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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

C-4000

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

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

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

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Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Rohm and Haas Australia Pty. Ltd. (ABN 29 004 513 188)
4th Floor, 969 Burke Road, Camberwell, VIC. 3124

and

Plastral Pty. Ltd. (ACN 000 144 132)
130 Denison Street, Hillsdale, NSW. 2036

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, CAS number, molecular and structural formulae, molecular weight, spectral data, method of detection, composition, degree of purity, import volume, details of use.

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, 2008

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
C-4000 (neat notified chemical)

OTHER NAME(S)
None

MOLECULAR WEIGHT
>500 Da

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

3. COMPOSITION

DEGREE OF PURITY >94%

ADDITIVES/ADJUVANTS None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Colourless to pale yellow liquid

Property	Value	Data Source/Justification
Freezing Point	-48.2°C	Measured
Boiling Point	213.8 °C at 101.3 kPa	Measured
Density	1013 kg/m^3 at 20 °C	Measured
Vapour Pressure	<.00235 x 10^{-8} kPa at 25°C	Measured
Water Solubility	<1.37 × 10^{-4} g/L at 20°C	Measured
Hydrolysis as a Function of pH	$t_{½}$ ≥45 days	Measured
Partition Coefficient (n-octanol/water)	log K_{OW} = 7.59	Estimated by KOWWIN (v1.67) (US EPA, 2009)
Adsorption/Desorption	log K_{OC} = 4.8 to 5.3 at 25°C	Measured
Dissociation Constant	Not determined	The notified chemical does not contain ionisable functionality
Particle Size	Not determined	The notified chemical is liquid
Flash Point	90.5 ± 0.6°C	Measured
Autoignition Temperature	Not determined	The notified chemical has a flash point of 90.5°C. The notifier advised that it is not expected to autoignite under normal conditions of use and handling
Explosive Properties	Not determined	Unlikely to have explosive properties, based on chemical structure

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

Reactivity

In a thermal stability study (see Appendix A), the mean recovery of the C-4000 test samples stored at 55°C was 68.8%. The mean recovery of the C-4000 control samples stored at room temperature was 119.6%. The significant difference in the recovery percent of the test samples versus the control samples indicated that C-4000 was not stable at 55°C.

No significant temperature change (greater than ± 5°C) occurred when the test substance, C-4000, was mixed initially, after 10 minutes, and after 24 hours with water, KMnO4, NH4H2PO4, turpentine, or zinc, indicating no significant oxidizing or reducing action, or chemical incompatibility with these substances (see Oxidizing Properties Report in Appendix A).

In hydrolysis as a function of pH study (see Appendix A), $t_{½}$ was determined to be ≥45 days at pH 4. At pH 7 & 9, $t_{½}$ was determined to be 147 days & 85 days, respectively. In another hydrolysis investigation (see Appendix A), the average amount of the notified chemical in the aged blended and sterile pH 7 samples was 77 and 550 ng/mL at day 0, respectively. In the aged blended samples, the concentration of the notified chemical decreased to approximately 14 ng/mL after 20 days, corresponding to approximately 18% of the initial measured concentration. In the sterile pH samples, the concentration of the notified chemical remained within 5% of the Day 0 value during the 20 day test. These results indicate either that the notified chemical does not undergo hydrolysis or that the hydrolytic process is very slow under these conditions.

Dangerous Goods classification
Based on the submitted physical-chemical data in the above table the notified chemical is not classified as follows according to the Australian Dangerous Goods Code (NTC, 2007). However, the data above do not address all Dangerous Goods endpoints. Therefore, consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia, but will be imported neat as product C-4000.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	1-3	3-10	3-10	3-10	3-10

PORT OF ENTRY
Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Rohm and Haas Australia Pty. Ltd.
Plastral Pty. Ltd.

TRANSPORTATION AND PACKAGING
The imported product will be packaged in 193 kg net steel drums and transported by road to the notifier's warehouse in Sydney. At the reformulator's site, the notified chemical will be reformulated into an additive mixture containing the notified chemical at 10% that will be packaged in 25 kg polypropylene bags and stored in the reformulator's warehouse until such time that it is distributed by road to up to 10 pipe manufacturers in Melbourne, Sydney and Brisbane. The bags of additive mixture containing the notified chemical at 10% will be stored in the various pipe manufacturers' warehouses until such time that it used in the manufacture of rigid PVC pipes and related articles.

USE
The notified chemical will be used as a processing additive in the manufacture of rigid PVC pipes and related articles. The main applications of these pipes will be in areas of sewage, electrical conduit, storm water and some will be used in collection of drinking water.

OPERATION DESCRIPTION
The notified chemical will be imported by ship and transported by road to the reformulator's facility in Sydney.

Reformulation
At the reformulator's site, neat notified chemical will be manually transferred into a weighing container. The contents of the weighing container are then transferred to a 1000 litre mixing vessel, which contains PVC powder and other ingredients. The mixing vessel is closed and the contents mixed by a mechanical stirrer until the mixture is homogeneous. The resulting PVC additive compound is a free-flowing powder containing up to 10% w/w of the notified chemical. In the resulting PVC additive compound, the notified chemical has been absorbed by the porous PVC powder.

The PVC additive compound is then transferred via a piped vacuum conveying method to either an extruder hopper for conversion to granules, or directly to a hopper on the bagging line where it is packed into 25kg polypropylene bags and palletised prior to distribution to PVC moulding/extrusion companies.

Moulding/Extrusion
The PVC additive compound is manually transferred from 25kg bags into a mixing vessel, where it is mixed with PVC resin. The resulting mix is transferred via piped vacuum conveying method to the extruder hopper from where it is fed into moulding/extrusion machines. The moulded or extruded articles are cooled, and removed and stacked/packed for storage. The final concentration of the notified chemical used in PVC material is expected to be at up to 2%. However, a proportion of the notified chemical is expected to degrade during processing.

Moulding and extrusion operators may handle the PVC additive compound during transferring and cleaning operations and will handle the PVC products during the stacking/packing operation.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transportation and storage workers	10-15	1-2	10
Mixing Plant Operators	2	7	10-30
Moulding/Extrusion Plant Operators	20-40	7	20-50

EXPOSURE DETAILS

Worker exposure to the notified chemical in neat form during the importation, transport and storage is not expected, except in the unlikely event of an accident where the packaging may be breached.

At the reformulation sites where the notified chemical is converted to granules, workers may be exposed to the notified chemical via dermal, ocular or inhalation routes during mixing, extrusion operations, and cleaning. Although the notified chemical is in liquid form and no dust generation is expected during weighing, the notified chemical will be present at up to 10% w/w in resulting PVC additive compound, which is formed after mixing the notified chemical with other ingredients. Therefore, spillages and dust generation during mixing, cleaning, and extrusion operations may also potentially cause mechanical irritation of the eyes, skin, nose, throat and mucous membranes The notifier has indicated that standard personal protective equipments such as safety glasses, dust respirator, impervious gloves and overalls, will be worn by workers at all times during mixing and bagging operations. The notifier has also indicated that mixing equipment is adjacent to local exhaust ventilation.

