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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Flame Retardant in King Pearl F, GF and LR Series

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.

This Public Report is 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:

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX:	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

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/1651	Expanz International Pty Ltd	Flame Retardant in King Pearl F, GF and LR Series	No	≤ 200 tonnes per annum	Flame retardant additive for expanded polystyrene for use in construction and appliance packaging

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.

Human health risk assessment
Provided that the stated workplace controls are being adhered to, the notified chemical is not considered to pose an unreasonable risk to the health of workers under the conditions of the occupational settings described.

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

There are uncertainties regarding the hazards of the chemical. In addition the notified chemical is anticipated to be persistent in the environment. Due to environmental distribution and its persistence, the use of the notified chemical may lead to secondary human exposure to the chemical or its degradants via the environment. Because the chemical is not bioaccumulative and the proposed use pattern in Australia is not expected to lead to high build-up of indoor dust containing the notified chemical, the secondary exposure to the public and consequent risk is expected to be reduced.

Environmental risk assessment
On the basis of the low hazard of the notified chemical, the current understanding of the notified chemical's degradants and the assessed use pattern, the notified chemical is not expected 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 during the manufacturing of expanded polystyrene (EPS) and articles:
  - Local exhaust ventilation when any dust is likely to be generated
  - Enclosed, automated systems where 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 during the manufacturing of expanded polystyrene (EPS) and articles, and installation of articles at the construction sites:
  - Avoid eye and skin contact and inhalation exposure
  - Avoid generation of dusts
  - Clean up spills promptly

- 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 during the manufacturing of expanded polystyrene (EPS) and articles, and installation of articles at the construction sites:
  - Dust mask
  - A respirator during cutting operations if ventilation is insufficient

  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 are 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 notified chemical is imported other than as a component of solid expandable polystyrene beads at a concentration of ≤ 1.6%;
  - articles for construction containing the notified chemical are installed in building interiors, unless lined or covered;
  - the notified chemical is to be used as a component of consumer products, such as bean bags, furniture or automotive components;
  - the notified chemical is to be used in food contact applications;
  - additional toxicological information becomes available on the notified chemical, or TBBPA ether brominated flame retardants. In particular, studies on repeated dose toxicity (preferably with a term longer than 90 days) and genotoxicity, such as an *in vivo* comet assay (liver);
  - additional information has become available to the person as to an adverse effect of degradants of the notified chemical or of TBBPA ether brominated flame retardants on occupational health and safety, public health, or the environment.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a flame retardant additive in expanded polystyrene for use in construction and appliance packaging, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

Safety Data Sheet
The SDS of the 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)
Expanz International Pty Ltd (ABN: 39 357 503 744)
Suite 1 - Level 1, 213 Lower Heidelberg Rd
EAST IVANHOE VIC 3079

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: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, impurities, additives/adjuvants and import volume

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: melting point, density, vapour pressure, hydrolysis as a function of pH, flash point, flammability, autoignition temperature, explosive properties and oxidising properties

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
EU REACH

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Marketed products containing the notified chemical will include:
King Pearl F, GF and LR Series

MOLECULAR WEIGHT
UVCB. Value for the main component is < 1,000 g/mol

ANALYTICAL DATA
Reference NMR, IR and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
The notified chemical is a UVCB.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: white powder

Property	Value	Data Source/Justification
Melting Point/Freezing Point	110 °C	SDS
Boiling Point	Not determined	Decomposition occurs at approximately 260 °C
Density	2,200 kg/m^3 (temperature unknown)	SDS
Vapour Pressure	3.59×10^{-14} kPa at 25 °C	Calculated using Modified Grain Method
Water Solubility	$< 0.42 \times 10^{-6}$ g/L	Measured
Hydrolysis as a Function of pH	Not determined	Contains no functionalities hydrolysable in the environmentally relevant pH range (4-9).
Partition Coefficient	log Pow > 6.5	Measured

(n-octanol/water)		
Adsorption/Desorption	log Koc = 8.1	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities
Particle Size	0.220 - 88.48 µm Inhalable fraction (< 100 µm): 100% Respirable fraction (< 10 µm): 37.62 - 41.52%	Measured
Particle Size for the Imported Beads	0.7-1.4 mm	Information provided by the notifier
Flash Point	Not determined	Not volatile or flammable. Used as flame retardant.
Autoignition Temperature	Not determined	Not expected to autoignite
Explosive Properties	Not determined	Not expected to be explosive, based on the chemical structure
Oxidising Properties	Not determined	Not expected to be oxidising, based on the chemical structure

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.

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 as a component of solid expandable polystyrene beads (flame retardant grade) at a concentration of ≤ 1.6%, and will be dispersed throughout the polymer matrix.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	50-100	50-100	50-100	50-100	50-200

PORT OF ENTRY
Melbourne, Sydney, Brisbane, Adelaide, Perth, Townsville, Launceston

IDENTITY OF RECIPIENTS
Expanz International Pty Ltd

TRANSPORTATION AND PACKAGING
The beads containing the notified chemical at ≤ 1.6% will be imported in 750 - 850 kg bulk bags, prior to undergoing processing to expand the beads and form them into various articles. The transport of beads and articles is expected to be by road or rail in Australia.

USE
The notified chemical will be used as a flame retardant additive for expanded polystyrene (EPS). It will be mostly used in the construction industry. A small proportion (< 1% of the import volume) will be used in appliance packaging. Beanbag and automotive use is not expected. Food contact use will not occur.

The articles containing the notified chemical used for construction will not be placed in direct contact with the internal surfaces of buildings. They may be applied externally. Where they are present as insulation inside an external wall, they will be used within the cavity. Internally-facing surfaces will be lined. EPS typical applications in construction include:

- Under the slab insulation

- Use as insulation under the floorboards of timber floor homes on stumps.
- Use as the core of a sandwich structured composite board, such as a structural insulation panel (SIP), or in sandwich panels in caravans or portable huts.
- Use as the outer panels in insulating concrete form (ICF) construction for external walls, where the internal wall face would be lined with plasterboard.
- Use in Exterior Insulation Finish systems where the EPS foam sheet is applied to the external of timber framing, with reinforcing mesh and a render finish system to fully encase it.
- Use in the decorative fascia on buildings, where the foam is cement rendered or urethane coated.
- Insulation under the vinyl siding applied to external walls.

Other applications include sandwich panels in commercial cool rooms, in pontoons that are encased in concrete, as pipe cradles, in bridge components, or as geofoam (engineered elevated road ways or embankments over unstable soil). There will also be very limited use of the chemical in foam packaging applications in Australia.

The notified chemical is intended to be used as a replacement for hexabromocyclododecane (HBCD). It is an "additive" flame retardant, indicating that it is incorporated in the polymer matrix, but is not chemically reacted into the matrix. Therefore it may be released from the surface of the articles in which it is incorporated. The tendency of the notified chemical for "blooming" or migration to the surface of articles is not known.

OPERATION DESCRIPTION

The notified chemical will be imported as a component of EPS beads (not yet expanded) at ≤ 1.6%. The beads will be supplied from the importer's warehouse to the foam manufacturing sites.

The EPS product manufacturing process for the foam is typically a three-step process.

