatic invertebrates
Acute algal toxicity	72 h EL50 > 100 mg WAF**/L (nominal concentration)	Not harmful to algae up to its water solubility limit

* Ethanol was used as a co-solvent in preparation of the test solution; ** WAF: Water Accommodated Fraction; *** Acetone was used as a co-solvent in preparation of the test solution;

[a] Not included in Appendix. Accessed from REACH dossier (REACH, 2019)

As stated in the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* for acute and chronic toxicities, where more than one acceptable test is available for the same taxonomic group, the most sensitive endpoint is generally used for classification. Based on the 48 h Daphnia EC50 = 0.27 mg/L, the notified chemical is formally classified as "Acute Category 1; Very toxic to aquatic life" under the GHS. Based on the acute toxicity and lack of ready biodegradation, the notified chemical is formally classified as "Chronic Category 1; Very toxic to aquatic life with long lasting effects" under the GHS (United Nations, 2009). None of the potential degradants of the notified chemical are known to have an adverse impact upon the environment, but investigations are ongoing (see Section 8).

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated based on the most sensitive endpoint for *Daphnia* as shown in the table below. An assessment factor of 100 was used given the acute endpoint for three trophic levels are available.

48 h EC50 for *Daphnia*	0.27	mg/L
Assessment Factor	100	
Mitigation Factor	1	
PNEC	2.7	µg/L

7.3. Environmental Risk Assessment

The notified chemical does not display the characteristics of a Persistent Organic Pollutant (POP), as is it not bioaccumulative. None of its degradants are known to have an adverse impact upon the environment, but investigations are ongoing (see Section 8). A Risk Quotient (PEC/PNEC) has not been calculated as release of the notified chemical to the aquatic environment will be limited, based on its reported use pattern. Therefore, based on the current understanding of the notified chemical and its degradants and the use as a component of foam sealants for construction, the notified chemical is not considered to pose an unreasonable risk to the environment.

8. OVERSEAS INVESTIGATIONS

The group of chemicals to which the notified chemical belongs has been the subject of work in Canada and the United States. A member of the group is currently listed on the EU CoRAP (Community Rolling Action Plan) for evaluation, due to suspected concerns on potential endocrine disruption, suspected PBT/vPvB characteristics, wide dispersive use and environmental exposure.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point -27 °C

Method	DIN ISO 3016
Remarks	Pour point. Study summary only provided.
Test Facility	Bayer (2012)

Boiling Point > 300 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.2 Boiling Temperature ATSM E537
Remarks	Differential Scanning Calorimetry. Study summary only provided
Test Facility	Bayer (2012)

Density Relative density 1.541 at 20 °C

Method	EC Council Regulation No 440/2008 A.3 Relative Density DIN ISO 1183
Remarks	U-tube method. Study summary only provided
Test Facility	Bayer (2012)

Viscosity 2036 mPa.s at 20 °C

Method	OECD TG 114 Viscosity of Liquids
Remarks	Dynamic viscosity. Study summary only provided
Test Facility	Bayer (2012)

Vapour Pressure 0.4 kPa at 20 °C
1.2 kPa at 50 °C
1.2 kPa at 55 °C

Method	EC Council Regulation No 440/2008 A.4 Vapour Pressure
Remarks	Statical method, stated to have large errors below 1 kPa. Study summary only provided
Test Facility	Bayer (2012)

Water Solubility 7.94×10^{-4} g/L at 20 °C

Method	OECD TG 105 Water Solubility EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks	Flask Method (preliminary water solubility test of the notified chemical with 1% acetonitrile as organic solubiliser in hydrolysis test)
Test Facility	Currenta (2013a)

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)*	*$t_{½}$ (hours)*
4	50	30.39
7	50	44.08
9	50	77.52

Remarks	The corresponding acid of the notified chemical is detected as a hydrolysis product.
Test Facility	Currenta (2013a)

Partition Coefficient (n-octanol/water) $\log P_{ow} = 10.2$

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method, the result was extrapolated.
Test Facility	Currenta (2013b)

Adsorption/Desorption log K_{oc} = 7.3

Method	OECD TG 121 Adsorption Coefficient Using HPLC Method
Remarks	The result was extrapolated.
Test Facility	Currenta (2013c)

Flash Point 207 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point
Remarks	Closed cup method. Study summary only provided
Test Facility	Bayer (2012)

Autoignition Temperature 370 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases) DIN 51794
Remarks	Study summary only provided
Test Facility	Bayer (2012)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical

METHOD OECD TG 401 Acute Oral Toxicity (1981)
Species/Strain Rat/Charles River
Vehicle corn oil
Remarks - Method Limit test (single dose)

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5 M, 5 F	5000	0/10

LD50 > 5000 mg/kg bw
Signs of Toxicity No signs of toxicity were observed.
Effects in Organs No test-item related effects were reported. A single incidence of dark areas on the thymus, and fluid distension in the uterus of another animal were considered incidental effects.
Remarks - Results No animal died during the study.

