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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Polymer in Infineum R408

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 the Environment, Water, Heritage and the Arts.

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 334-336 Illawarra Road, Marrickville NSW 2204.

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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FULL PUBLIC REPORT

Polymer in Infineum R408

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Infineum Australia Pty Ltd (ABN 24 084 881 863)
Level 2, 6 Riverside Quay
SOUTHBANK VIC 3006

NOTIFICATION CATEGORY
Standard: 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 Formula, Structural Formula, Molecular Weight, Spectral Data, Purity, Details of Impurities, Import Volume, Identity of Recipients and Information on Use.

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

NOTIFICATION IN OTHER COUNTRIES
Korea, USA, Japan, EU

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Infineum R408 (< 40% notified polymer)

MOLECULAR WEIGHT
> 1000 Da.

PURITY
> 90%

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

3. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Dark brown resinous solid

Property	Value	Data Source/Justification
Pour Point	72°C	Measured
Boiling Point	> 240°C at 101.3 kPa	Measured
Density	1080 kg/m^3 at 22°C	Measured
Vapour Pressure	1.2 x 10^{-8} kPa at 25°C	Measured
Water Solubility	< 0.001 g/L at 20°C	Measured
Hydrolysis as a Function of pH	Not measured due to low water solubility	Any hydrolysis would be very slow under environmental conditions due to the low water solubility
Partition Coefficient (n-octanol/water)	log P_{ow} > 6 at 25°C	Measured
Adsorption/Desorption	log K_{oc} > 5.4 at 25°C	Measured
Dissociation Constant	pKa = 13.1	Measured

Flash Point	112°C at 101.3 kPa	Measured
Autoignition Temperature	> 400°C	Measured
Oxidising Properties	Not expected to be oxidising	Measured
Explosive Properties	Not explosive	Measured

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

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified polymer will be imported at < 40% in a fuel additive Infineum R408 which will be blended into fuels at < 500 ppm.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 20	< 20	< 50	< 50	< 50

PORT OF ENTRY
Melbourne, Sydney, Brisbane.

IDENTITY OF RECIPIENTS
Formulators of diesel fuels.

TRANSPORTATION AND PACKAGING
The notified polymer will be imported by sea at < 40% as a component of a fuel additive Infineum R408 in bulk vessels or 205 L steel drums. The additive containing the notified polymer will be transported by road to storage facilities and customer warehouses for blending into diesel fuels which will be distributed to service stations throughout Australia.

USE
The notified polymer will be used as a fuel additive at < 500 ppm in finished diesel fuels.

OPERATION DESCRIPTION
Blending
Workers at blending sites will attach a flexible hose to the import containers and pump the fuel additive containing the notified polymer to a blend tank. The fuel additive will be blended with diesel fuel and other additives to form finished fuels. A small sample will be collected in a container via a small valve in the blending vessel. After blending, the finished fuels containing the notified polymer will be pumped into road tankers for distribution to fuel distribution outlets and service stations throughout Australia.

Use of finished fuels
At fuel distribution outlets and service stations, diesel fuels will be pumped from the road tanker to underground tanks via a hose.

Customers will pump the diesel fuels from the underground tanks via the bowser to the fuel tank of their vehicles.

5. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

EXPOSURE DETAILS
Transport
Transport and storage workers are not likely to be exposed to the notified polymer except in the case of an accident involving damage to the packaging.

Blending
Workers involved in blending operations (1-4 workers per site) may encounter dermal and ocular exposure to spills, drips and splashes of the imported fuel additive containing the notified polymer at < 40% during connection and disconnection of hoses from import containers to the blending vessel.

Workers may also encounter dermal and ocular exposure to the notified polymer at < 500 ppm in the finished diesel fuels during connection and disconnection of hoses from the blending vessel to the road tankers, quality assurance testing and maintenance on hoses and blending equipment.