During moulding/extrusion operations, workers may be exposed to the notified chemical via dermal, ocular or inhalation routes during mixing of the PVC additive compound containing notified chemical at 10% w/w with PVC resin. As PVC compound is heated at high temperature, fumes and vapours can also be generated. The notifier has indicated that standard personal protective equipments such as safety glasses, impervious gloves and overalls, will be worn by worker at all times at mixing plant and bagging operations. If dust is generated during transferring operations, operators are instructed to wear dust masks. The notifier has also indicated that local exhaust ventilation is also installed above moulding/extrusion equipment to prevent workers from breathing dust and particulates

Workers could also have dermal exposure to the notified chemical through touching pipes. As notified chemical is expected to degrades during processing, the concentration of the notified chemical will be <2%. It is also expected that workers will wear gloves during touching these pipes. Therefore, exposure is expected to be low.

Overall, considering the low concentration of the notified chemical and use of local exhaust ventilation and PPE, exposure of workers to the notified chemical is expected to be low.

6.1.2. Public exposure

Neither the imported notified chemical nor the reformulated PVC additive compound containing the notified chemical will be sold to the public. Therefore, general public will not be exposed to the notified chemical as such.

However, some of the PVC pipes containing the notified chemical will be used for the collection of drinking water associated with the installation of domestic water tanks. The general public, in this case, may be exposed to the notified chemical through the ingestion of drinking water, which has been in contact with the pipes made from the notified chemical (at up to 2%).

The notifier has provided a study investigating aqueous hydrolysis and leaching of the notified chemical (see Appendix A). In this study, PVC pipe samples and PVC plaque samples were tested to investigate the leaching of the notified chemical from these materials into tap water. PVC pipe and plaque samples were immersed in water for 2 days. Culture water was renewed every 24 hours to ensure that saturating concentrations of the notified chemical in the culture water were never achieved. The concentration of the notified chemical was below the minimum level of detection (MQL = 0.624 ppb or 0.624 µg/L); indicating that virtually none of the notified chemical had leached from the PVC. Breakdown of the notified chemical in water under some conditions cannot be ruled out, based on the effects in aged tap water in the comparative hydrolysis study. Partial decomposition of the notified polymer during processing would reduce concentration of the notified polymer in pipes. However, taking into account the low limit of detection, it is likely that minimal leaching of the notified chemical from PVC occurred in the study. The low water solubility of the notified chemical (<1mg/L) would also reduce the potential for leaching.

Therefore, based on the facts that the notified chemical is not sold to the general public as such, the concentration in pipes is low (up to 2%) and indications that there is very low potential of leaching of notified chemical from PVC pipes, exposure of general public is expected to be very low.

6.2. Human health effects assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 >2000 mg/kg bw low toxicity
Rat, acute dermal toxicity	LD50 >2000 mg/kg bw low toxicity
Rat, acute inhalation toxicity	not determined
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro–Human Blood Lymphocytes	non genotoxic
Rat, repeat dose oral toxicity – 28 days.	NOAEL 723 mg/kg/day for males, 898 mg/kg/day for females
Developmental effects	NOEL >1000 mg/kg bw/day

Toxicokinetics, metabolism and distribution.
No data were provided to assess toxicokinetics, metabolism and distribution of the notified chemical. Based on high partition coefficients (log Pow 7.59; mol wt >500 Da) and the lack of systemic effects in the acute dermal toxicity study, dermal absorption of the notified chemical is expected to be limited.

Acute toxicity.
The notified chemical is of low acute oral and dermal toxicity, with oral and dermal LD50 of being >2000 mg/kg bw. No acute inhalation toxicity data was provided.

Irritation and Sensitisation.
The notified chemical was slightly irritating to the skin and eyes of rabbit. It was not a skin sensitiser, based on the results of the LLNA in mice.

Repeated Dose Toxicity (sub acute, sub chronic, chronic).
In a subacute oral toxicity study, rats were fed 300, 1000 and 10000 ppm of the notified chemical for 28 days. There were no deaths and no test substance-related effects on clinical observations, body weights, food consumption, functional observational battery, locomotor activity, ophthalmic examinations or oestrous or spermatogenic evaluations. There were also no test substance-related effects on haematology parameters and clinical chemistry in any treated group females or 300 and 1,000 ppm males. Higher total serum cholesterol (up 23.6%) was observed in the 10,000 ppm males, which was considered to be test substance-related.

The No Observed Adverse Effect Level (NOAEL) was established as dietary concentration of 10,000 ppm

(approximately 723 mg/kg/day for males, 898 mg/kg/day for females), based on the conclusion that minimal level of response in the liver and thyroid of the rats in the 10,000 ppm group, were an adaptive response and not manifestation of overt toxicity.

Mutagenicity.
The notified chemical was found to be negative in a bacterial reverse mutation test, and also showed no evidence of clastogenicity in a Mammalian Chromosome Aberration Test, using human blood lymphocytes. Therefore, based on the available information, the notified chemical is unlikely to be genotoxic.

Carcinogenicity:
No data were provided to assess the potential for carcinogenicity of the notified chemical.

Toxicity for reproduction:
No data were provided to assess the potential for reproductive toxicity. However, in a developmental study, the No Observed Effect Level (NOEL) was established as >1000 mg/kg bw/day, based on no evidence of treatment-related developmental or maternal toxicity at the highest dose tested.

Health hazard classification
Based on the data provided, the notified chemical is not classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety
The primary risk to workers from exposure to the notified chemical is slight skin and eye irritation.

There is a potential for dermal and ocular exposure to the notified chemical during various processes involving the notified chemical such as importation, transport, storage, reformulation, moulding/extrusion, cleaning, maintenance, and handling PVC pipes and related articles containing the notified chemical. Exposure during importation, transport and storage is not expected, except in an accident where the packaging may be breached. The highest potential for exposure to workers is during reformulation where workers will be handling neat notified chemical. Although the notified chemical has low volatility and direct inhalation is unlikely, there is some potential for inhalation of the PVC additive compound containing the notified chemical if dust is generated during various operations.

The potential risk of irritation and inhalation of dust to workers will be minimised by the use of safe work practices and engineering controls such as local exhaust ventilation. The use of standard PPE such as safety glasses, dust respirator, impervious gloves and overalls during mixing and bagging and use of safety glasses, impervious gloves and overalls during moulding/extrusion will also be practised. Furthermore, the risk to workers of handling PVC pipes containing the notified chemical is also low, due to the low concentration of the notified chemical being present in the PVC pipes and the fact that the notified chemical is being bound within the PVC polymer matrix and is not bioavailable. Therefore, based on the use of safe work practices, PPE and local exhaust ventilation, the risk of exposure to workers handling the notified chemical is not considered to be unacceptable.