CONCLUSION The notified chemical is of low acute toxicity via the oral route.

TEST FACILITY Life Science Research (LSR) (1987a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical

METHOD OECD TG 402 Acute Dermal Toxicity (1981)
Species/Strain Rabbit/New Zealand White
Vehicle N/A
Type of dressing Occlusive
Remarks - Method Limit test (single dose)

RESULTS

Group	*Number and Sex of Animals*	*Dose (mL/kg bw)*	*Mortality*
1	5 M, 5 F	2	0/10

LD50 > 2000 mg/kg bw
Signs of Toxicity - Local No signs of dermal reaction were observed.
Signs of Toxicity - Systemic No significant signs of systemic toxicity were observed.
Effects in Organs Necropsy did not reveal any abnormality considered to be related to treatment.
Remarks - Results No animal died during the study.

CONCLUSION The notified chemical has low acute dermal toxicity.

TEST FACILITY LSR (1987b)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 (1981) Acute Dermal Irritation/Corrosion
Species/Strain Rabbit/New Zealand White
Number of Animals 3 M, 3F

Vehicle	N/A
Observation Period	72 hours post-exposure
Type of Dressing	Semi-occlusive
Remarks - Method	GLP study A single dose of 0.5 mL of the test chemical was applied to the clipped skin of six rabbits under semi-occlusive conditions for 4 hours. Reactions were recorded 1, 24, 48 and 72 hours following exposure.

RESULTS

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Erythema/Eschar	0	0.25	0	0	1	0.25	1	< 48 hours	0
Oedema	0	0	0	0	0	0	0	N/A	0

* Calculated on the basis of the scores at 1, 24, 48, and 72 hours for EACH animals

Remarks - Results	Two animals showed slight erythema (score: 1) 1 hour post-exposure, reversible within 24 hours. A third rabbit also had slight erythema (score: 1) 1 hour post-exposure, still visible within 24 hours but reversible within 48 hours. No other effects were seen.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	LSR (1987c)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 (1981) Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	2 F, 4 M
Observation Period	72 hours post-exposure
Remarks - Method	N/A

RESULTS

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Conjunctiva: redness	1	0.25	0.25	0.25	0.25	0.25	2	< 24 hours	0
Conjunctiva: chemosis	0	0	0	0	0	0	0	N/A	0
Conjunctiva: discharge	1	0.25	0.25	0	0.25	0	2	< 24 hours	0
Corneal opacity	0	0	0	0	0	0	0	N/A	0
Iridial inflammation	0	0	0	0	0	0	0	N/A	0

* Calculated on the basis of the scores at 1, 24, 48, and 72 hours for EACH animals

Remarks - Results	All animals showed some redness of the treated eye, and four rabbits also had discharge, 1 hour following exposure. These effects had resolved within 24 hours. All reactions were graded 1, except for one rabbit showing redness and discharge scores of 2.

Two rabbits had a response to pain rated 1 'Practically no initial pain', the other rabbits had no observable response to pain.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY LSR (1987d)

B.5. Skin sensitisation – Modified Buehler test method

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation – Modified Buehler test method

Species/Strain Guinea pig/Dunkin-Hartley

PRELIMINARY STUDY Maximum Non-irritating Concentration: 100%
Intradermal: N/A
Topical: The test substance was applied under occlusive dressing at a concentration of 10, 30, 50 and 100% on the skin of 4 guinea pigs (sex not provided) for 6 hours.

The undiluted test material (100%) was chosen for induction and challenge.

MAIN STUDY

Number of Animals Test Group: 10 M, 10 F Control Group: 5 M, 5 F

Vehicle Paraffin oil

Positive control Dinitrochlorobenzene 0.1% (w/v)

INDUCTION PHASE Induction Concentration: 100%
Intradermal: N/A
Topical: Each animal was exposed to undiluted test substance under occlusive patch for 6 hours, on days 1, 8 and 15 of the main study. Control group was not treated during induction but received the same treatment as treated animals for challenge phase.

Signs of Irritation No irritation was seen.

CHALLENGE PHASE

1st challenge Topical: On day 29 of the main study, the test and control animals were exposed to undiluted test substance under occlusive patch for 6 hours. On the day following exposure, each animal was examined for erythema and swelling of the treated area.