Dermal, ocular and inhalation exposure is expected to be minimised by the use of ventilation, closed blending vessels and automated controls. Workers are also expected to wear personal protective equipment (PPE) such as gloves, safety glasses, overalls and safety shoes to minimise dermal and ocular exposure.

Use of finished fuels
Worker exposure to the notified polymer at concentrations of < 500 ppm could occur during the transfer of finished fuels to storage tanks and fueling of vehicles or equipment. The main route of exposure is expected to be dermal, although ocular exposure to splashes is also possible. Exposure during end use is expected to be minimised by the low (< 500 ppm) concentrations of the notified polymer in the diesel fuels and through good hygiene practices.

6.1.2. Public exposure
The fuel additive package containing the notified polymer at a concentration of < 40% will not be sold to the public and therefore exposure would only occur in the event of an accident during transportation.

The public may experience accidental dermal and ocular exposure to diesel fuels containing the notified polymer at < 500 ppm when filling vehicles and equipment. However, direct exposure is expected to be low due to the low concentration in diesel fuels (< 500 ppm).

6.2. Human health effects assessment

The results from toxicological investigations conducted on the notified polymer are summarised in the table below.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	low oral toxicity LD50 > 2000 mg/kg bw
Rabbit, skin irritation	slightly irritating
Eye irritation - BCOP	equivocal (potential for irritation)
Guinea pig, skin sensitisation –non-adjuvant test.	evidence of sensitisation
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration in human lymphocytes	non genotoxic

Toxicokinetics
Dermal absorption of the notified polymer is not expected to be significant based on its high molecular weight (> 1000 Da), low water solubility (< 1.0 mg/L) and high partition coefficient (log Pow > 6). However, the low molecular weight species present in the notified polymer may be absorbed more readily. This is also suggested by the sensitisation responses observed with the notified polymer.

Absorption of the notified polymer from the gastro-intestinal tract is expected to be limited by its water solubility and molecular weight. Any uptake is likely to occur via micellular solubilisation, given its highly lipophilic nature and low water solubility. The low molecular weight species may also undergo some absorption. The kidney effects observed in male rats in the repeat dose study may be indicative of absorption.

Acute toxicity
The notified polymer was found to be of low toxicity in a rat acute oral toxicity study conducted according to OECD TG 423 (Huntingdon, 2003e). No mortality occurred during the study and clinical signs were limited to increased salivation and brown staining in two of three test animals which had cleared within 1 hour following treatment. The acute oral LD50 was determined to be > 2000 mg/kg bw.

The toxicity of the notified polymer following acute dermal exposure was not determined. However, given the expected low dermal and demonstrated low oral toxicity (acute and sub-acute), the notified polymer is not considered to be toxic via the dermal route.

The acute inhalation toxicity of the notified polymer was not determined. The notified polymer has a low vapour pressure and is not intentionally aerosolised during use and thus is unlikely to be available for inhalation. If inhalation were to occur, the notified polymer may be absorbed directly across the respiratory tract epithelium, based on its high partition coefficient.

Irritation and Sensitisation

The notified polymer was found to be slightly irritating, producing slight to moderate erythema that resolved within 15 days in a skin irritation test in rabbits (see Appendix B for further details). These effects were not sufficient to warrant hazard classification.

A bovine corneal opacity and permeability (BCOP) test (recently adopted by the OECD on 7 September 2009) was conducted on the notified polymer to determine whether it was corrosive or severely irritating to the eye (see Appendix B for further details). This test method was recommended by the Interagency Co-ordinating Committee on the Validation of Alternative Methods (ICCVAM) to also be used as a screening test to identify substances not labelled as irritants (when using the EU or GHS hazard classifications systems) (ICCVAM, 2009). Substances used to validate the BCOP test for this purpose included some with similar functional groups to those found in the notified polymer. Therefore, the test is expected to be a reliable method for determining the irritancy potential of the notified polymer.