Although the neat notified chemical is a liquid, nuisance dust could be generated during reformulation and during handling of PVC additive compound. Therefore, an exposure standard for nuisance dust should be maintained below the NOHSC exposure standard of 10 mg/m^3.

6.3.2. Public health
The notified chemical and the reformulated PVC additive compound containing the notified chemical will not be sold to the general public. Therefore, general public will not be exposed to the notified chemical as such.

However, some of the PVC pipes containing the notified chemical will be used for the collection of drinking water associated with the installation of domestic water tanks. The general public, may be exposed to the notified chemical through the ingestion of drinking water, which has been in contact with the pipes made from the notified chemical (at up to 2%), if the notified chemical is leached from pipes containing it.

However, the results of a leaching study investigating aqueous hydrolysis and leaching of the notified chemical, indicated that the concentration of the notified chemical was below the minimum level of detection (MQL = 0.624 ppb or 0.624 µg/L). Therefore, negligible amounts of the notified chemical are expected to be leached from the PVC pipes. This is due to the low concentration of the notified chemical being present in the PVC pipes and that the notified chemical being bound within the PVC polymer matrix and is not bioavailable.

Furthermore, the notified chemical is considered to be of low hazard, based on relatively high NOAEL of 723 mg/kg/day for males and 898 mg/kg/day for females, established in the 28 day study, and the lack of any developmental effects and the establishment of a developmental or maternal toxicity NOEL of >1000 mg/kg bw/day. Therefore, the risk of systemic effects to the general public from repeated exposure, based on the assumption of very low potential of leaching of the notified chemical from PVC pipes, is not considered to be unacceptable.

A quantitative assessment of consumption of drinking water, as a potential source of exposure if the notified chemical is leached from pipes containing it, was also undertaken. The Australian Drinking Water Guidelines (Chapter 6, NHMRC, 2004) provide information on deriving of guideline values for chemicals, including for chemicals that can be leached from pipes and fittings, using the following formula and parameters:

$$\text{Guideline value} = \frac{\text{Animal dose} \times \text{Human weight} \times \text{Proportion of intake from water}}{\text{Volume of water consumed} \times \text{Safety factor}}$$

Human weight = 60 kg
Proportion of intake from water = 20%
Volume of water consumed = 2 L/day
Animal dose = NOAEL of 723 mg/kg/day for males, established in the 28 day study in rats with the notified chemical
Safety factor = 1000 (Variation between animals (x10) and species (x10) and NOAEL was from a subchronic study (x10)

Using the above parameters, a guideline value of 4.3 mg/L was calculated for the notified chemical in drinking water. The guideline value is the concentration that is based on the present knowledge, does not result in any significant risk to the health of the consumers over a lifetime of consumption and is consistent with water of great quality.

As there were no residues detected in the leaching study (< detection limit of 0.624 µg/L) and based on the estimated guideline value of 4.3 mg/L, the notified chemical incorporated in pipes at 2% will not expected to cause a concern for public health.

Therefore, based on the facts that the notified chemical is not sold to the general public as such, there is expected to be low potential of leaching of the notified chemical from PVC pipes, the notified chemical is present at a low concentration in the PVC pipes, and that the notified chemical is expected to be of low hazard, the risk to the general public is not considered to be unacceptable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

During reformulation and moulding, potential release of the notified chemical to the environment may occur from spills (estimated to be a maximum of 1% of the annual import volume of notified chemical), cleaning of reformulation and moulding equipment (<1%) and residue in empty import or product containers (<2%). Spills and residues are expected to be collected and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

The notified chemical will be moulded into rigid PVC pipes and related articles. During the extrusion process the notified chemical will irreversibly bind to the inert PVC polymer matrix. The moulded articles will be used in a variety of sewage and storm water plumbing applications.

RELEASE OF CHEMICAL FROM DISPOSAL
The notified chemical will share the fate of the PVC articles into which it is irreversibly bound. The PVC articles containing the notified chemical are expected to be disposed of to landfill at the end of their useful life.

7.1.2 Environmental fate

The vast majority of the imported quantity of the notified chemical will be incorporated into PVC articles. The notified chemical will be irreversibly bound into the inert PVC polymer matrix, and in this form is not expected to be mobile or bioavailable. Additionally, leaching studies indicate that the notified chemical is not likely to leach from the PVC articles.

Notified chemical disposed of to landfill as wastes and residues from reformulation are expected to be immobile, due to the strong sorption of the notified chemical to soils. The notified chemical is readily biodegradable, as testing in accordance with the guidelines of OECD 301D indicates that >60% degradation occurred within a 10-day window when nominal concentrations of the notified chemical are low (2 mg/L). Whilst another biodegradability study only achieved >48% degradation over 28 days (OECD 301B), the differences in biodegradation results could be attributed to the origin of the inoculum and/or the increased nominal test substance concentration (19.9 mg TOC /L) and the limiting effect on the rate of hydrolysis due to the low water solubility of the notified chemical. As only limited and diffuse release of the notified chemical to the environment is likely when the notified chemical is used as proposed, the results and classification of the biodegradability test OECD 301D results are considered more appropriate for the biodegradability classification of the notified chemical in this case.

The notified chemical is not expected to be bioaccumulative, as although the partition coefficient is high (log K_{OW} = 7.59) the estimated bioconcentration factor is low when corrected for size/diameter, ionisation and potential metabolism by fish the bioconcentration factor was reduced (log BCF_{corr} = 0.8) (Dimitrov et al., 2005).
In landfill, the notified chemical will degrade biotically and abiotically to form water and oxides of sulfur and carbon.

For the details of the environmental fate studies, refer to Appendix C.

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 is not expected based on its reported use pattern.

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on filtered water accommodated fractions (filtered WAFs) of 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	96 h LC50 >0.508 mg/L*	Not harmful to fish up to the limit of its solubility in water
Daphnia Toxicity	48 h EC50 >0.290 mg/L*	Not harmful to aquatic invertebrates up to the limit of its solubility in water
Algal Toxicity	96 h E_rC50 >0.225 mg/L*	Not harmful to algae up to the limit of its solubility in water
Inhibition of Bacterial Respiration	0.5 h IC50 >1000 mg/L	Not harmful to microbial respiration

*Mean measured concentration

Under the Globally Harmonised System of Classification and Labelling of Chemicals (United Nations, 2009) the notified chemical is not harmful to fish, aquatic invertebrates, and algae, up to the limit of its solubility in water. As the notified chemical has been demonstrated to be biodegradable, it has therefore not been classified for long-term effects.

7.2.1 Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has not been calculated as ecotoxicologically significant release of the notified chemical to the aquatic compartment is not expected based on its reported use pattern.