2nd challenge Topical: N/A

Remarks - Method N/A

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	100 %	0/20	0/20	N/A	N/A
Control Group	100 %	0/10	0/10	N/A	N/A

Remarks - Results After challenge, a very faint erythema was observed in one animal of the control group at the 48 hour examination. No dermal reactions were observed in treated guinea pigs.

The animals challenged with the positive control dinitrochlorobenzene showed faint confluent erythema (grade 1) in 8/9 surviving animals, confirming the validity of the test system.

CONCLUSION There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY LSR (1987e)

B.6. Repeat dose toxicity (oral) 28 day

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (1981)
Species/Strain	Rat/CD (Sprague-Dawley)
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 28 days Dose regimen: *ad libitum* except overnight Post-exposure observation period: none (no satellite group)
Vehicle	N/A
Remarks - Method	No satellite group was used for recovery period of 14 days post-exposure. Urinalysis was carried out on the controls and high dose animals. The study used an extra group of rats (n = 5/sex), treated with a positive control substance at a concentration of 15000 ppm in the diet.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration (units)*		*Mortality*
		ppm	*mg/kg bw/day males/females*	
control	10 F, 10 M	0	0	0
low dose	10 F, 10 M	200	21 /23	0
mid dose	10 F, 10 M	2000	213 / 233	1/10 (M)
high dose	10 F, 10 M	20000	2210 / 2450	0
positive control	5 F, 5 M	15000	1370 / 1650	
control recovery	-	-	-	-
high dose recovery	-	-	-	-

Mortality and Time to Death

One male rat, from the mid dose group, died before the end of the study (during routine blood sampling).

Clinical Observations

No clinical signs of toxicity were observed in treated rats. Food consumption was slightly lower in female rats compared with controls during the first two weeks. High-dosed female rats had slightly lower body weight gain compared with controls.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical chemistry: Two changes were observed. Plasma phosphorus concentrations were significantly lower in low-dosed and mid-dosed female rats and high-dosed male and female rats, compared with control. A 'marginally low alanine-transferase' activity was observed in high-dosed female rats, significantly different from controls.

Haematology: Mean values of prothrombin time were significantly shorter in treated groups compared with control rats, but not at the individual level.
Urinalysis: Urinary composition was unaffected by treatment.

Effects in Organs

The treatment did not affect absolute or relative organ weights during the study.

A number of lesions were observed that were not considered to be treatment-related by the study authors:

- Cortical scar of the kidney and craniopharyngeal cyst of the pituitary gland in one high-dosed male
- Interstitial inflammation of the prostate in one high-dosed male
- Stomach *lamina propria* inflammation in one high-dosed male
- Phthisis bulbi of the eye in one low-dosed male rat and one mid-dosed female
- Physiological dilatation of the uterus in two low-dosed females
- Pigmented macrophages of popliteal lymph nodes in one mid-dosed male

Minor macroscopic changes were noted in the appearance of some tissues, including lungs, cervical lymph nodes, pancreas, but none of these changes was statistically significant compared with controls.

Remarks – Results
The oral dietary administration of the test substance caused some minor changes in treated rats. However none of these effects was considered adverse. Effects on the liver and testes were seen in the positive control group. A No Observed Adverse Effect Level was not assigned by the study author.

CONCLUSION
The chemical produced no evidence of toxicity up to the highest dose tested.

TEST FACILITY LSR (1988)

B.7. Repeat dose toxicity (oral) 90 days

TEST SUBSTANCE	Notified chemical 95.5%
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents
Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week
Vehicle	Arachis oil
Remarks - Method	No major deviations from study plan. No dose adjustment was made for purity.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
control	10 M, 10 F	0	0
low dose	10 M, 10 F	100	0
mid dose	10 M, 10 F	300	0
high dose	10 M, 10 F	1000	0

Mortality and Time to Death
No mortality occurred throughout the study.

Clinical Observations
No clinical signs of toxicity were observed up to the highest dose tested.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Clinical chemistry – Mean calcium values were statistically significantly higher for both sexes at 300 and 1000 mg/kg bw/day compared with controls. Creatinine levels were statistically significantly higher in high-dosed females compared with controls, and 2/10 had values outside the historical control range.

Urinalysis – not examined.

Haematology – Platelet values were statistically significantly higher for mid- and high-dosed males compared with controls. Mean corpuscular volume values were statistically significantly higher for all treated females compared with controls. There was a statistically significant increase in circulating neutrophils at high dose in both sexes, compared with controls.

Effects in Organs
Gross necropsy – Red discolouration of the lungs observed in 1/10 mid-dosed male, 3/10 mid-dosed females and 5/10 high-dosed females was considered to result from the test methodology. No other significant abnormalities were reported.