According to the OECD guidelines for the BCOP test, substances considered to be corrosive or severe eye irritants have an *in vitro* irritancy score (IVIS) ≥ 55.1 The IVIS for the notified polymer = 0.7 ± 1.2 (comparable to the levels of the control) which indicated it is not corrosive or a severe eye irritant. However, the nature of the test substance may not have allowed for an unequivocal determination. In the test, 750 µL of 0.9% sodium chloride solution was applied to the cornea (as per the treatment of negative controls) prior to placement of a moulded portion of the notified polymer onto the cornea. Thus, the notified polymer may not have been in full contact with the surface of the cornea, perhaps not allowing for proper evaluation of its irritancy potential. Therefore, the results of this study were considered equivocal. Structurally related chemicals are known to be moderately irritating to the eye and thus, the notified polymer may have the potential to be irritating to the eye.

The skin sensitisation potential of the notified polymer was evaluated using a guinea pig skin sensitisation study (Buehler method) and a local lymph node assay (LLNA) (see Appendix B for details). A higher incidence and severity of positive skin responses in the test group animals (50% of test animals) following challenge with the notified polymer at 50% compared to the vehicle control group were considered indicative of a skin sensitisation response in the guinea pig study. In addition, a lymphocyte proliferative response indicative of skin sensitisation was observed using the stimulation index (SI) endpoint with an EC3 value of close to 25%. This response was confirmed by the flow cytometry analysis endpoint in an alternative LLNA study (ICCVAM, 1999). Therefore, based on the results of these studies, it was concluded the notified polymer has the potential to be a skin sensitiser.

Repeated Dose Toxicity

The notified polymer was administered by oral gavage to rats in a 4-week study (see Appendix B for details). Adverse effects were limited to cortical tubules with hyaline droplets in the kidneys of male rats treated with 150 and 1000 mg/kg bw/day. However, the effect was believed to be symptomatic of hydrocarbon nephropathy syndrome which is unique to male rats and not toxicologically significant to humans (OECD, 2002). The No Observed Adverse Effect Level (NOAEL) in this study was established as 1000 mg/kg bw/day, based on the lack of adverse, dose-dependent toxicological findings relevant to other species at any dose level.

Genotoxicity

The notified polymer (in dimethylsulfoxide (DMSO)) did not induce an increase in revertant colonies in a bacterial reverse mutation assay (Ames test). The test used both the plate incorporation method and the preincubation method at a maximum exposure concentration of 5000 µg/plate and was conducted both with and without metabolic activation (Huntingdon, 2003g). No evidence of reduction of the background lawn or cytotoxicity was reported.

The notified polymer was found to be non-clastogenic in a chromosome aberration study in human lymphocytes,

in vitro (see Appendix B for further details).

Health hazard classification
Based on the skin sensitisation studies the notified polymer is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following classification:
R43 May cause sensitisation by skin contact

6.3. Human health risk characterisation

6.3.1. Occupational health and safety
Dermal and ocular exposure to the notified polymer is possible for workers during handling of the fuel additive package (< 40% concentration). The primary risk to workers involved in these operations is a skin sensitisation reaction. The notifier states that PPE such as gloves, safety glasses, overalls and safety shoes are expected to be worn by workers during handling of the fuel additive package. The use of PPE and engineering controls in place are expected to limit the risk of sensitisation.

Dermal and ocular exposure of workers may occur during handling of diesel fuels containing the notified polymer (< 500 ppm). There is a potential risk of skin sensitisation to these workers, particularly end users of the diesel fuels as they are not expected to wear PPE. Although the risk of skin sensitisation cannot be ruled out entirely, it is not considered to be significant at the low concentrations at which the notified polymer will be present (< 500 ppm). The risk would be further minimised by the use of appropriate PPE.

The notified polymer may have the potential to cause slight irritation based on the irritant properties of structurally related chemicals. However, the risk of irritation to workers is not considered unacceptable considering the anticipated use of safety goggles during handling as a component (< 40%) of a fuel additive package and the low concentration (< 500 ppm) which end users may experience accidental ocular exposure when handling diesel fuels.