7.3. Environmental risk assessment

The notified chemical will be used as a processing additive in PVC pipe and related articles. The majority of the notified chemical will be irreversibly bound within the inert polymer matrix and will not be mobile or bioavailable. On the basis of the low toxicity to aquatic organisms and the very low potential for exposure to the aquatic environment, the notified chemical is not expected to pose a risk to the environment when used as proposed.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

Based on the data provided, the notified chemical is not classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

Human health risk assessment

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

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

Environmental risk assessment

On the basis of the reported use pattern, the notified chemical is not expected to pose a risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced :
  - Local exhaust ventilation where dust is present

- Employers should implement the following safe work practices to minimise occupational exposure to the notified chemical during reformulation and handling of additive compound:
  - Avoid contact with skin and eyes
  - Do not inhale dust

- An exposure standard for nuisance dust should be maintained below the NOHSC exposure standard of 10 mg/m^3 during reformulation and handling of additive compound.

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

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

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

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

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(2) of the Act; if
- the function or use of the chemical has changed from processing additive (at up to 2%) in the manufacture of rigid PVC pipes and related articles, in the areas of sewage, electrical conduit, storm water and in collection of drinking water, or is likely to change significantly;
- the amount of chemical being introduced has increased from ten tonnes/annum, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

No additional secondary notification conditions are stipulated.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point -48.2°C.

Method ASTM method D 1015-99 (3).
Remarks Because the notified chemical was a liquid at room temperature, "freezing point" was determined instead of "melting point."
Test Facility ABC Laboratories, Inc. (2007a)

Boiling Point 213.8 °C at 101.3 kPa

Method OECD TG 103 Boiling Point.
U.S. EPA Product Properties Test Guidelines, OPPTS 830.7220.
Remarks A Mettler FP900 Thermosystem consisting of a Mettler FP81HT MBC Cell attached to a Mettler FP90 Central processor was used to determine the boiling point of the test substance.
Test Facility ABC Laboratories, Inc. (2007b)

Density 1013 kg/m^3 at 20 °C

Method U.S. EPA Product Properties Test Guidelines, OPPTS 830.7300.
Remarks The relative density and density of C-4000 were determined using a 25 mL glass pycnometer at 20 °C.
Test Facility ABC Laboratories, Inc. (2007c)

Vapour Pressure <.00235 x 10^{-8} kPa at 25°C

Method OECD TG 104 Vapour Pressure.
U.S. EPA Product Properties Test Guidelines, OPPTS 830.7950
Remarks Determined by the Gas Saturation Method.
Test Facility ABC Laboratories, Inc. (2007d)

Water Solubility <1.37 × 10^{-4} g/L at 20°C

Method Modification of OECD Guideline 105 and OPPTS Guideline 830.7840.
Remarks Column elution method. Water was circulated through glass beads dosed with the test substance over a period of four days (20°C) to achieve a saturated solution. Analysis by LC-MS/MS indicated that solubility values ranged from 9.56 to 137 ng/mL, and therefore the solubility of the test substance is less than the highest solubility determined (i.e.<137 ng/mL).
No light scattering or undissolved particles were observed in test samples, confirming that the solutions were clear and no colloidal matter was present. The measured pH ranged from 6.68 to 8.04.
Test Facility ABC Laboratories, Inc (2007e)

Hydrolysis as a Function of pH $t_{½}$ ≥45 days

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$ days*
4	25	45
7	25	147
9	25	85

Remarks There were no significant deviations to protocol. As there were no reported circumstances that would bias or affect the integrity of these results, this study is considered to be valid.
Test Facility ABC Laboratories, Inc (2009)

Adsorption/Desorption
– main test log K_{OC} = 4.8 to 5.3 at 25°C

Method OECD TG 106 Adsorption - Desorption Using a Batch Equilibrium Method.

Soil Type	*Organic Carbon Content (%)*	*CEC (cmol(+)/kg)*	*Adsorption/ Desorption (%)*	*log K_{OC}*
loam	1.26	17.4	100/0	5.2
clay	2.87	29.8	100/0	4.8
clay loam	0.994	10.6	100/0	5.3

Remarks No significant deviations from protocol were reported. The loam, clay and clay loam soils were sampled from Jiangsu, Jilin and Jiangxi, respectively. The pH of the soil samples and the soil classification system were not reported, but the soil characterisation parameters are not in accordance with the FOA and US system. The concentration analyses were conducted by HPLC and the percentage of mass balance for the loam, clay and clay loam soils was determined to be 87.3-88.4%, 81.2-83.8% and 91.4-92.9%, respectively. Based on a 5 g soil sample size and 100 mL aqueous phase in contact with the soil, K_d was calculated to be 2000. The test substance is therefore immobile in soil (McCall et al., 1980).

Test Facility Nanjing Institute of Sciences, SEPA (2007a)

Flash Point 90.5 ± 0.6°C

Method EC Directive 92/69/EEC A.9 Flash Point.
U.S. EPA Product Properties Test Guidelines, OPPTS 830.6315

Remarks A Pensky-Martens closed cup flash tester was used with a heating block equipped with a propane tank and rubber tubing to deliver the propane fuel which produced the flame for the flash point test.

Test Facility ABC Laboratories, Inc. (2007b)

Oxidizing Properties No significant oxidizing or reducing action, or chemical incompatibility with water, KMnO4, NH4H2PO4, turpentine, or zinc.

Method U.S. EPA Product Properties Test Guidelines, OPPTS 830.6314

Remarks No significant temperature change (greater than ± 5°C) occurred when the test substance, C-4000, was mixed initially, after 10 minutes, and after 24 hours with water, KMnO4, NH4H2PO4, turpentine, or zinc, indicating no significant oxidizing or reducing action, or chemical incompatibility with these substances.

Test Facility ABC Laboratories, Inc. (2007g)

Thermal Stability Testing C-4000 was not stable at 55°C

Method OECD TG 113 Screening Test for Thermal Stability and Stability in Air.

Remarks Samples of C-4000 were analyzed by LC-MS/MS after 14 days of storage at 55°C. Control samples were analyzed after 14 days at room temperature. The mean recovery of the C-4000 test samples stored at 55°C was 68.8%. The mean recovery of the C-4000 control samples stored at room temperature was 119.6%. The significant difference in the recovery percent of the test samples versus the control samples indicated that C-4000 was not stable at 55°C.

Test Facility ABC Laboratories, Inc. (2007f)

Comparative Aqueous Hydrolysis and PVC Leaching Investigations

Aims The aims of the study were to: (a) to investigate the aqueous hydrolysis of the notified chemical in aged blended water and sterile pH 7 buffer (2) to investigate the leaching of the notified chemical from PVC samples and PLV plaques into tap water.

Method Hydrolysis Investigation:
Two matrices, aged blended water and pH 7 buffer, were used. The aged blended water was an aged laboratory freshwater prepared by blending naturally hard well water with

well water that was demineralised by reverse osmosis, and then biologically aged (held in a tank containing aquatic organism).

A 0.099 mL volume of the stock solution of notified chemical at 101 mg /mL was added to two 2-L glass aspirator bottle to prepare the notified chemical treatments, one containing 1L of pH 7 buffer, and the other containing 1L of aged blended water. Aspirator bottles were processes as per the procedure. Samples were taken in duplicate at initiation, then following 1, 2, 5, 7, 12, and 20 days of incubation at 25°C. Samples were further processed and analysed.