Organ weights – There was a statistically significant decrease in the absolute heart weight and relative heart

weight in all treated male rats compared with controls. As absolute and relative heart weight values of 6/10 control rats were outside the historical control range values, the statistical significance was considered to be related to the unusually high control values. No other variation in organ weights was observed.

Histopathology – A number of histopathological variations were observed in treated rats:

- Minimal to mild degeneration/inflammation of the oesophagus in 1/10 high-dosed male, also observed in 2/10 control males and 2/10 control females;
- Minimal to mild degeneration/inflammation of the heart in 3/10 high-dosed males and 1/10 high-dosed female, also observed in 2/10 control males and 1/10 control female;
- Renal changes in 2 males and 2 females at high dose, including moderate nephropathy, minimal to mild basophilia and minimal mineralisation of the corticomedullar junction (not observed in control rats);
- Hepatic changes in 2 males and 3 females at high dose, including mild periportal pigmentation and minimal inflammation and infiltration, also observed in 2/10 control males.

Remarks – Results

The study authors considered there were no significant treatment-related adverse effects due to the administration of the test substance.

CONCLUSION

The No Observed Effect Level (NOEL) was established as 1000 mg/kg bw/day by the study authors, based on the absence of adverse effects up to the highest dose.

TEST FACILITY Envigo, 2018

B.8. Genotoxicity – bacteria (2017)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test

Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2*uvrA*
Metabolic Activation System	Rat liver homogenate metabolizing system (10% liver S9 in standard co factors)
Concentration Range in Main Test	a) With metabolic activation: 0, 15, 50, 150, 500, 1500, 5000 µg/plate b) Without metabolic activation: 0, 15, 50, 150, 500, 1500, 5000 µg/plate
Vehicle	Acetone
Remarks - Method	Two experiments were conducted: • Experiment 1 – Plate incorporation method The chemical was tested at concentrations of 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate in triplicates against each tester strain, with and without metabolic activation. • Experiment 2 – Pre-incubation method Using the results of Experiment 1, the dose range for the second experiment was 15, 50, 150, 500, 1500 and 5000 µg/plate.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:* *Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5000	> 5000	≥ 5000	None
Test 2	> 5000	> 5000	≥ 5000	None
Test 3	> 5000	> 5000	≥ 5000	None
Present				
Test 1	> 5000	> 5000	≥ 5000	None
Test 2	> 5000	> 5000	≥ 5000	None
Test 3	> 5000	> 5000	≥ 5000	None

Remarks - Results Cytotoxicity was not observed in either experiment.

A precipitate was observed at 5000 µg/plate, which did not affect scoring. There were no increases in the frequency of revertant colonies for any of the bacterial strains, up to the highest concentration, with and without metabolic activation (S9-mix) in Experiments 1 and 2.

CONCLUSION The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY Envigo, 2017a

B.9. Genotoxicity – bacteria (1987)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test (1983)
Plate incorporation procedure
Species/Strain *Salmonella typhimurium*: TA1538, TA1535, TA1537, TA98, TA100
Metabolic Activation System Rat liver microsome preparation (S-9 mix) treated with Aroclor 1254
Concentration Range in Main Test a) With metabolic activation: 50–5000 µg/plate
b) Without metabolic activation: 50–5000 µg/plate
Vehicle Dimethyl sulfoxide (DMSO)
Remarks - Method A preliminary cytotoxicity test was conducted (2.5–5000 µg/plate) to determine the minimum level causing a visible thinning of the bacterial lawn. This level is used as top concentration in the main test.

In the main test, five concentrations of the test material (50–5000 µg/plate) were used in triplicates for each strain. Tests were conducted twice for each strain.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:* *Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5000	Not observed	> 5000	None
Test 2		Not observed	> 5000	None
Present				
Test 1	> 5000	Not observed	> 5000	None
Test 2		Not observed	> 5000	None

Remarks - Results There was no increase in the number of revertant colonies in any of the strains tested with the notified chemical, with or without metabolic activation. The positive controls showed the expected increases in revertant colonies, confirming the validity of the test system.

CONCLUSION The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY LSR (1987f)

B.10. Genotoxicity – *in vitro* (gene mutation assay)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 476 *In vitro* Mammalian Cell Gene Mutation Test (1997)
Species/Strain Chinese hamster
Cell Type/Cell Line V79 cells
Metabolic Activation System Mammalian liver microsome preparation (S9 mix) treated with phenobarbital/β-naphthoflavone

Vehicle: Acetone 0.5 %

Remarks - Method: The test substance at 0.05 mg/mL and 500 mg/mL in acetone was found to be homogeneous and stable at room temperature for at least 24 h.

A preliminary toxicity test was conducted to determine the concentrations used for the main experiment.