The risk to workers handling the imported fuel additive package (< 40% notified polymer) is not considered unacceptable, assuming that all potentially exposed skin is covered using appropriate PPE. The risk to workers handling finished fuel products is not considered unacceptable given the low concentrations of the notified polymer in these products (< 500 ppm).

6.3.2. Public health
The public may experience mainly dermal exposure to the notified polymer in finished fuel products (< 500 ppm). There is a risk of skin sensitisation but it is not considered to be unacceptable due to the low concentration of the notified polymer in the fuel.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified polymer is not expected to be released to the environment when it is blended into fuels, as blending will take place in closed systems. Minor spills will be contained and collected for safe disposal at an approved facility. Residues in drums will be destroyed during metals reclamation or disposed of with the empty drums.

RELEASE OF CHEMICAL FROM USE
Small amounts may be spilt to the ground when vehicles are refuelled, but the notified polymer will otherwise be consumed with the diesel fuel during engine operation.

RELEASE OF CHEMICAL FROM DISPOSAL
The notified polymer is identified by the notifier as not suitable for landfill. The preferred disposal option is thermal decomposition at an approved facility.

7.1.2 Environmental fate

The notified polymer has low water solubility and is not readily biodegradable. It is expected to remain immobile and slowly degrade *in situ* if spilt to soil during vehicle refuelling or disposed of to landfill as drum residues. Bioaccumulation in fish is not expected based on the structure and properties of the notified polymer, and the low likelihood of aquatic release when it is used as proposed as a diesel fuel additive.

7.1.3 Predicted Environmental Concentration (PEC)

It is neither necessary nor meaningful to determine the PEC as the notified polymer is not expected to be released to aquatic environments when it is used as proposed as a diesel fuel additive.

7.2. Environmental effects assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 > 0.179 mg/L	Not toxic to limit of water solubility
Daphnia Toxicity	EC50 > 0.265 mg/L	Not toxic to limit of water solubility
Algal Toxicity	EC50 > 0.093 mg/L	Not toxic to limit of water solubility
Inhibition of Bacterial Respiration	EC50 = 400 mg/L	Not harmful

The notified polymer showed no toxicity to fish, daphnids or algae when tested as water accommodated fractions prepared at nominal loadings of 1000 mg/L.

7.2.1 Predicted No-Effect Concentration (PNEC)

The PNEC cannot be determined as the median effect concentrations exceed the water solubility of the notified polymer.

7.3. Environmental risk assessment

The Risk Quotient (PEC/PNEC) cannot be determined. The notified polymer is not considered to pose a risk to the environment, as it is not toxic to aquatic life at concentrations up to the limit of aqueous solubility and will be destroyed during use as a fuel additive, with a low likelihood of aquatic release.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

Based on the available data the notified polymer is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)]. The classification and labelling details are:

R43 May cause sensitisation by skin contact

As a comparison only, the classification of the notified polymer using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	***Hazard statement***
Skin sensitisation	1	May cause an allergic skin reaction
Chronic toxicity	4	May cause long lasting harmful effects to aquatic life.

Human health risk assessment

Under the conditions of the occupational settings described, and assuming that measures are in place to minimise dermal exposure, the notified polymer is not considered to pose an unacceptable risk to the health of workers.

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

Environmental risk assessment
On the basis of the reported use pattern, the notified polymer is not considered to pose a risk to the environment.

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- Safe Work Australia, should consider the following health hazard classification for the notified polymer:
  - R43 May cause sensitisation by skin contact

- Use the following risk phrases for products/mixtures containing the notified polymer:
  - Conc ≥ 1%: R43

- The following safety phrases should appear on the MSDS and label for the notified polymer and products containing the notified polymer:
  - S24 Avoid contact with skin
  - S27 Take off immediately all contaminated clothing
  - S28 After contact with skin, wash immediately with plenty of water
  - S36 Wear suitable protective clothing
  - S37 Wear suitable gloves

- The MSDS for imported products containing the notified polymer should be amended as follows:
  - Inclusion of the full chemical name.