1. Pre-expansion: Workers will cut open the bottom of the bag of beads, which is positioned above the steam chamber, and the beads will be dropped into the chamber (pre-foamer) by gravity. The pre-foamer will be enclosed, and any vapours and excess steam will be vented outside of the building. Polystyrene beads will be expanded to around 40 to 60 times their original size using steam as the heat source. The pentane and steam will normally be exhausted from the process. The expanded beads will be moved through ducts using a pneumatic system into storage hoppers for conditioning. Workers will control and direct the transfer processes.

2. Conditioning: The expanded beads will be then stored in hoppers for a period to mature before the moulding process. Due to passive off-gassing, some pentane gas may be present in and around the storage hoppers.

3. Moulding: Once conditioning is completed, the pre-expanded polystyrene beads will be gravity-filled into a mould where more steam is introduced. This process will be mostly automated. The pre-foamed beads will expand further, completely filling the mould cavity and fusing together to produce articles. The polystyrene articles may be stored for a period to dry, reducing the water content. The process can be accelerated by placing the articles in curing ovens, normally set at around 70 °C.

The moulded articles will be then manually removed from the mould and will be transferred to the cutting machine. Workers will control and direct the transfer processes. Polystyrene articles may be cut to size using a hot-wire cutting table and more complex shapes are cut using a computer controlled hot-wire cutting machine. During this process, pyrolysis products can potentially be released.

A small proportion of the articles may also be cut with a bandsaw or a Stanley knife at the moulding facility and may be glued. The proportion cut by bandsaw/knife compared to hot-wire cutting would be < 5%.

Off-cuts of expanded polystyrene will be recycled on-site at the moulding facility. The foam as a thermoplastic will be re-moulded using hot-melt extrusion or cold compression into other types of articles.

At the construction sites, the moulded foam articles containing the notified chemical will be handled by the construction workers, who may also cut the articles to the desired size. Cutting at the end use site will typically be done with a Stanley knife, scoring on either side of the article and then snapping it to the correct length.

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)*
Warehouse and transport workers	1-2	100-200
EPS manufacturing workers	8-12	300
Manufacturing of articles for construction	8-12	300
Construction workers	8-12	300

EXPOSURE DETAILS

Warehouse and transport workers
Transport and storage workers may come into contact with the notified chemical at ≤ 1.6% concentration in unexpanded beads, only in the event of accidental rupture of containers.

EPS manufacturing workers
Workers may potentially be exposed to the notified chemical at ≤ 1.6% during the manual transfer process when manufacturing expanded polystyrene foam. The notified chemical has a very low estimated vapour pressure. The particle size of the imported beads, from which finer particles have been removed, is 0.7 to 1.4 mm. Therefore inhalation exposure from the imported beads is not likely to occur and dermal exposure during this process is also expected to be low.

Workers will wear protective clothing and dust masks during all transfer operations.

Manufacturing of articles for construction
Factory workers will be exposed to the moulded expanded foam during manufacture and handling of various types of articles used in the construction industry, where operations will include hot-wire cutting, sawing and gluing the foam. When carried out at factory sites, these operations will be likely to be automated using purpose-designed machinery supplied with local ventilation. Workers may wear a respirator during cutting operations if ventilation is insufficient.

The main potential exposure to the notified chemical will be from inhalation of any dust which may be generated and from dermal contact with articles containing the notified chemical at ≤ 1.6%. Where EPS is cut by bandsaw at the factory sites, the cutting equipment is fitted with dust extraction systems. Inhalation exposure to pyrolysis products of the notified chemical during hot-wire cutting would be reduced by the local exhaust ventilation in place, and respiratory protection may also be worn. Exposure to the notified chemical from dermal contact to articles may occur but is expected to be low, as it is present at a low concentration and dispersed throughout the articles.

Personal protective equipment (PPE) expected to be worn by workers, such as protective clothing and dust masks, would reduce the exposure further.

Construction workers
Construction workers will handle the finished articles. Many are pre-fabricated according to specifications, however cutting of articles may occur at construction sites, without engineering controls. Construction workers may have dermal and inhalation exposure to the notified chemical through these processes. PPE worn by workers, such as protective clothing and dust masks, are expected to minimise the exposure.

Following incorporation of the notified chemical into the moulded articles, the notified chemical is not expected to be available for exposure via the dermal route. Very small amounts of notified chemical may be available at the surface of the articles due to leaching or blooming. However, the dermal exposure from contact with articles is expected to be very low.

Foam packaging
Some worker exposure to foam packaging for appliances containing the notified chemical may occur, but is expected to be lower than that of construction workers.

6.1.2. Public Exposure

Direct exposure
The public will not be exposed to the notified chemical prior to it being incorporated into articles. Direct public exposure to articles containing the notified chemical will be limited, as almost all these articles will be used in construction (on external surfaces or covered with another material). A very small proportion of the articles containing the notified chemical will be used for packaging, where only short-term contact is expected. However the notified chemical will not be used in articles with frequent household use and contact, such as furniture. Based on the proposed use scenarios, public exposure to the notified chemical from handling articles or contact with construction articles (indoors and outdoors) is not expected.

Indirect exposure
The chemical is expected to be persistent but not bioaccumulative. It can be released into the general environment through release into the atmosphere or wastewater from its industrial uses and disposal, and leaching and emission from landfill, and from end-of-life scenarios of buildings. Release into local environments such as inside houses is not expected to occur as a result of the proposed use of the notified chemical in construction materials.

The distribution of notified chemical into the different environmental compartments (air, water, soil and sediment) is described in Section 7. Indirect exposure of humans to the notified chemical in the environment may occur by consumption of food and drinking water, inhalation of air and ingestion of soil and dust (particularly by children). However the overall exposure is expected to be reduced by the low use concentration ($\leq$ 1.6%) in articles.

The analogue chemical has been detected in air at levels of 0.19 pg/m^3 to 1.3 pg/m^3 at sites around the Great Lakes in the USA (confidential). Concentrations were correlated with proximity to population centres and with the levels of other flame retardants. A research group (confidential) detected the analogue chemical in various environmental compartments including sediments (0.7 to 292.7 ng/g), soil (up to 0.58 ng/g) and molluscs (average 0.15 ng/g dry weight).

The ingestion of dust/soil is considered a major potential source of indirect human exposure to chemicals. Adults may ingest soil or dust particles that adhere to food, cigarettes or their hands. The potential for exposure via ingestion could be greater for young children because they are more likely to ingest soil than adults as a result of behavioural patterns during childhood, and inadvertent dust ingestion among young children may occur through mouthing of objects or hands. As the notified chemical will not be used for indoor furniture, any indirect exposure to dust would be primarily outdoors and expected to be of a low magnitude.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical or the analogue 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 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity – 90 days	NOAEL = 1,000 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days*	NOAEL not established
Mouse, repeat dose oral toxicity – 90 days*	NOAEL not established
Mutagenicity – bacterial reverse mutation	non mutagenic
Mutagenicity – bacterial reverse mutation*	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test	non genotoxic
Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test	non genotoxic
Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test*	non genotoxic

*Studies on the analogue chemical

The analogue chemical has a similar structure to the main component of the notified chemical. The two chemicals have similar molecular weight, water solubility, and log Pow. Therefore, the notified chemical is expected to have a similar toxicity profile to the analogue chemical.