PVC Leaching Investigation:
Two matrices. PVC pipe and PVC plaque, were tested to investigate the leaching of the notified chemical from these materials into tap water.

For extraction, PVC pipes were placed into polypropylene bottles, and 10 mL of tap water (pH = 7.4) was added to each bottle. The samples were capped and shaken for 24 hours. The water was then decanted into Nalgene bottles. A second 10 mL aliquot of tap water was added to the samples and samples were again shaken and decanted to form a second sample. The samples were analysed directly, and were also diluted by combining a 5-mL aliquot of methanol with a 4-mL aliquot of the sample (1:1 dilution). A tap water blank was also analysed.

PVC plaques samples were analysed in the same manner as PVC pipes stated above, except that only 6.5 mL of tap water was added for the first extraction, and a tap water blank was not re-analysed.

Results

Hydrolysis Investigation:

- At Day 0, the average amount of the notified chemical in the aged blended and sterile pH 7 samples was 77 and 550 ng/mL, respectively.
- In the aged blended samples, the concentration of the notified chemical decreased to approximately 14 ng/mL after 20 days, corresponding to approximately 18% of the initial measured concentration.
- In the sterile pH samples, the concentration of the notified chemical remained within 5% of the Day 0 value during the 20 day test. These results indicate either that the notified chemical does not undergo hydrolysis or that the hydrolytic process is very slow under these conditions.

PVC Leaching Investigation:

- No peak above the minimum quantifiable limit (MQL) was detected in the testing.

Conclusions

Under the condition noted in these tests for the notified chemical, the data support four conclusions:

- Aqueous concentrations of the notified chemical in buffered, sterile water at neutral pH and 25°C did not decline, as a half-life of 300 days was calculated.
- Aqueous concentration of the notified chemical in non-sterile, aged blended water at 25°C declined rapidly, as a half-life of 9.3 days was calculated.
- The results of hydrolysis investigation would indicate that the decline of notified chemical may be related to biological pathways and not necessarily hydrolysis.
- Aqueous concentration of the notified chemical in tap water containing PVC pipe samples [1x6 cm] were less than the MQL (0.624 ppb or 0.624 µg/L) after two 24 hour periods, with blank tap water added at the beginning of each period.
- Aqueous concentration of the notified chemical in tap water containing PVC plaque samples [1x2.4x0.3 cm] were less than the MQL (0.624 ppb or 0.624 µg/L) after two 24 hour periods, with blank tap water added at the beginning of each period.

Test Facility

ABC Laboratories, Inc. (2008a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (>94%)
METHOD	OECD TG 425 Acute Oral Toxicity: Up-and-Down Procedure. EPA Health Effects Test Guidelines, OPPTS 870.1100 December 2002
Species/Strain	Rat/Wistar albino
Vehicle	None
Remarks - Method	Initially, a single female rat was dosed orally with the notified chemical at a dose of 300 mg/kg bw. Since the animal survived, additional female animals were dosed, one at a time, by a single ordered dose progression, as follows: 550, 1750, 2000, 2000, 2000, 2000, 2000 mg/kg bw. The rats were observed at ½, 1, 2 and 4 hours post dose and once daily thereafter for 14 days for toxicity and pharmacological effects. The Estimated LD_{50} and 95% Confidence Limits were calculated using AOT425 Statistical Program provided by the EPA.
RESULTS	
LD50	>2,000 mg/kg bw
Signs of Toxicity	All animals survived at 300, 550, 1750, or 2000 mg/kg as a single oral dose provided. There were no abnormal physical signs noted during the observation period.
Effects in Organs	Four animals received 300 and 550 mg/kg bw notified chemical appeared normal at necropsy. Mottled kidneys and adrenals appearing larger than normal were noted in the rat at 1750 mg/kg bw. Red areas on the thymus or a large red spot on the thymus were noted in two animals dosed at 2000 mg/kg bw. A red capsule (~2mm) was found attached to abdominal fat in the animal dosed at 200 mg/kg; this finding does not appear to be due to the toxic effects of the test article. A bifurcated spleen was also noted in this same animal, however, this abnormality is probably not due to the toxic effects of the test article.
CONCLUSION	The notified chemical is of low acute toxicity via the oral route.
TEST FACILITY	MB Research Laboratories (2007a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical (>94%)
METHOD	OECD TG 402 Acute Dermal Toxicity. EPA Health Effects Testing Guidelines, OPPTS Series 870.1200, August 1998.
Species/Strain	Rat/Wistar albino
Vehicle	Nil
Type of dressing	Occlusive
Remarks - Method	No significant protocol deviations. Five healthy male and female rats were dosed dermally with the notified chemical at 2000 mg/kg bw. The test article was kept in contact with the skin for 24 hours. Animals were observed for toxicity and pharmacological effects at 1, 2 and 4 hours after application and once daily thereafter for 14 days.
RESULTS	

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	No dermal effects were observed in the males. Erythema, brown areas and flaking skin were noted in the females through Day 5. No abnormal dermal effects were observed in the females after Day 5.
Signs of Toxicity - Systemic	All ten animals survived the 2000 mg/kg bw dermal application of the notified chemical. All animals had normal body weight gains except that one female lost body weight from Day 7 to Day 14.Instances of diarrhoea, wetness and soiling of the anogenital area and few faeces were observed during the study.
Effects in Organs	Necropsy revealed slightly mottled kidneys in one female. All other animals appeared normal at necropsy.

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

TEST FACILITY MB Research Laboratories (2007b)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical (>94%)

METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EPA Health Effects Testing Guidelines, OPPTS Series 870.2500, August 1998
Species/Strain	Rabbit/New Zealand White
Number of Animals	2 males and 1 female
Vehicle	Nil
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.66	0	0	1	48 hours	0
Oedema	0	0	0	0	0	0

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

Remarks - Results There were no abnormal physical signs noted during the observation period. Two animals lost weight during the study. Body weight changes were normal in the remaining animal.

CONCLUSION The notified chemical is slightly irritating to the skin.

TEST FACILITY MB Research Laboratories (2007c)

B.4. Irritation – eye

TEST SUBSTANCE Notified chemical (>94%)

METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EPA Health Effects Testing Guidelines, OPPTS Series 870.2400, final guideline, August 1998.
Species/Strain	Rabbit/New Zealand White
Number of Animals	2 males and 1 female
Observation Period	72 hours
Remarks - Method	The treated and control eye of each rabbit was washed with saline following the 24-hour observation interval for approximately one minute using a volume and velocity of flow which did not cause injury.