Health Surveillance

- As the notified polymer is a skin sensitiser, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of skin allergies.

CONTROL MEASURES
Occupational Health and Safety

- Employers should ensure the following isolation and engineering controls to minimise occupational exposure to the notified polymer:
  - Prevention of leaks and spills
  - Automated processes

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified polymer:
  - Avoid skin contact
  - Workers must have adequate education and training before handling the notified chemical
  - Avoid spills and splashing during use.
  - After exposure, any contaminated PPE should be thoroughly cleaned before re-use.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified polymer as introduced:
  - Impervious gloves and long-sleeved protective clothing

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

- 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.

Environment

- Recovered fluids or produced water ("slops") containing the notified polymer should not be released to the aquatic environment.

Disposal

- The notified polymer should be disposed of by thermal decomposition at an approved facility, or to landfill after containment with absorbent material.

Emergency procedures

- Spills or accidental release of the notified polymer should be handled by 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:

(2) Under Section 64(2) of the Act; if
- the function or use of the polymer has changed from diesel fuel additive, or is likely to change significantly;
- the amount of polymer being introduced has increased from 50 tonnes, or is likely to increase, significantly;
- the polymer has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the polymer on occupational health and safety, public health, or the environment.

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

Material Safety Data Sheet
The MSDS of a product containing the notified polymer 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

Pour Point 72°C

Method ASTM Test method D97-87.
Test Facility Huntingdon (2003a)

Boiling Point >240°C at 101.3 kPa

Method OECD TG 103 Boiling Point.
EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Decomposition occurred at temperatures above 240 °C without boiling.
Test Facility Huntingdon (2003a)

Density 1080 kg/m^3 at 22°C

Method OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Remarks Pycnometer method
Test Facility Huntingdon (2003a)

Vapour Pressure 1.2 x 10^{-8} kPa at 25°C

Method OECD TG 104 Vapour Pressure.
EC Directive 92/69/EEC A.4 Vapour Pressure.
Test Facility Huntingdon (2003a)

Water Solubility < 0.001 g/L at 20°C

Method OECD TG 120 Solution/Extraction Behaviour of Polymers in Water.
Remarks Flask Method. The guideline requirement that ground polymer be sieved to between 125 and 250 µm could not be complied with because of caking. This behaviour also precluded the need to centrifuge or filter samples before analysis. Aqueous samples were extracted with ethyl acetate and analysed by HPLC. Major species had solubilities between 0.01 and 0.1 mg/L, while a minor component (the most mobile) had an estimated solubility of 0.5-1 mg/L.
Test Facility Huntingdon (2003a)

Hydrolysis as a Function of pH

Remarks The hydrolysis of the notified polymer could not be examined because of its very low water solubility and the lack of a sufficiently sensitive analytical method (Huntingdon, 2003b). Hydrolysis under environmental conditions is expected to be very slow because of the limited solubility.

Partition Coefficient (n-octanol/water) log P_{ow} > 6 at 25°C

Method OECD TG 121 Partition Coefficient (n-octanol/water), HPLC Method.
EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks HPLC Method. The test substance was retained on the column longer than the reference substance DDT. Preliminary estimation for a low molecular weight (dimeric) component using the fragment method provided a value of 12.9.
Test Facility Huntingdon (2003c)

Adsorption/Desorption – screening test

log K_{oc} > 5.4 at 25°C

Method	OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks	The test substance was retained on the column longer than the reference substance DDT.
Test Facility	Huntingdon (2003a)

Dissociation Constant

pKa = 13.1

Method	OECD TG 112 Dissociation Constants in Water.
Remarks	The dissociation constant was determined by measuring absorbance at 305 nm, using ethanol as cosolvent.
Test Facility	Huntingdon (2003d)