Toxicokinetics, metabolism and distribution
Results from a study on the toxicokinetics and absorption, distribution, metabolism, and excretion (ADME) profile of the analogue indicated that it was poorly and slowly absorbed across the gut lumen following oral administration of a single dose or multiple doses (20 mg/kg bw) in rats. Maximum blood concentration was not reached until 7.5 hours after the oral gavage dosing. This slow absorption resulted in extensive excretion in the faeces (95% by 36 hours). Urinary elimination was minimal (< 0.1%). Blood toxicokinetic data revealed that the systemic availability of the analogue via oral dosing was 2.2% of the total dose. However, absorption from the intestines into portal blood was higher as the amounts of analogue in liver tissues were in the range of 5–7% of the total dose administered. The analogue absorbed into the systemic compartment was eliminated from the blood slowly. The slow elimination reflected a restricted and selective liver tissue disposition, and this disposition appeared to be the major mechanism for blood clearance. After the oral administration, 1% of the dose was eliminated in bile in 24 hours as metabolites. In *in vitro* experiments utilising hepatocytes or liver microsomal protein, no metabolism of the analogue was detectable. These data indicate that the analogue is poorly absorbed from the gastrointestinal tract, selectively dispositioned into the liver, slowly metabolised and mainly eliminated through faeces (confidential). A dermal absorption study (confidential) found that the analogue chemical had low dermal penetration *in vivo* in rats (1%), *in vitro* in rats (0.3%) and *in vitro* in humans (0.2%). The amount retained in dosed skin was significant (26%, 23% and 53% respectively). Metabolism in the skin was not observed.

Acute toxicity
The notified chemical was found to have low acute oral and dermal toxicity in rats. No inhalation toxicity data are available.

Irritation
The notified chemical was found to be non-irritating to the skin and slightly irritating to eyes based on studies in rabbits. The results of the eye irritation study do not warrant a hazard classification under the GHS.

Sensitisation
In a mouse Local Lymph Node Assay (LLNA), the notified chemical showed no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation.

Repeated dose toxicity
In a 90 day repeated dose oral toxicity study, effects noted in the study were mostly related to reduced food intake and recoverable changes in haematological and clinical chemistry parameters in the animals treated at 500 mg/kg bw/day and above. Statistically significant decrease in encephalon weights was observed in the treatment recovery group when compared with the control recovery group. However, there was no specific histopathological change or injury noted in the test animals. A No Observed Adverse Effect Level (NOAEL) was established for the notified chemical as 1,000 mg/kg bw/day, based on the highest dose tested. The conclusion may not be reliable, as compared with the OECD TG 408 protocol, some organ weights were not measured and details for the study were not reported.

Similar results were observed in 90 day repeated dose oral toxicity studies conducted on the analogue chemical in rats or mice although no NOAELs were established by the study authors. Rats had granulomatous inflammation in the lungs and assumed this to be due to aspiration of the test substance. This effect was not observed in mice.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation assay, was not clastogenic in an *in vitro* mammalian chromosome aberration test and was not genotoxic in an *in vivo* mammalian erythrocyte micronucleus test. The results of bacterial reverse mutation assay and *in vivo* mammalian erythrocyte micronucleus test on the analogue chemical also were negative.

For the *in vivo* mammalian erythrocyte micronucleus tests provided for the notified chemical and the analogue chemical, it was impossible to verify whether the test substance had reached the bone marrow, as no cytotoxicity was observed.

Earlier genotoxicity studies on the analogue chemical have been reported (confidential). They indicated a positive response in Salmonella typhimurium strains in a bacterial reverse mutation study (TA100 and TA1535 in the presence and absence of metabolic activation and TA98 in the absence of metabolic activation). The analogue chemical was reported to be negative in an unscheduled DNA synthesis assay, and negative in an *in vitro* Sister Chromatid Exchanges Assay in a Chinese Hamster ovary cells.

A test such as an *in vivo* comet assay (liver) would provide further evidence regarding the genotoxic potential of the notified chemical.

Carcinogenicity
In tests with other brominated chemicals, cancer target organs were not always identified in 3-month studies (NTP, 2014a). While a 90-day repeated dose oral toxicity study on the analogue chemical (confidential) did not identify treatment related target organ toxicity in either rats or mice, it is uncertain if this result would predict positive or negative carcinogenic activity after longer term administration of the analogue chemical.

The notified chemical contains a chemical structure similar to tetrabromobisphenol A (TBBPA). An initial assessment of TBBPA by the USA EPA (US EPA, 2015) indicates that in a cancer bioassay (NTP, 2014b) there was clear evidence in rats for TBBPA to cause carcinogenic effects in the uterus as well as induce hemangiosarcomas and hemangiomas in all organs. There was some evidence of carcinogenic activity in male mice treated with TBBPA based on the increased incidences of hepatoblastoma. However, there was no evidence of carcinogenic activity of TBBPA in female mice. Possible mode of action for TBBPA to induce tumours is not clearly understood.

It is also noted that the potential degradation product of the notified chemical is related to a known carcinogen, 1-propanol, 2,3-dibromo- (CAS No. 96-13-9).

Based on the information available, the potential for carcinogenicity for the notified chemical cannot be completely ruled out.

Potential for Developmental Effects
The initial assessment of TBBPA by the USA EPA (US EPA, 2015) indicates that there is a possible concern for developmental effects based on slight kidney lesions in newborn rats exposed to the chemical. The lesions persisted after cessation of exposure, possibly due to immature metabolic capability or immature kidneys (Fukuda *et al.*, 2004). A study also found very slight hepatocyte necrosis in offspring of female mice exposed to TBBPA during gestation (Tada *et al.*, 2006). However, many other subchronic, reproductive and developmental toxicity studies conducted on TBBPA in rodents did not find any adverse effects. A potential degradation product of the notified chemical is classified as a reproductive toxicant.

Based on the information available, the potential for the notified chemical to cause developmental effects upon repeated or prolonged exposure is uncertain.

Endocrine disruption
In vitro information on the analogue chemical indicates that it does not appear to interfere with the action of CYP17, an enzyme which catalyses an important step in sex steroidogenesis (confidential). In a separate *in vitro* study the analogue chemical competed with thyroid hormone precursor thyroxine (T4) for binding to human transthyretin, but did not show thyroid hormone (T3) mimicking activity. It did not appear to interfere with the arylhydrocarbon receptor (AR), progesterone receptor (PR) or estrogen receptor activity (confidential).

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
Studies submitted on the notified chemical (a TBBPA ether) and on an analogue indicated that the notified chemical is of low acute and repeated dose toxicity and is not irritating or a skin sensitiser. There are factors which introduce uncertainty about some hazard endpoints.