In the main study, six concentrations of the test item were used (3–486 µg/mL). Two independent experiments were conducted, each using duplicate cultures. In experiment I, cells were exposed to the test item for 4 hours, with and without metabolic activation. In experiment II, cells were exposed to the test item for 4 hours with or 24 hours without metabolic activation.

The concentrations that could be tested were limited by phase separation at 54 µg/mL and above. Cultures at the highest concentration of 486 µg/mL were not evaluated, to avoid use of too many insoluble concentrations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Experiment I	3, 9, 18, 54 [PS], 162 [PS], 486* [PS]	4 h	7 days post-treatment
Experiment II	3, 9, 18, 54 [PS], 162 [PS], 486* [PS]	24 h	7 days post-treatment
Present			
Experiment I	3, 9, 18, 54 [PS], 162 [PS], 486* [PS]	4 h	7 days post-treatment
Experiment II	3, 9, 18, 54 [PS], 162 [PS], 486* [PS]	4 h	7 days post-treatment

[PS] Phase separation

*Cultures at this concentration were removed from the analysis because of phase separation

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation/Phase separation*	*Genotoxic Effect*
Absent				
Experiment I	> 5800	> 486	≥ 54	Not observed
Experiment II	> 5800	> 486	≥ 54	Not observed
Present				
Experiment I	> 5800	> 486	≥ 54	Not observed
Experiment I	> 5800	> 486	≥ 54	Not observed

Remarks - Results

Preliminary test

No toxicity occurred up to the maximum concentration tested in the preliminary test, with or without metabolic activation. Phase separation was observed at the end of the test for all concentrations tested, indicating the poor solubility of the test item.
Concentrations chosen for the main study included a range of soluble and insoluble concentrations.

Main study

In experiments I and II, no reproducible increase in mutant colony numbers was observed up to the highest concentration analysed (162 µg/mL), with or without metabolic activation. Slight marginal increases (induction factor between 1.5–1.7 compared with the solvent control) were observed in some of the studies. They were not considered to meet the criteria for a positive response because they were less than the threefold increase threshold, were not dose dependant and/or were not seen in both cultures of the main study.

Test conditions may have been affected by the phase separation occurring at concentrations ≥ 54 µg/mL.

CONCLUSION	The notified chemical was not genotoxic to V79 Chinese hamster cells treated *in vitro* under the conditions of the test.
TEST FACILITY	Harlan CCR, 2013

B.11. Genotoxicity – *in vitro* (chromosome aberration assay)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 *In vitro* Mammalian Chromosomal Aberration Test (1983)
Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	Rat liver microsome preparation (S9 mix)
Vehicle	Dimethyl sulfoxide (DMSO)
Physical Form	Liquid
Remarks - Method	A preliminary test was conducted to assess the toxicity of the test item in order to choose concentrations for the main study. In the main study, cell cultures were exposed to the test item up to 1000 µg/mL, with or without metabolic activation. Initial exposure period was 2 hours in a shaking bath followed by 22 hours continuous exposure in static conditions. Cell division was stopped, using colcemid. Mitotic indexes were measured by examining 1000 cells per culture. Chromosome aberrations were measured by examining 100 metaphases per culture. Positive controls (Cyclophosphamide at 0.6 µg/mL and Chlorambucil at 0.1µg/mL) were used in the main test.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Preliminary test	0, 1.6, 8, 40, 200, 1000	24 h	24 h
Main test	0, 40, 200, 1000	24 h	24 h
Present			
Preliminary test	0, 1.6, 8, 40, 200, 1000	2 h	24 h
Main test	0, 40, 200, 1000	2 h	24 h

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Cytogenetic test	≥ 1000	> 1000	None observed	Weakly positive at 1000 µg/mL
Present				
Cytogenetic test	≥ 1000	> 1000	None observed	Weakly positive at 1000 µg/mL

Remarks - Results

Preliminary test

Mean mitotic activity was only slightly decreased at the highest concentration of the test item (7.3 compared with 8.5 in the control group). Therefore, 1000 µg/mL was chosen as the highest concentration for the main cytogenetic test.

Cytogenetic test

There was a slight increase in the number of cells with aberrations at all concentrations tested compared with the control group. While the mean incidence of aberrant cells (including gaps) was 1.3% in the control group (range 1–3%), it was 2.8% (range 2–4), 2% (range 0–3) and 4.2% (range 3–5) with increasing concentrations of the test item. The study authors considered that the increased incidence of 4.2% overall (4.3% and 4% with and without metabolic activation respectively) at the highest

concentration of 1000 µg/mL had a biological and statistical significance. The incidence of aberrant cells without gaps was also statistically significant at this concentration. Statistical significance was calculated on the pooled values of aberrations with and without gaps. The positive controls produced the expected high increases in cells with aberrations, confirming the validity of the test system.