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	0	0	0	0	0
Conjunctiva: chemosis	0	0.33	0.66	2	24	0
Conjunctiva: discharge	0	0.33	0.33	1	24	0
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results There were no abnormal physical signs noted during the observation period.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY MB Research Laboratories (2007d)

B.5. Repeat dose toxicity

TEST SUBSTANCE Notified chemical (>85%)

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
OPPTS Guideline 870.3050

Species/Strain Rat/Crl:CD(SD)
Route of Administration Oral – diet
Exposure Information Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: None
Vehicle
Remarks - Method No significant deviations from the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
Control (0 ppm)	10 M & 10 F	0	0
low dose (300 ppm)	10 M & 10 F	22 (males), 26 (females)	0
mid dose (1000 ppm)	10 M & 10 F	77 (males), 84 (females)	0
high dose (10,000 ppm)	10 M & 10 F	723 (males), 898 (females)	0

Mortality and Time to Death
There was no death during the study.

Clinical Observations
There were no test substance-related effects on clinical observations, body weights, food consumption, functional observational battery, locomotor activity, ophthalmic examinations or oestrous or spermatogenic evaluations.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
There were no test substance-related effects on haematology parameters. There was no test substance-related effects in clinical chemistry in any test substance-treated group females or the 300 and 1,000 ppm males. Higher total serum cholesterol (up 23.6%) was observed in the 10,000 ppm males. As the mean cholesterol (68 mg/dL) in the 10,000 ppm group males was higher than the mean cholesterol (52 mg/dL) observed in the WIL Historical Reference Range Values for 9 to 12 weeks old male rats, it was considered to be test substance-related.

Effects in Organs

Male and female rats in the 10,000 ppm group had higher absolute and relative to body liver weights, but the differences were statistically significant only on a relative basis. There was minimal enlargement of centrilobular hepatocytes due to cytoplasmic hypertrophy of a few 10,000 ppm group males and females. The liver cells were enlarged due to a minimal increased amount of dense eosinophilic cytoplasm, which resulted in a more prominent appearance of the central zones of the hepatic lobules. This minimal hepatocellular hypertrophy could correlate with the minimal, but statistically significant increase in liver weights when expressed as the liver to body weight ratio and was considered to be a test substance-related effect. However, the mean absolute and relative liver weights were within the range of WIL Historical Control values and were not considered adverse. Thus, the liver changes were considered to be an adaptive response, in contrast to toxicity.

Minimal or mild hypertrophy and hyperplasia of the follicular epithelial cells of the thyroid was observed in animals of all groups, including controls, with a higher incidence in the high dose group. Although this thyroid change occurred in animals of other groups without hepatocellular hypertrophy, the slight increased incidence of the thyroid follicular epithelial hyperplasia and hypertrophy, particularly in the 10,000 ppm group females, may be related to the hepatocellular hypertrophy in the animals of this group. As stated above, the mean absolute and relative liver weights were within the range of WIL Historical Control values and were not considered adverse. Thus, based on types of responses observed, the minimal level of severity, and the incidence data, the liver and thyroid changes were considered to be an adaptive response in this species, rather than a manifestation of overt toxicity.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as dietary concentration of 10,000 ppm (approximately 723 mg/kg bw/day for males, 898 mg/kg bw/day for females), based on the conclusion that minimal level of response in the liver and thyroid of the rats in the 10,000 ppm group, were an adaptive response and not manifestation of overt toxicity.

TEST FACILITY	WIL Research Laboratories, LLC (2009a)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical (>94%)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EPA Health Effects Testing Guidelines, OPPTS Guideline 870.5100, 1998. Plate Incorporation Method
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Liver fraction (S9 mix) from rats pretreated with Aroclor
Concentration Range in Main Test	a) With metabolic activation: 50, 150, 500, 1500 & 5000 µg/plate b) Without metabolic activation: 50, 150, 500, 1500 & 5000 µg/plate
Vehicle	DMSO
Remarks - Method	No significant protocol deviations. In the initial toxicity-mutation assay (Test 1), the dose levels tested were 1.5, 5, 15, 150, 500, 1500 & 5000 µg/plate. In the confirmatory mutagenicity assay (Test 2), the dose levels tested were 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	Not observed up to 5000	Not performed	≥500*	Negative
Test 2	Not performed	Not observed up to 5000	≥500 (*Salmonella* strains)* ≥1500 (WP2uvrA strain)*	Negative
Present				
Test 1	Not observed up to 5000	Not performed	1500*	Negative
Test 2	Not performed	Not observed up to 5000	≥500 (*Salmonella* strains)* ≥1500 (WP2uvrA strain)*	Negative

*Non-interfering precipitate. In Test 2, with & without metabolic activation, only 3 replicate plates had interfering precipitate at 5000 µg/plate among all the strains tested.

Remarks - Results: In the two tests, neither an increase in the number of revertant colonies or a dose-related response was observed with or without metabolic activation. The positive controls (2-nitrofluorene, 2-aminoanthracene, sodium azide, methyl methanesulfonate) showed a distinct increase in induced revertant colonies.

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

TEST FACILITY: BioReliance (2007)

B.7. Genotoxicity – in vitro

TEST SUBSTANCE: Notified chemical (>85%)

METHOD: OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
US EPA Health Effects Test Guidelines, OPPTS 870.5375 (1998)

Species/Strain: Human
Cell Type/Cell Line: Human Peripheral Blood Lymphocytes
Metabolic Activation System: Liver fraction (S9 mix) from rats pretreated with Aroclor
Vehicle: DMSO
Remarks - Method: No significant protocol deviations.
In the preliminary toxicity assay, the maximum dose tested was 5000 µg/mL. Visible precipitate was observed in treatment medium at dose levels ≥500 µg/mL and dose levels ≤150 µg/mL were insoluble in treatment medium at the beginning and conclusion of the treatment period. At the conclusion of the treatment period, haemolysis was observed at dose levels ≥500 µg/mL in the S9-activated 4-hour exposure group. Substantial toxicity (defined as at least 50% reduction in mitotic index relative to the solvent control) was not observed at any dose level in any of the three treatment groups. Based on these findings, the doses chosen for the chromosome aberration assay ranged from 62.5 to 1000 µg/mL for all three treatment groups. Mitomycin C and cyclophosphamide were used as positive controls.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 62.5, 125*, 250*, 500*, 1000, MMC*	4 h	20 h
Test 2	0*, 62.5, 125*, 250*, 500*, 1000, MMC*	20 h	20 h
Present			
Test 1	0*, 62.5, 125*, 250*, 500*, 1000, CP*	4 h	20 h
Test 2	Not performed		

*Cultures selected for metaphase analysis.
MMC=Mitomycin C, CP=Cyclophosphamide

RESULTS: An additional dose level of 62.5 µg/mL was tested as a safeguard against excessive toxicity at higher dose levels but was not required for microscopic examination. Dose level of 1000 µg/mL was not analysed due to excessive precipitation.

No relevant increase in the number of cells containing numerical chromosomal aberrations was observed in the absence and the presence of metabolic activation.

The frequencies of chromosome aberrations in the positive and the solvent controls fulfilled the requirements for a valid test.