- The *in vivo* clastogenicity studies did not have evidence that the chemical had reached the bone marrow, and thus were not able to rule out adverse effects. The *in vitro* mutagenicity studies submitted were negative, however earlier studies on the analogue chemical reported some positive results.
- The potential for carcinogenicity cannot be ruled out, based on structural similarity to TBBPA, and similarity of a potential breakdown product to another carcinogen, 1-propanol, 2,3-dibromo-. It was noted that carcinogenicity of other brominated chemicals was not determined without longer term studies than those currently available for the notified chemical.
- Reproductive/developmental effects have been seen in other brominated related chemicals mentioned above for carcinogenicity.

Information on the analogue chemical indicates that the notified chemical would have low absorption from the gastrointestinal tract, and slow metabolism. Percutaneous absorption of the analogue was low, with a significant amount retained on the dosed skin. Low bioavailability may reduce the potential for systemic toxicity.

6.3.1. Occupational Health and Safety

Several factors would reduce potential worker exposure to the notified chemical during the initial stages of processing. When imported, it is present at a low concentration (≤ 1.6%) in preformed unexpanded EPS beads, and the beads have been processed to remove inhalable and respirable particles. The pre-expansion, conditioning and moulding processes are expected to be carried out under controlled factory conditions. Therefore dermal or inhalation exposure of workers during these stages is expected to be low.

After the moulding process, cutting of articles by blade or hot-wire processes may occur under factory conditions. Inhalation of vapour or dust is possible, the latter also potentially leading to ingestion. Some dermal exposure from handling of the articles may also occur, as the notified chemical is not chemically bound into the polymer matrix. Local exhaust ventilation systems and PPE are expected to be used at the factory locations, and to reduce any worker exposure during these processes.

Handling of articles containing the notified chemical will also occur at diverse end use construction sites during installation of articles. Cutting of the articles with blades may also occur as part of this process. The sites may be indoor or outdoor and are not expected to have ventilation controls that might reduce inhalation of dust, however it is stated that construction workers will wear dust masks. The duration of exposure at each site would be short-term, although workers may carry out similar processes at multiple construction sites.

Noting the uncertainties in the human health hazard, and provided that the stated workplace controls are being adhered to, the notified chemical is not considered to pose an unreasonable risk to the health of workers under the conditions of the occupational settings described.

This risk assessment does not cover the exposure of workers during end-of-life activities of articles containing the notified chemical, such as removal and disposal of articles from construction.

6.3.2. Public Health

The notified chemical and the unexpanded polystyrene beads containing it at ≤ 1.6% will not be available to the public. The public may have incidental dermal contact with moulded EPS articles containing the notified chemical. The vast majority of these articles will be used in construction for industrial and residential buildings and will not be in direct contact with the public as the articles are not used for the interior of buildings. Dermal exposure to the public is therefore expected to be very low. Inhalation exposure is also expected to be very low, due to the low vapour pressure of the notified chemical and its use mainly in enclosed or non-accessible locations. Overall the direct exposure of the public to the chemical is considered low.

Indirect exposure of the public to the notified chemical may occur through the outdoor 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. Because of the proposed pattern of use, significant exposure to dust from articles in the interior of dwellings is not expected. 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.

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

6.3.3 Overseas investigations

Due to concerns with a TBBPA ether type of brominated flame retardant related to the notified chemical, Ministerial Conditions under the Canadian Environmental Protection Act, 1999 have been applied to that chemical. The conditions control the specific uses of the chemical and require a multi-generational fish study and an amphibian metamorphosis assay prior to exceeding a specified volume.

Two TBBPA ether brominated flame retardants related to the notified chemical are currently listed on the EU CoRAP (Community Rolling Action Plan) for evaluation by Germany in 2017, due to suspected concerns on potential endocrine disruption, suspected PBT/vPvB, and high aggregated tonnage.

7. ENVIRONMENTAL IMPLICATIONS

The notified chemical is a member of a class of chemicals known as brominated flame retardants (BFRs). This class of chemical 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 expected to be persistent in the environment. It is a replacement BFR for HCBD.

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia as a component of EPS beads. The beads will be supplied to local foam manufacturing sites where they undergo processing to expand and form into various products, mostly used in the construction industry.

The foam manufacturing process from EPS beads is typically automated in an enclosed environment. Any waste produced during the manufacturing process is expected to be disposed of in accordance with local government regulations. Accidental spills of the products containing the notified chemical during import, storage, foam manufacturing or transport will be collected for reuse or disposal, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The foam containing the notified chemical will be mostly used in the construction industry as insulation inside external walls. A small proportion will be used in packaging. The foam used in construction is likely to be covered and protected by layers of other construction materials and coatings. However, over the lifetime of the buildings, there may be a low level of release. The release material is mostly in dust form and likely to end up in soil.

RELEASE OF CHEMICAL FROM DISPOSAL

The foam and package containing the notified chemical will be disposed of to landfill at the end of their useful lives. Empty bulk bags containing residual notified chemical will be reused where possible and eventually disposed of to landfill.

7.1.2. Environmental Fate

As a result of its use pattern, the majority of the products containing the notified chemical are expected to be disposed of to landfill at the end of their useful lives. 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. Based on its low water solubility ($< 0.42 \times 10^{-6}$ g/L) and high log K_{oc} (8.1), the notified chemical is expected to be immobile in soil. A ready biodegradation test conducted on the notified chemical shows that it is not readily biodegradable (no degradation over 28 days) and therefore so it is likely to be persistent in the environment. However, the notified chemical is unlikely to be bioaccumulative as indicated by its bioaccumulation test results (BCF $\leq$ 94). For details of the biodegradation and bioaccumulation studies, refer to Appendix C. In landfill, the notified chemical will be bound within the solid matrix and expected to slowly degrade via biotic and abiotic processes to form simpler organic compounds potentially including ones already used as brominated flame retardant additives. Eventually these are expected to further degrade to 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

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 > LOD*	Not harmful to fish up to its water solubility limit
Daphnia Toxicity	EC50 > LOD*	Not harmful to aquatic invertebrates up to its water solubility limit
Algal Toxicity	EC50 > LOD*	Not harmful to alga up to its water solubility limit

*LOD: Limit of detection of 89.6 ng/mL

Based on the above ecotoxicological endpoints for the notified chemical, it is not expected to be harmful to aquatic life up to the limit of its water solubility. Therefore, the notified chemical is not formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) for acute and chronic toxicities (United Nations, 2009). None of the potential degradant BFRs are known to have an adverse impact upon the environment, but investigations on the degradants including the structurally similar TBBPA may be ongoing.

7.2.1. Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) for the aquatic compartment has not been calculated as the notified chemical is not considered to be harmful to aquatic organisms up to its water solubility limit.