CONCLUSION The notified chemical was weakly clastogenic to human lymphocytes treated *in vitro* under the conditions of the test.

TEST FACILITY LSR (1987g)

B.12. Genotoxicity – *in vivo* (micronucleus test)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test (1984)

Species/Strain Mice/CD-1
Route of Administration Dermal – non-occluded
Intraperitoneal
Vehicle Corn oil
Remarks - Method <u>Preliminary test</u>
Groups of mice (n = 2/sex/dose) were administered single intraperitoneal doses of the test item at 250, 500, 1000 or 2000 mg/kg bw and killed 72 hours post-treatment for examination.

<u>Main test – Intraperitoneal route</u>
Groups of mice (n = 5/sex/dose) were administered single intraperitoneal doses of the test item at 0, 80, 400 or 2000 mg/kg bw and killed 24 hours after treatment. In the control group and the high dose group, additional animals (n = 10/sex/dose) were used, and 5 animals of each group and sex were killed for examination 48 and 72 hours post-exposure.
A positive control (Chlorambucil) was orally administered to mice at 30 mg/kg bw.

<u>Main test – Dermal route</u>
Groups of mice (n = 10/sex/dose) were exposed to a daily dose of either corn oil or 2000 mg/kg bw of the test item on shaved skin, for 5 consecutive days. Examination was conducted 18 and 48 hours post the final treatment.

Intraperitoneal route	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	15 M, 15 F	0	24, 48, 72
II (low dose)	5 M, 5 F	80	24
III (mid dose)	5 M, 5 F	400	24
IV (high dose)	15 M, 15 F	2000	24, 48, 72
V (positive control)	5 M, 5 F	30	24

Dermal route	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	10 M, 10 F	0	18, 48
II (dosed group)	10 M, 10 F	2000	18, 48

RESULTS

Doses Producing Toxicity No mortality occurred before the scheduled terminations. No toxicity was observed during the study at any of the doses tested, as measured by the ratio of polychromatic and mature erythrocytes. Significant weight loss was not seen after dosing.
Genotoxic Effects There was no statistically significant increase of micronuclei in the erythrocytes of treated mice compared with controls.

Remarks - Results	In the preliminary test, slight piloerection was observed in all 4 animals at 1000 mg/kg bw and moderate piloerection in 2 male mice at 500 mg/kg bw. No clinical signs were noted in the main study.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this *in vivo* micronucleus test.
TEST FACILITY	LSR (1987h)

B.13. Developmental toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 414 Prenatal Developmental Toxicity Study
Species/Strain	Rat/Sprague-Dawley
Route of Administration	Oral – gavage
Exposure Information	Exposure days: gestation days (GD) 5–19
Vehicle	Arachis oil
Remarks - Method	The notified chemical was administered to groups of mated female rats during gestation days (GD) 5–19. All females were terminated on GD 20 and subjected to gross necropsy including examination of the uterine contents. The number of *corpora lutea*; number, position and type of implantation; placental weights; foetal weight; sex and external and internal macroscopic appearance were recorded. Half of each litter were examined for detailed skeletal development and the remaining half were subjected to detailed visceral examination. A minor deviation from the study plan was reported. Data for female No. 20 of the control group were discarded from analysis because of measurement errors.

RESULTS

Group	*Number of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	24 F	0	0
Low	24 F	250	0
Intermediate	24 F	500	0
High	24 F	1000	0

Mortality and Time to Death

No mortality was observed throughout the study.

Effects on Dams

No treatment-related effects were observed in treated female rats.

Apart from one female each from the control, 250 and 1000 mg/kg bw/day groups, all treated female rats were found to be pregnant. There was no resorption loss in any of the groups. No effects were observed for the number of implantations, number of early or late resorptions, live litter size, post-implantation loss or sex ratio in any of the treated groups. In all dose groups the mean total placental weight was higher compared with the controls, but statistically significant only at 250 mg/kg bw/day. Individual values of placental weight at 250 mg/kg bw/day were reported to be within the historical control value range for 22/23 female rats, therefore the results were considered as normal biological variations.

Effects on Foetuses

Foetal viability – Weights of foetuses were similar in each group. There was a higher percentage of small foetuses in the control group (1.2%) than in the test groups (0.3–0.6%). One foetus, also from the control group, had a haematoma on the back.