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	>5000	>1000	1000	Negative
Test 2	>5000	>1000	1000	Negative
Present				
Test 1	>5000	>1000	1000	Negative
Test 2	-	-	-	-

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

TEST FACILITY BioReliance (2008)

B.8. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified chemical (>94%)

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain Mouse/CBA/Ca

Vehicle Acetone:olive oil (4:1)

Remarks - Method No significant protocol deviations.
Following a preliminary screening test, three groups, each of five animals, were treated with 50 µl (25 µl per ear) of the undiluted test material or the test material as a solution in acetone:olive oil (4:1) at concentrations of 50% or 25% v/v. A further group of five animals was treated with vehicle only.

RESULTS

Concentration (% v/v) in vehicle	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	593.89	1.00
25% in vehicle	955.95	1.61
50% in vehicle	1462.81	2.46
100 (undiluted)	1093.86	1.84
Positive Control (α-Hexylcinnamaldehyde)		
5% in vehicle	Not available	2.50
10% in vehicle	Not available	4.03
25% in vehicle	Not available	9.13

Remarks - Results There were no deaths. No signs of systemic toxicity were noted in the test or control animals during the test.

CONCLUSION There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY SafePharm Laboratories Ltd (2007)

B.9. Developmental toxicity

TEST SUBSTANCE Notified chemical (>85%)

METHOD OECD Guideline 414, Prenatal Developmental Toxicity Study
OPPTS 870.3700, Prenatal Developmental Toxicity Study

Species/Strain	Rat/Crl:CD(SD)
Route of Administration	Oral – gavage
Exposure Information	Exposure days: gestation days 6 though 19
Vehicle	Corn oil
Remarks - Method	No significant protocol variation.

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
Control	25	0	0
Low dose	25	30	0
Mid dose	25	180	0
High dose	25	1000	0

Mortality and Time to Death
There was no mortality during the study. However, one female in the control group was euthanized in extremis following body weight loss and minimal food consumption.

Effects on Dams
There were no test substance-related internal findings at any dosage level. There were also no adverse clinical findings noted for females in any group at the daily examinations, at the time of dosing or approximately 1 hour following dose administration. Mean maternal body weights, body weight gains and food consumption were also unaffected by test substance administration.

Effects on Foetus
Intrauterine growth and survival of foetuses were unaffected by test substance administration at all dosage levels. No test substance-related foetal morphological malformations or developmental variations were noted for any foetus in this study.

CONCLUSION
The No Observed Effect Level (NOEL) was established as >1000 mg/kg bw/day in this study, based on no evidence of treatment-related developmental or maternal toxicity at the highest dose tested.

TEST FACILITY WIL Research Laboratory, LLC (2009b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I)
Inoculum	Secondary effluent from a domestic wastewater treatment plant
Exposure Period	28 day
Auxiliary Solvent	None
Analytical Monitoring	Not reported
Remarks - Method	In accordance with the guidelines above, the dissolved oxygen uptake of inoculated medium containing the test substance (2 mg/L) in completely filled closed bottles stored in the dark was measured over 28 days at 20°C. A reference control (aniline, 2 mg/L) and toxicity control (aniline and test substance, 2mg/L) were run in parallel. Biodegradation was determined by measuring the oxygen depletion in the medium, corrected for the blank, and expressed as a percentage of the theoretical oxygen demand (ThOD: 4.3 mg/L).

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	88.0	7	85.2
11	98.5	11	87.2
28	98.5	28	96.6

Remarks - Results	Study summary provided only. No deviations to protocol were reported. The reference control achieved greater than 60% degradation within 14 days, thereby verifying that the microbial inoculum was viable and active. The toxicity test achieved greater than 25% degradation (90%) within 14 days, and therefore confirms that the test substance is not inhibitory to the test micro-organisms. All other acceptability criteria were satisfied, thus validating the test. The test substance attained greater than 60% degradation within a 10-day window and is considered to be readily biodegradable under the conditions of the test.
CONCLUSION	The notified chemical is readily biodegradable
TEST FACILITY	Nanjing Institute of Environmental Sciences, SEPA (2007b)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Notified chemical (.94%)
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sludge from a domestic sewage wastewater treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	The guidelines were modified to trap evolved CO_2 with 0.2 *N* KOH solution for subsequent inorganic carbon analysis (Tekmar-Dohrman Phoenix 8000 TOC analyser).
Remarks - Method	The production of CO_2 of inoculated medium containing the test substance (nominally 19.9 mg TOC/L) was measured over 28 days at

23.5 to 33.9°C and pH 7.29 to 7.58. A reference control (sodium acetate, 20 mg TOC/L) was run in parallel. The percentage biodegradation is expressed as a ratio of evolved carbon dioxide, corrected for the blank, to the initial theoretical carbon added as test substance.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	11.1	6	66.6
10	30.9	10	76.2
20	46.0	20	77.8
28	48.4	28	79.9

Remarks - Results

The protocol specifies that the temperature should range no more than 22 ± 2°C. However, the mean and standard deviation of the temperature measurements was 23.8 ± 0.5°C, and the temperature spiked as high as 33.9°C for 5 h and 26.2°C for 20 h. As the periodic average was reported to be within the protocol specified range and the time the temperature was out of the specified range was not significant, this protocol deviation is not expected to affect the integrity of the study.
The reference control achieved greater than 60% degradation within a 10-day window, thereby verifying that the microbial inoculum was viable and active.
The test substance did not achieve the pass level of 60% degradation within a 10-day window of the test duration and is therefore not considered to be readily biodegradable under the conditions of this test.

CONCLUSION The notified chemical is not readily biodegradable

TEST FACILITY ABC Laboratories, Inc (2007h)

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 *Oncorhynchus mykiss* (Rainbow trout)
Exposure Period 96 hours
Auxiliary Solvent Acetone (0.1 mL/L water)
Water Hardness 132 mg $CaCO_3$/L
Analytical Monitoring LC-MS/MS was used for the determination of the concentration of the test substance in the test solutions.
Remarks – Method After a range-finding test, a definitive limit test was conducted with filtered water accommodated fractions (filtered-WAFs), due to the low water solubility of the notified chemical, at a nominal loading rate of 10 mg/L.
The notified chemical (1 g) was dissolved in acetone (10 mL) to prepare the primary standard. The primary standard was diluted with water to achieve the loading rate of 10 mg test substance/L. The test medium was stirred for 19 h and allowed to stand for 1 h. The filtered-WAF was achieved by draining the lower aqueous phase through a medium porosity glass filter tube (discarding the first 100 mL).
Ten fish were introduced into each duplicate of the control, vehicle control (0.1 mL acetone/L water) and filtered-WAF. Over a period of four days under static conditions, the fish were observed daily for mortality and sub-lethal effects. Test conditions were: 14.3 to 15.5°C, 9.4 to10.3 mg O_2/L, pH 7.7 to 8.5.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal loading	*Actual*		*1h*	*24h*	*48h*	*72h*	*96h*
0	0	2 × 10	0	0	0	0	0
10	0.508*	2 × 10	0	0	0	0	0

*Mean measured concentration of the test substance at 0 h (0.621 mg/L) and 96 h (0.395 mg/L).