7.3. Environmental Risk Assessment

The notified chemical and its degradants are expected to be persistent in the environment, but not expected to be bioaccumulative. The risk quotient (Q = PEC/PNEC) of the notified chemical has not been calculated as the notified chemical is not considered to be harmful to aquatic organisms up to its water solubility limit and no significant release of the notified chemical to the aquatic environment is expected from the reported use pattern. None of its degradants are known to have an adverse impact upon the environment, but investigations may be ongoing. Small amounts of dust containing the notified chemical are also expected to enter the terrestrial environment. However, based on this very limited release neither the notified chemical nor its degradants are likely to reach eco-toxicologically relevant levels. Therefore, on the basis of the low hazard of the notified chemical, the current understanding of the notified chemical's degradants, including any that may be structurally similar to TBBPA and this assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Water Solubility $< 0.42 \times 10^{-6}$ g/L

Method OECD TG 105 Water Solubility
EC Council Regulation No 440/2008 A.6 Water Solubility
Remarks Column Elution Method
Test Facility IMI (2010)

Partition Coefficient (n-octanol/water) $\log P_{ow} > 6.5$

Method OECD TG 117 Partition Coefficient (n-octanol/water).
EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks HPLC Method
Test Facility APM (2014a)

Adsorption/Desorption $\log K_{oc} = 8.1$

Method OECD TG 121 Adsorption Coefficient
Remarks HPLC method, extrapolated
Test Facility APM (2014b)

Particle Size 0.220 - 88.48 μm
D10 (the diameter at which 10% of the sample's mass is comprised of particles with a diameter less than this value) = 2.515 μm
D50 (the diameter at which 50% of the sample's mass is comprised of particles with a diameter less than this value) = 13.68 μm
D90 (the diameter at which 90% of the sample's mass is comprised of particles with a diameter less than this value) = 37.15 μm

Method OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions

Range (μm)	*Mass (%)*
≤ 94.55	100
≤ 40.15	91.91
≤ 13.76	50.24
≤ 9.983	37.62
≤ 2.762	11.26

Test Facility Shanghai Academy of Public Measurement (2014)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 425 Acute Oral Toxicity: Up-and-Down Procedure (2008)
- Species/Strain: Rat/Wistar
- Vehicle: Arachis oil BP
- Remarks - Method: No protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	1 F	175	0/1
2	1 F	500	0/1
3	3 F	2,000	0/3

- LD50: > 2,000 mg/kg bw
- Signs of Toxicity: Hunched posture was observed during the day of dosing in 2 animals treated at 2,000 mg/kg bw and the effects persisted in one animal one day after the dosing.
- Effects in Organs: No abnormalities were observed at necropsy.
- Remarks - Results: Expected bodyweight gains were noted for all animals during the study.

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

TEST FACILITY: Harlan Laboratories Ltd (2010a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 402 Acute Dermal Toxicity – Limit Test (1987)
EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal) – Limit Test
- Species/Strain: Rat/Wistar
- Vehicle: Moistened with Arachis oil BP
- Type of dressing: Semi-occlusive
- Remarks - Method: No protocol deviations

RESULTS

Number and Sex of Animals	*Dose (mg/kg bw)*	*Mortality*
5 per sex	2,000	0/10

- LD50: > 2,000 mg/kg bw
- Signs of Toxicity - Local: No signs of skin irritation were observed.
- Signs of Toxicity - Systemic: No signs of systemic toxicity were observed.
- Effects in Organs: No abnormalities were observed at necropsy.
- Remarks - Results: Expected bodyweight gains were noted for 4 male and 2 female animals during the study. One male animal gained bodyweight in the first week and had bodyweight loss in the second week. One female animal gained bodyweight in the first week and its bodyweight did not change in the second week. Bodyweight of 2 females did not change in the first week and they gained bodyweight in the second week.

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

TEST FACILITY: Harlan Laboratories Ltd (2010b)

B.3. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion (2002) EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Vehicle	None
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	No protocol deviations were noted. The absorption of the test substance was not determined.

RESULTS

Remarks - Results	No signs of skin irritation were observed. Expected bodyweight gains were noted for all animals during the study.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	Harlan Laboratories Ltd (2010c)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion (2002) EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Observation Period	72 hours
Remarks - Method	No protocol deviations were noted.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.3	0.3	0.3	2	< 48 h	0
Conjunctiva: chemosis	0.3	0.3	0.3	2	< 48 h	0
Conjunctiva: discharge	0.3	0.3	0.3	2	< 48 h	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results	No corneal or iridial effects were observed during the study. Moderate conjunctival irritation for redness, chemosis and discharge was observed in all treated eyes 1 hour after treatment, with minimal conjunctival irritation at the 24-hour observation. All effects disappeared at the 48-hour observation. Expected bodyweight gains were noted for all animals during the study.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	Harlan Laboratories Ltd (2010d)

B.5. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2002)
Species/Strain	Mouse/CBA/Ca
Vehicle	Dimethyl formamide
Preliminary study	Yes
Positive control	α-Hexylcinnamaldehyde
Remarks - Method	No protocol deviations

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5 F	1218.12 ± 429.47	-
5	5 F	1382.11 ± 261.64	1.13
10	5 F	1765.90 ± 329.19	1.45
25	5 F	1636.20 ± 244.73	1.34
Positive Control			
15	5 F	7863.87 ± 3064.07	6.46

Remarks - Results	There were no deaths or signs of systemic toxicity observed in test animals. Expected bodyweight gains were noted for all animals during the study.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Harlan Laboratories Ltd (2010e)

B.6. Repeat dose toxicity – rats

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents
Species/Strain	Rats/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Corn oil
Remarks - Method	The treatment doses were determined based on previously conducted study results of acute oral toxicity and 28-day repeated dose oral toxicity in rats (these reports were not provided). Some organ weights were not measured, including thymus, uterus, epididmides and ovaries. For histopathological examination, spinal cord, gross lesions, parathyroid, thymus, oesophagus, salivary glands, gonads, accessory sex organs, female mammary gland, prostate and peripheral nerve were not examined. The report appeared to be abridged. Individual animal and daily data were not provided in the report. Details on histopathological changes were not presented in the report.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
control	10 per sex	0	0/20
low dose	10 per sex	250	0/20
mid dose	10 per sex	500	0/20
high dose	10 per sex	1,000	0/20
control recovery	10 per sex	0	0/20
high dose recovery	10 per sex	1,000	0/20

Mortality and Time to Death

There was not mortality.

Clinical Observations

No significant clinical signs of disturbances of the general behaviour related to the test substance administration were noted in the animals.

There was no statistically significant difference of body weight in all animals. In week 7 of the dosing period, food consumption of males in the high dose group was significantly lower than that of the control group ($p < 0.05$). Food consumption of the females in the high dose recovery group in weeks of 6, 7, 8, 9, 10, 13, 14 and 15 during the dosing period and total food consumption were significantly decreased compared with the control recovery group ($p < 0.05$). There was no other statistically significant change of body weight, food consumption and food efficiency in other treatment groups during the treatment period, compared with the control group or the control recovery group.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

For haematology, there was significant decrease of platelet count (PLT) and prothrombin (PT) in males in the high dose group ($p < 0.05$). Statistically significant decrease of neutrophils (NEUT) percentage and increase of lymphocytes (LYMPH) percentage were noted in males in the mid dose group ($p < 0.05$). Statistically significant increase of NEUT percentage was noted in females in the high dose group ($p < 0.05$). Statistically significant decrease in LYMPH percentage was observed in females in the mid dose and high dose groups ($p < 0.05$) compared to that of the control group. Statistically significant increase in PLT and eosinophils (EO) percentage were noted in the high dose recovery group compared to those of control recovery group ($p < 0.05$). There was no other statistically significant change of haematological parameters in other treated groups during the treatment period, compared with the control group or the control recovery group.