Visceral findings – There were no statistically significant visceral abnormalities at any doses tested. A number of notable variations were observed in 36/169 (21.6%), 35/168 (20.7%) and 32/163 (19.7%) of foetuses at low, mid and high doses respectively, compared with 26/161 (17%) in controls. These findings were not considered by the study authors to be treatment-related. The main findings included:

- Non-uniform patterning of the rugae (internal tissue of stomach or palate) in 8/169 (4.6%), 9/168 (4.6%) and 11/163 (6.9%) of foetuses at low, mid and high doses respectively, compared with 5/161 (3.1%) in controls.
- Kinked ureter in 17/169 (10.2%), 16/168 (9.8%) and 10/163 (6.1%) of foetuses at low, mid and high doses respectively, compared with 8/161 (5.4%) in controls.
- Partially undescended lobe of the thymus in 6/169 (3.4%), 8/168 (4.6%) and 8/163 (5.2%) of foetuses at low, mid and high doses respectively, compared with 5/161 (3.2%) in controls.

Skeletal findings – There were a few statistically significant skeletal abnormalities in foetuses:

- At 1000 mg/kg bw/day, a statistically significant increase in unossified areas in frontal and occipital regions was observed in 5% and 4.7% of the foetuses respectively, when compared with controls (0 and 0.7% respectively). Although there was no dose-response relationship in this increase, this result was above the historical control data and considered treatment-related.
- At 500 and 250 mg/kg bw/day, there was a statistically significant decreased incidence of incomplete ossification of sacral arch in 9/157 (5.5%) and 11/156 (7.1%) of foetuses respectively, when compared with 27/149 (17.6%) in controls. As the group mean values were within the historical control data and a decreased incidence was not observed at the highest dose, this observation was considered incidental.

A number of non-statistically significant skeletal variations were also observed:

- Incomplete ossification of interparietal region in 10, 10.5 and 10.3% of foetuses at low, mid and high doses respectively, compared with 5.8% in controls;
- Incomplete ossification of zygomatic process of maxilla in 6.3, 5 and 6.5% of foetuses at low, mid and high doses respectively, compared with 2% in controls;
- Incomplete ossification of hyoid in 10.1, 7.6 and 13.5% of foetuses at low, mid and high doses respectively, compared with 5.9% in controls;
- Ossification of ventral arch of vertebra 1 in 23.9, 14.7 and 21.9% of foetuses at low, mid and high doses respectively, compared with 13.7% in controls.

Overall, the skeletal findings were not considered by the study authors to represent adverse effects to the foetal development. For the ossification variations that were statistically significant, the study authors stated: "Although there were no dose-relationship, group mean values for these alterations were above the historical control data ranges and, as such their relation to treatment cannot be ignored."

Remarks - Results

One female from the control group had a uterus filled with colourless liquid and was not pregnant.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) for developmental toxicity was established by the study authors as 1000 mg/kg bw/day, based on the absence of significant adverse effect in dams and foetal development.

TEST FACILITY Envigo, 2017b

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Bioaccumulation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 305 Bioconcentration: Dietary Exposure
Species	Rainbow trout (*Oncorhynchus mykiss)*
Exposure Period	Exposure: 28 days Depuration: 28 days
Auxiliary Solvent	Diethylether
Concentration Range	Nominal: 1000 mg/kg Initial measured: 652 mg/kg
Analytical Monitoring	Liquid Chromatography – Tandem Mass Spectrometry (LC-MS/MS)
Remarks - Method	A limit test was run based on results of a preliminary test. The test substance was dissolved in diethylether. The solution was spread among feed particles through a spray application while mixing by rotation to ensure a homogenous distribution before letting the solvent evaporate. The spiked pellets were dispersed on the bottom of a stainless-steel container and left for at least 24 h in a fume hood before testing to ensure complete evaporation of the solvent. Fish for both control and treatment groups were sampled twice (days 14 and 28) during the uptake phase and five times (days 3, 7, 14, 21 and 28) during the depuration phase for chemical analysis.
RESULTS	
Biomagnification Factor (BMF)	0.038
LC50	> 1000 mg/kg (nominal concentration)
Remarks - Results	The OECD TG 305 set water temperature variation of ± 2°C. However, during the first 3 days and at day 7 of exposure, the temperature fell to 12.3°C and at day 39, the temperature rose to 19°C due to a technical problem. As both control and treatment vessels experienced the same temperature regime, this deviation was considered not to impact the validity of the test. During uptake, the test substance was detected in control fish. Means in controls were 37.3 µg/kg and 32.1 µg/kg on days 14 and 28, which corresponds to 0.936% and 0.374% of the mean concentration in the exposure groups. This was attributed to carryover effects from handling procedures as the aquaria were placed next to each other during experimentation. Nevertheless, this was not considered to affect the validity of the test since the stock control sample showed that fish were not pre-exposed or contaminated. Other validity criteria for the test were satisfied. Dissolved oxygen concentration was ≥ 87% during the test.
CONCLUSION	The test substance is not bioaccumulative through ingestion in rainbow trout.
TEST FACILITY	IME (2018)

C.1.2. Inherent biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 302C Inherent Biodegradability: Modified MITI Test (II)
Inoculum	40% activated sludge from each of two domestic STPs, and 20% activated sludge from an industrial STP
Exposure Period	28 days
Auxiliary Solvent	None

Analytical Monitoring	Biochemical Oxygen Demand (BOD) by OxiTop System
Remarks – Method	No major deviations from the test guidelines were reported. The test substance was added directly to the test vessels. A toxicity control was not run as results from the microbial activity inhibition test indicate the chosen test substance concentration in this test was not inhibitory to microorganisms.