LC50	>0.508 mg/L at 96 hours.
NOEC	0.508 mg/L at 96 hours.
Remarks – Results	All test solutions appeared clear and colourless with no visible particulates, surface film, undissolved test substance or precipitate, except for the 10 mg/L filtered-WAF exhibited a slight cloudiness at test termination. After 96 hours, constant conditions were maintained and there was no observed sub-lethal effects or mortality in the control or vehicle control, thereby validating the test. There were no observed sub-lethal effects or mortality in the 0.508 mg test substance/L treatments, the highest achievable concentration tested, and therefore the 96 h LC50 is >0.508 mg/L. The 96 hour no-observed-effect concentration was the mean measured concentration of 0.508 mg/L, the highest test substance treatment with no abnormal effects or mortality.

CONCLUSION The notified chemical is not harmful to fish up to the limit of its solubility in water

TEST FACILITY ABC Laboratories, Inc (2008b)

C.2.2. Acute toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD OECD TG 203 Fish, Acute Toxicity Test – Semi-static.

Species	*Brachydanio rerio* (Zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	None reported
Water Hardness	10~250 mg $CaCO_3$/L
Analytical Monitoring	The method used to determine the concentrations of the test substance in the test media was not reported.
Remarks – Method	A definitive limit test was conducted at a nominal loading rate of 100 and 150 mg/L. A blank control and positive control (potassium dichromate) were run in parallel. Ten fish were introduced into each control and test substance test media. Over a period of four days, the fish were observed daily for mortality and sub-lethal effects. Test conditions were: 24.1 to 24.7°C, 7.1 to 7.3 mg O_2/L, pH 7.7 to 8.0.

RESULTS

Concentration mg/L	*Number of Fish*	*Mortality*				
Nominal loading		*1h*	*24h*	*48h*	*72h*	*96h*
0	10	0	0	0	0	0
100	10	0	0	0	0	0
150	10	0	0	0	0	0

LC50	>150 mg/L at 96 hours.
NOEC (or LOEC)	150 mg/L
Remarks – Results	Summary study report provided only. As there were no reported deviations to protocol and all acceptability criteria were reportedly fulfilled, the test is likely to be valid. However, as the test substance is

not expected to be soluble at the nominal concentrations used in this test, and as the extent of test substance dissolution was not discussed in the report, these results should be treated with caution.

CONCLUSION Under the conditions of this test, the notified chemical is not expected to be harmful to fish

TEST FACILITY Nanjing Institute of Environmental Sciences, SEPA (2007c)

C.2.3. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 *Daphnia* sp. Acute Immobilisation Test - Static
Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent Acetone (0.1 mL/L water)
Water Hardness 140 mg $CaCO_3$/L
Analytical Monitoring LC-MS/MS was used for the determination of the concentration of the test substance in the test solutions.
Remarks - Method After a range-finding test, a definitive limit test was conducted with filtered water accommodated fractions (filtered-WAFs – prepared as described in Section C.2.1. Acute toxicity to fish), due to the low water solubility of the notified chemical, at a nominal loading rate of 10mg/L. Four replicates of the control, vehicle control (0.1 mL acetone/L water) were prepared and each contained five daphnids. The daphnia were observed for immobilisation over two days. Test conditions were: artificial light dark cycle of 16 to 8 hours, 19.8 to 20.9°C, pH 8.3 to 8.5, 5.7 to 8.4 mg O_2/L. Daphnia unable to swim within 15 seconds of gentle agitation were considered to be immobile.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal loading	*Actual*		*24 h*	*48 h [acute]*
0	0	20	0	0
10	0.290*	20	0	0

* Mean measured concentration of the test substance at 0 h (0.335 mg/L) and 96 h (0.246 mg/L).

EC50 >0.290 mg/L at 48 hours
NOEC 0.290 mg/L at 48 hours
Remarks - Results After 48 hours, immobility or sub-lethal effects were not observed in the control and vehicle control, and other validation criteria were satisfied. Based on the mean measured concentration in the filtered-WAF treatments, the 48-hour EC50 for *Daphnia magna* exposed to the test substance was estimated to be >0.290 mg/L, the highest achievable concentration tested. The 48-hour no observed-effect concentration was the mean measured concentration of 0.290 mg/L, the highest test substance treatment with no abnormal effects or immobility.

CONCLUSION The notified chemical is not harmful to aquatic invertebrates up to the limit of its solubility in water

TEST FACILITY ABC Laboratories, Inc (2008c)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella sucapitata* (formerly *Selenastrum capricornutum*)
Exposure Period	96 hours
Concentration Range	0-10 mg/L (filtered-WAF); 0-0.371 mg/L (measured)
Auxiliary Solvent	Acetone (0.1 mL/L water)
Water Hardness	Not reported
Analytical Monitoring	LC-MS/MS was used for the determination of the concentration of the test substance in the test solutions.
Remarks - Method	After a range-finding test, algae were exposed to a control, vehicle control (0.1 mL acetone/L water) and filtered water accommodated fraction of the test material at a single nominal loading rate of 10 mg/L (filtered-WAFs – prepared as described in Section C.2.1. Acute toxicity to fish). The test mixtures were irradiated 24 h/day at pH 7.42 to 9.15 and 24 ± 2°C for a period of 96 hours. Statistical analyses were performed using SAS software to estimate NOECs by one-way analysis of variance (ANOVA) procedure and one-tailed Dunnett's test, and median effective concentrations by logistic (signmoid shaped) modelling.

RESULTS

Biomass		*Growth*	
E_bC_{50} *mg/L at 96 h*	*NOEC mg/L*	E_rC_{50} *mg/L at 96 h*	*NOEC mg/L*
>0.225*	0.225*	>0.225*	0.225*

*Geometric mean concentrations

Remarks - Results	Cell growth of the control increased 43-fold after 96 h, and test acceptability criteria were met, thereby validating this test.
CONCLUSION	The notified chemical is not harmful to algae up to the limit of its solubility in water
TEST FACILITY	ABC Laboratories, Inc (2008d)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical (≥86% purity)
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Sewage sludge from domestic sewage treatment plant
Exposure Period	30 minute
Concentration Range	10-1000 mg/L
Remarks – Method	No significant deviation to test protocol were reported.
RESULTS	
IC50	>1,000 mg/L
NOEC	Not reported
Remarks – Results	All acceptability criteria were met, thereby validating this test. The test substance showed 0, 0, 0, 18.1, and 0% inhibition at test concentrations of 10, 32, 100, 320, and 1,000 mg whole product/L. Under the conditions of the study, the estimated IC50 for the test substance was >1,000 mg whole product/L based on the nominal loading rate.
CONCLUSION	The notified chemical is not harmful to microbial respiration.
TEST FACILITY	ABC Laboratories, Inc (2008e)

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