For clinical biochemistry, in male rats, there was significant increase of total protein (TP) in the low dose group, significant decrease of alkaline phosphatase (ALP) and creatinine (CRE) in the high dose group and significant increase of Cl^- concentration in the high dose group compared with the control group ($p < 0.05$). Statistically significant increase of aspartate aminotransferase (AST) and significant decrease of glucose (GLU) in males in the high dose recovery group was noted compared with the control recovery group ($p < 0.05$). For the female rats, there was statistically significant decrease of alanine aminotransferase (ALT) in the low dose and mid dose groups and significant increase of Cl^- concentration in the mid dose group compared with the control group ($p < 0.05$). There was no statistically significant change of any other blood chemistry parameters in treated groups during the treatment period, compared with the control group or the control recovery group.

There were no specific urinalysis changes in treated animals, except that the specific gravity in the treatment recovery group was statistically significantly higher.

Effects in Organs

No treatment related effects were reported during gross necropsy.

No significant morphological changes were noted in encephalon, heart, liver, kidneys, stomach and esophageal, duodenum and large intestine, adrenals, spleen, lung, testes, ovary, uterus for all animals. However, statistically significant decrease in encephalon weights was reported in the high dose recovery group compared with the control recovery group ($p < 0.05$).

There was no other statistically significant change reported in organ weights of treated animals.

No histopathological effects related to treatment were reported except for some inflammatory cells in the liver and renal interstitium of a few high dose animals.

Remarks – Results
The food intake in animals was partly affected by the test substance administration. A few changes in haematological parameters (PLT, prothrombin time, neutrophil percentage) and biochemical indicators (ALP, CRE, AST and GLU) were noted. However, some haematological (prothrombin time) and biochemical parameters (ALP, CRE) of the high dose recovery group had resolved in the recovery period. There was no significant histopathological change and specific injury noted in the test animals treated with the test substance.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established by the study authors as 1,000 mg/kg bw/day, based on the highest dose tested.

TEST FACILITY Tianjin Centers for Disease Control and Prevention (2014)

B.7. Repeat dose toxicity – rats (analogue)

TEST SUBSTANCE Analogue chemical

METHOD Similar to OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents

Species/Strain	Rats/F344/NTac
Route of Administration	Oral – gavage
Exposure Information	Total exposure weeks: 14 weeks Dose regimen: 5 days per week
Vehicle	Corn oil
Remarks - Method	The treatment doses were determined based on the relatively low toxicity reported in the literature. Urinalysis measurement was not conducted. Individual animal and daily data were not provided in the report. The test was conducted in conjunction with the 90-day repeated dose oral toxicity study in mice (see Appendix B.8.). Review of tissues from the respiratory system was conducted to determine the nature of the pulmonary granulomatous and chronic active inflammatory lesions that occurred during the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 per sex	0	1 F/20
Low dose	10 per sex	62.5	2 M/20
Mid low dose	10 per sex	125	0/20
Mid dose	10 per sex	250	0/20
Mid High dose	10 per sex	500	0/20
High dose	10 per sex	1,000	0/20

Mortality and Time to Death
One male in the 62.5 mg/kg bw/day group died early (natural death on day 37) and had lesions of minimal cardiomyopathy, minimal chronic liver inflammation, minimal liver cytoplasmic vacuolisation, acute and minimal pulmonary inflammation. Another male in the 62.5 mg/kg bw/day group died of a dosing accident on day 40. One control group female died in week 8.

Clinical Observations
Mean body weights and body weight gains in all animals were similar to those of the vehicle controls. No treatment related clinical findings or gross lesions were noted.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
In males, statistically significant changes were noted for the following:

Effects Observed	*Dose Group (mg/kg bw/day)*	*Time of Observation*
Increase in platelets	125 and 1,000	week 14
Increase in segmented neutrophils and eosinophils	500	day 23
Increase in albumin	62.5, 250 and 500	day 23
Increase in alanine aminotransferase	62.5	day 23
Decrease in cholesterol	250 and 1,000	all time points
Decrease in mean cell haemoglobin	125, 250, 500 and 1,000	day 23
Decrease in urea nitrogen	250	week 14
Decrease in creatinine	1,000	day 4
Decrease in sorbitol dehydrogenase	125	day 23
Decrease in sorbitol dehydrogenase	1,000	week 14

In females, statistically significant changes were noted for the following:

Effects Observed	*Dose Group (mg/kg bw/day)*	*Time of Observation*
Increase in platelets	125	week 14
Increase in alanine aminotransferase	62.5	week 14
Increase in alanine aminotransferase	125, 250, 500 and 1,000	day 23
Increase in alkaline phosphatase	125	day 4
Decrease in cholesterol	250, 500 and 1,000	all time points
Decrease in creatinine	1,000	day 4
Decrease in alkaline phosphatase	1,000	week 14
Decrease in thyroid stimulating hormone	1,000	week 14

These effects, except for decrease in cholesterol, were not considered by the study authors to be adverse.

Decreases in cholesterol concentrations occurred in male and female rats treated at 250 mg/kg bw/day or higher. This effect was observed at all time points despite the inconsistency within the dosed groups. However, only females in the 500 mg/kg bw/day group demonstrated decreases at all time points. The toxicological relevance of the effects is unknown, but could suggest alterations in cholesterol metabolism related to treatment.

Liver enzyme levels decreased in males and females treated at 125 mg/kg bw/day or higher when normalised on a microsomal protein level. However, this decrease was not considered by the study authors to be biologically relevant as the absolute values of the liver enzymes did not increase with the dose levels in both sexes.

Effects in Organs
There were statistically significant absolute kidney weight increases for the males in the 250 mg/kg bw/day group. Statistically significant relative liver weight increases were observed in the 62.5, 250 and 1,000 mg/kg bw/day groups for the males and in the 1,000 mg/kg bw/day group for the females. Absolute liver weights for the males in the 62.5 mg/kg bw/day group were also statistically significantly increased.

In the lung, Incidences of granulomatous inflammation in the lung in males at 62.5, 125, 250, and 500 mg/kg bw/day and in females at 125 mg/kg bw/day or higher were significantly greater than those in the vehicle control group. The incidences of chronic active inflammation were significantly increased in females at 250 mg/kg bw/day or higher and the incidence of this lesion was significantly decreased in males at 62.5 mg/kg bw/day. Review of the lung tissues indicated that these lesions were likely associated with the aspirations of the gavage material and infections of pathogenic microorganisms (see below in Remarks – Results). The lung lesions were not observed in the concurrent mouse study (see Appendix B.8) and the study authors did not consider the effects were related to the toxicity of the test substance.

Testis or epididymis weights of the treated males were unaffected. There were no changes in the number of sperm or spermatids and sperm motility. There were no oestrous cycle changes observed in treated females.

There were no treatment related changes noted by the study authors in thyroxine, triiodothyronine, or thyroid stimulating hormone levels.