RESULTS

Test Substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	1	1	26
14	7	14	63
28	7	28	61

Remarks – Results	All validity criteria for the test were satisfied. The degree of degradation of the test substance after 28 days was 7%.

CONCLUSION The test substance is not inherently biodegradable

TEST FACILITY Currenta (2012a)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 203 Fish, Acute Toxicity Test – Static
Species	Rainbow trout - *Salmo gairdneri*
Exposure Period	96 hours
Auxiliary Solvent	Ethanol
Water Hardness	198 – 208 mg $CaCO_3$/L
Analytical Monitoring	Yes
Remarks – Method	No major deviations from the test guidelines were reported. Test concentrations were selected based on preliminary test results. The test concentrations we/re prepared individually by adding ethanol (2 mL) to the appropriate weights of test material, and then adding these mixtures directly to the dilution water (20 L).

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*
Nominal	*Actual*		*96 h*
Pool Control	0	10	0
62.5	3.14	10	0
125	5.73	10	0
250	31.34	10	0
500	15.62	10	0
1,000	15.66	10	0

LL50	> 1,000 mg/L nominal concentration at 96 hours
Remarks – Results	All validity criteria for the test were satisfied. The dissolved oxygen concentration in the test solution during the test was ≥ 69%. Undissolved test material was observed at all test concentrations. Analytical results showed that the material was poorly soluble in water and not homogeneously dispersed in the test medium. Thus, the results were presented based on nominal concentrations.

CONCLUSION The test substance is not harmful to fish up to its water solubility limit.

TEST FACILITY LSR (1989a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 *Daphnia sp.* Acute Immobilisation Test and Reproduction Test – Static

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Acetone
Water Hardness	196 – 204 mg $CaCO_3$/L
Analytical Monitoring	HPLC-UV
Remarks - Method	No major deviations from the test guidelines were reported. Test concentrations were selected based on preliminary test results. A solution of the test material was prepared in acetone (10 mg/mL) and diluted to give an aqueous stock at 1 mg/L. Test solutions were prepared by further diluting this aqueous stock.

RESULTS

Concentration mg WAF/L		*Number of D. magna*	*Number Immobilised*
Nominal	*Initial Measured*		*48 h*
Pool Control	Pool Control	20	0
0.063	0.049	20	1
0.125	0.105	20	0
0.25	0.22	20	3
0.5	0.432	20	16
1	0.767	20	18

LC50	0.27 mg/L (95% CL of 0.23 – 0.32 mg/L) at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The dissolved oxygen concentration in the test solution during the test was ≥ 94%. The mean measured concentration of the test substance in samples taken at the start of the test ranged between 77 and 88% of nominal values; after 48 hours they ranged between 64 and 124% of nominal values.

CONCLUSION The test substance is very toxic to aquatic invertebrates.

TEST FACILITY LSR (1989b)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test
EC Council Regulation No 440/2008 C.3 Algal Inhibition Test

Species	*Desmodesmus subspicatus* (formerly *Scenedesmus subspicatus*)
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L Actual: < LOQ (0.0334 mg/L)
Auxiliary Solvent	None
Water Hardness	22.5 mg $CaCO_3$/L
Analytical Monitoring	Yes
Remarks - Method	A limit test was run with no major deviations from the test guidelines. The test concentration was prepared by adding the test material to dilution water (1 L) and ultrasonicated for 60 seconds, then stirring for 24 hours. Undissolved particles of the test item were removed by filtration (0.45 ± 0.2 µm) and the dissolved part or water accommodated fractions (WAFs)

were used for testing. The test water was sampled for analysis of test substance at 0 and 72 hours.

RESULTS

Biomass		*Growth*	
EbL50	*NOEL*	*ErL50*	*NOEL*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
> 100	≥ 100	> 100	≥ 100

Remarks - Results All the validity criteria for the test were satisfied. The mean cell density in the control increased more than 16 times by 72 h.

CONCLUSION The test substance is not harmful to algae up to its water solubility limit.

TEST FACILITY Currenta (2012b)

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