Remarks – Results

Granulomatous inflammation in the lung of all treated animals was characterised by foci of vacuolated mononuclear and some multinucleated macrophages within the alveoli lumens, and less often in the terminal bronchioles, with minimal to no perivascular involvement. The effect was noted in all treated groups, but the severity of this lesion did not increase with the dose levels. Some macrophages contained linear clear spaces consistent with sterol clefts and others contained small refractile globules, which might have been corn oil (the vehicle used). After special studies were performed to determine the pathogenesis of this lesion, the study authors concluded that this lung lesion was most likely caused by the procedure of gavage. High viscosity of the corn oil might have caused the material to adhere to the gavage needles that resulted in a small amount of gavage material (corn oil and test article) being aspirated by the test animals during removal.

Chronic active inflammation seen in the vehicle control and treated rats was characterised by dense perivascular accumulations of lymphocytes with fewer macrophages, granulocytes and erythrocytes. This lesion was morphologically different from the lesion associated with aspiration of gavage solution and was in a different location within the lung. No Sudan black positive material was identified within these lesions and the study authors considered that the lesions were morphologically consistent with *Pneumocystis carinii* infection (Livingston *et al.*, 2011). The exact aetiology of the lung lesions was uncertain as the study was not performed to determine the causative agent of the chronic active inflammation. However, due to the morphological similarity, the study authors considered that *P. carinii* infections were most likely the cause.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was not established by the study authors.

TEST FACILITY Confidential

B.8. Repeat dose toxicity – mice (analogue)

TEST SUBSTANCE Analogue chemical

METHOD Similar to OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents

Species/Strain	Mice/B6C3F1/N
Route of Administration	Oral – gavage
Exposure Information	Total exposure weeks: 14 weeks Dose regimen: 5 days per week
Vehicle	Corn oil
Remarks - Method	The test was conducted in conjunction with the 90-day repeated dose oral toxicity study for rats (see Appendix B.7.). The treatment doses were determined based on the relatively low toxicity reported in the literature. Clinical chemistry and urinalysis measurement was not conducted. Individual animal and daily data were not provided in the report.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 per sex	0	0/20
Low dose	10 per sex	125	0/20
Mid low dose	10 per sex	250	0/20
Mid dose	10 per sex	500	0/20
Mid high dose	10 per sex	1,000	0/20
High dose	10 per sex	2,000	0/20

Mortality and Time to Death

There was not morality.

Clinical Observations

No treatment related clinical findings or treatment related gross lesions were found in males or females tested. The final mean body weights and body weight gains in all males were similar to those of the vehicle control group. However, the final mean body weight of females in the 250 mg/kg bw/day group was 11% greater than that of the vehicle controls.

Laboratory Findings –Haematology

No changes were reported in the haematology parameters except for females at 2,000 mg/kg bw/day that showed statistically significant increase in segmented neutrophils.

Microsomal protein levels increased in treated mice at doses ≥ 250 mg/kg bw/day.

Liver enzyme levels showed an apparent decrease in treated groups of males and females when normalised on a microsomal protein level. However, this decrease was not considered to be biologically relevant because the absolute values for the liver enzymes did not increase with the treatment.

Effects in Organs

There were no treatment related effects on absolute or relative organ weights in all animals. Absolute liver weights had statistically significant increases in the 125, 250 and 2,000 mg/kg bw/day groups. However, the relative liver weight increases were not statistically significant. Therefore these effects were not considered by the study authors to be related to the test substance administration.

Testis or epididymis weights of the treated males were unaffected. There were no changes in the number of sperm or spermatids and sperm motility. There were no oestrous cycle changes in the treated females except one female in the vehicle control and one female each in the 1,000 and 2,000 mg/kg bw/day groups.

There were no reported gross or histopathological lesions related to treatment.

Remarks – Results

There were no granulomatous lesions, no foreign material, and no conclusive Sudan black positivity in the additional review of lung tissues. The reason for lack of similar effects as seen in rats (see Appendix B.7) was unknown and might be due to better gavage techniques used in the mouse study and/or the smaller gavage needle bore/diameters used for the mice.

CONCLUSION

A NOAEL was not established by the study authors.

TEST FACILITY	Confidential

B.9. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test EC Council Regulation No 440/2008 B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria Plate incorporation procedure (Test 1)/Pre incubation procedure (Test 2)
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA$^-$
Metabolic Activation System	A rat liver homogenate metabolising system (10% liver S9 in standard co-factors)
Concentration Range in Main Test	With or without metabolic activation: 0, 50, 150, 500, 1,500 and 5,000 µg/plate
Vehicle	Dimethyl sulphoxide (DMSO)
Remarks - Method	No protocol deviations

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 5,000			
Test 1		> 5,000	≥ 1,500	negative
Test 2		> 5,000	≥ 500	negative
Present	> 5,000			
Test 1		> 5,000	≥ 1,500	negative
Test 2		> 5,000	≥ 500	negative

Remarks - Results

No toxic effects or biologically relevant increases in revertant colony numbers were noted in any of the tester strains with or without metabolic activation.

The concurrent positive and negative controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

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

TEST FACILITY

Harlan Laboratories Ltd (2010f)

B.10. Genotoxicity – bacteria (analogue)

TEST SUBSTANCE

Analogue chemical

METHOD

Similar to OECD TG 471 Bacterial Reverse Mutation Test
Pre incubation procedure

Species/Strain: *Salmonella typhimurium*: TA98, TA100, TA102

Metabolic Activation System: Metabolic activation enzymes from Aroclor 1254-induced male Sprague Dawley rat liver and cofactors

Concentration Range in Main Test: With or without metabolic activation: 0, 100, 333, 1,000, 3,333 and 10,000 µg/plate

Vehicle: Dimethyl sulphoxide (DMSO)

Remarks - Method: *Escherichia coli* strains were not included. No preliminary test was conducted.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity	*Precipitation*	*Genotoxic Effect*
Absent			
Test	≥ 3,333	≥ 1,000	negative
Present			
Test	≥ 3,333	≥ 1,000	negative

Remarks - Results

No toxic effects or biologically relevant increases in revertant colony numbers were noted with any of tester strains with or without metabolic activation.

The concurrent positive and negative controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

The test substance was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY Confidential

B.11. Genotoxicity – *in vitro* mammalian chromosome aberration test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test
Cell Type/Cell Line Chinese Hamster Lung Fibroblast (CHL)
Metabolic Activation System Rat liver S9 fractions and cofactors
Vehicle Dimethyl sulfoxide (DMSO)
Remarks - Method All cultures were selected for metaphase analysis. The report appeared to be abridged.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0, 156, 312, 625	6 h	24 h
Test 2	0, 156, 312, 625	24 h	24 h
Present			
Test 1	0, 156, 312, 625	6 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	≥ 625*			
Test 1		> 625	not reported	negative
Test 2		> 625	not reported	negative
Present	≥ 625*			
Test 1		> 625	not reported	negative

*The preliminary cytotoxicity test was conducted without metabolic activation.

Remarks - Results Repeatable and dose-response increase of chromosome aberration were not noted in the test.

The concurrent positive and negative controls produced satisfactory responses, thus confirming the validity of the test system.

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

TEST FACILITY Tianjin Centers for Disease Control and Prevention (2015a)

B.12. Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 474 Mammalian Erythrocyte Micronucleus Test
Species/Strain Mice/Kunming, specific-pathogen-free (SPF) grade
Route of Administration Oral – gavage
Vehicle Vegetable oil
Remarks - Method Only one dose level of 2,000 mg/kg bw was tested. The report appeared to be abridged.

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	5 per sex	0	24
II (single dose)	5 per sex	2,000	24
III (positive control, CP)	5 per sex	40	24

CP = cyclophosphamide

RESULTS

Doses Producing Toxicity	No significant cytotoxicity was noted for the test substance.
Genotoxic Effects	The mean number of polychromatic erythrocytes with micronuclei (PCEs) was not increased after the treatment with the test substance as compared to the mean values of the negative control.
Remarks - Results	The positive control showed a distinct increase of induced micronucleus frequency, confirming the validity of the test system. As there was no cytotoxicity observed after treatment, it was not possible to confirm that the test substance reached the bone marrow.

CONCLUSION The notified chemical was not considered by the study authors to be clastogenic under the conditions of this *in vivo* mammalian erythrocyte micronucleus test.

TEST FACILITY Tianjin Centers for Disease Control and Prevention (2015b)

B.13. Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test (analogue)

TEST SUBSTANCE Analogue chemical

METHOD Similar to OECD TG 474 Mammalian Erythrocyte Micronucleus Test

Species/Strain	Mice/B6C3F1/N
Route of Administration	Oral – gavage
Vehicle	Corn oil
Remarks - Method	No concurrent positive control was included. The test was conducted in conjunction with the 90-day repeated dose oral toxicity study (see Appendix B.8). At the termination of the study, peripheral blood samples were obtained from the animals and the erythrocytes were examined for micronucleus formation.

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Sacrifice Time (days)*
I (vehicle control)	5 per sex	0	90
II	5 per sex	125	90
III	5 per sex	250	90
IV	5 per sex	500	90
V	5 per sex	1,000	90
VI	5 per sex	2,000	90

RESULTS

Doses Producing Toxicity	No significant changes in the percentage of polychromatic erythrocytes among total red blood cells were observed in the treated mice.
Genotoxic Effects	No significant increases in the frequencies of micronucleated normochromatic erythrocytes (NCE) were observed in peripheral blood samples from male or female mice.
Remarks - Results	As there was no change in the NCE/PCE ratio after the treatment indicating cytotoxicity to the test substance at the dose levels tested, it was not possible to confirm that the test substance reached the bone marrow.

CONCLUSION The test substance was not considered by the study authors to be clastogenic under the conditions of this *in vivo* mammalian erythrocyte micronucleus test.

TEST FACILITY Confidential

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test
Inoculum	Activated sludge from a domestic STP
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	BOD by Oxitop® electrodes
Remarks - Method	No significant deviations from the test guidelines were reported. The test substance was directly added to the test vessels. A toxicity control was run.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	0.5	1	17.9
14	-6.9	14	85.7
28	-1.6	28	97.0

Remarks - Results	All validity criteria for the test were satisfied. The toxicity control exceeded 25% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The test substance was not degraded after 28 days.
CONCLUSION	The test substance is not readily biodegradable
TEST FACILITY	APM (2014c)

C.1.2. Bioaccumulation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 305 Bioconcentration: Flow-through Fish Test
Species	Medaka (*Oryzias latipes*)
Exposure Period	63 days
Auxiliary Solvent	Tetrahydrofuran (THF)
Concentration Range	Nominal: High concentration of 0.01 mg/L and Low concentration of 0.001 mg/L Actual: High concentration of 0.00907 mg/L and Low concentration of 0.00117 mg/L
Analytical Monitoring	High performance liquid chromatography (HPLC)
Remarks - Method	No significant deviations from the test guidelines were reported. The test substance was dissolved in THF before adding to the test vessels. The test substance concentrations in the test water were analysed at 9, 14, 19, 28, 34, 41, 48 and 62 days. The test substance concentrations in fish were analysed at 9, 14, 28, 41 and 62 days.
RESULTS	
Bioconcentration Factor (BCF)	High concentration level: BCF < 9 to 45 Low concentration level: BCF < 76 to 94
LC50	> 1 mg/L
Remarks - Results	The validity criteria for the test were satisfied. Dissolved oxygen concentration in the test water was ≥ 60% during the test. The measured test substance concentrations were within ±20% of the mean measured

concentration during the test.

CONCLUSION Bioaccumulation potential of the test substance is low.

TEST FACILITY Mitsubishi Chemical Medience Corporation (2012)

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 Chinese Rare Minnow *Gobiocypris rarus*
Exposure Period 96 hours
Auxiliary Solvent None
Water Hardness 155 mg $CaCO_3$/L
Analytical Monitoring Ultra performance liquid chromatography (UPLC)
Remarks – Method A limit test was run with no significant deviations from the test guidelines. A nominal concentration of 100 mg/L of test substance was prepared and stirred in the dark for 72 hours followed by filtration (0.45 µm) to make a saturated solution of the test substance.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*
Nominal	*Actual*		*96 h*
Control	< LOD*	10	0
100	< LOD*	10	0

*LOD: Limit of detection of 89.6 ng/mL

LC50 > LOD* at 96 hours
Remarks – Results All validity criteria for the test were satisfied. The dissolved oxygen concentration in the solution during the test was > 65%.

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

TEST FACILITY APM (2014d)

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 None
Water Hardness 165 mg $CaCO_3$/L
Analytical Monitoring UPLC
Remarks - Method A limit test was run with no significant deviations from the test guidelines. 101.8 mg test substance was dissolved in 1 L test water and stirred in the dark for 72 hours followed by filtration (0.45 µm) to make a saturated solution of the test substance.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*
Nominal	*Actual*		*48 h*
Control	< LOD*	20	0

102	< LOD*	20	0

*LOD: Limit of detection of 89.6 ng/mL

EC50 > LOD* at 48 hours

Remarks - Results All validity criteria for the test were satisfied. The dissolved oxygen concentration in the solution during the test was ≥ 8.29 mg/L at 20°C (≥ 91%, USGS, 2011).

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

TEST FACILITY APM (2014e)

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 *Pseudokirchneriella subcapitata*
Exposure Period 72 hours
Concentration Range Nominal: 100 mg/L
Actual: < LOD*
Auxiliary Solvent None
Water Hardness Not provided
Analytical Monitoring UPLC
Remarks - Method A limit test was run with no significant deviations from the test guidelines. A nominal concentration of 100 mg/L of test substance was prepared and stirred in the dark for 72 hours followed by filtration (0.45 µm) to make a saturated solution of the test substance.

RESULTS

Biomass		*Growth*	
EC50 at 72 h	*NOEC at 72 h*	*EC50 at 72 h*	*NOEC at 72 h*
> LOD*	≥ LOD*	> LOD*	≥ LOD*

*LOD: Limit of detection of 89.6 ng/mL

Remarks - Results All validity criteria for the test were satisfied. The mean cell density in the control increased by 122 times. The mean coefficient of variation for section by section specific growth rates in the control was 31.7%. The coefficient of variation of average specific growth rates during the test in replicate control was 1.23%.

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

TEST FACILITY APM (2014f)

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