Flash Point

112ºC at 101.3 kPa

Method	EC Directive 92/69/EEC A.9 Flash Point.
Remarks	Pensky-Martens method
Test Facility	Huntingdon (2003a)

Autoignition Temperature

> 400ºC

Method	EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility	Huntingdon (2003a)

Explosive Properties

Not explosive

Method	EC Directive 92/69/EEC A.14 Explosive Properties.
Test Facility	Huntingdon (2003a)

Oxidizing Properties

Not oxidising

Method	EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Test Facility	Huntingdon (2003a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Irritation – skin

TEST SUBSTANCE: Notified polymer

METHOD: OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain: Rabbit/New Zealand White
Number of Animals: 3 Females
Observation Period: 15 days
Type of Dressing: Semi-occlusive.
Remarks - Method: The notified polymer was placed on gauze pads which were placed in aluminium foil containers and heated to 90ºC in an oven to ensure the substance was in liquid form. The liquid was allowed to spread evenly over the gauze and cooled to room temperature before treatment. No other 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	1	2	1	2	< 15 Days	0
Oedema	0	0	0	0	-	0

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

Remarks - Results: Very slight or moderate erythema was apparent in two animals up to Day 8 after bandage removal and in the remaining animal up to 72 hours after bandage removal. A residue of test substance that initially interfered with the assessment of the test site was noted in two animals up to the 48 hr observation. The loss of flexibility that was evident in the same two animals throughout the study period was considered to have been caused by adhesion of the test substance to the skin.

CONCLUSION: The notified chemical is slightly irritating to the skin.

TEST FACILITY: Huntingdon (2003e)

B.2. Irritation – eye – Bovine Corneal Opacity and Permeability Assay

TEST SUBSTANCE: Notified polymer

METHOD: Similar to OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants

Remarks - Method: Positive control: 20% imidazole in 0.9% Sodium Chloride solution
Negative control: 0.9% Sodium Chloride solution

Measurements were made in triplicate (3 separate corneas treated with the test substance, positive and negative controls).

Treatment with the test substance using the closed chamber method involved placing 750 µL of 0.9% sodium chloride solution in the anterior compartment of the holder. The corneas were incubated for approximately 4 hrs at 32ºC ± 2ºC.

A thin section of the notified polymer that had been shaped to approximately match the size and curvature of the cornea was then gently lowered onto the surface of the cornea. This was necessary due to the resinous nature of the notified polymer.

The permeability of each cornea was determined by measuring the optical density at 490 nm (OD_{490}) using a spectrophotometer. The OD_{490} value was compared to the OD_{490} value of the negative control to determine the Corrected OD_{490} value.

The *In Vitro* Irritancy Score was calculated using the formula:
In Vitro Irritancy Score = Corrected Opacity Value + 15 x Corrected OD_{490} value.

According to OECD TG 437, a substance that induces an *In Vitro* Irritancy Score ≥ 55.1 is defined as a corrosive or severe irritant.

RESULTS

Measurements for determining the Corrected Opacity Value and Corrected OD_{490} value for the notified polymer

Cornea	*Opacity*			*Permeability*
	Pre-treatment	Post-treatment	Change	Corrected OD_{490} value
1	6	6	0	0.006
2	6	6	0	-0.001
3	5	7	2	0.003
Mean	**-**	**-**	**0.667 ± 1.155**	**0.003 ± 0.004**

In Vitro Irritancy Score = Corrected Opacity Value + 15 x Corrected OD_{490} value where:
The Corrected Opacity Value = 0.667
The Corrected OD_{490} value = 0.003
Therefore, the *In Vitro* Irritancy Score = 0.7 ± 1.2

Remarks - Results

No opaque spots or other irregularities were found on the corneas treated with the notified polymer. The corneas treated with the negative control were clear. The corneas treated with the positive control, were very opaque and the *In Vitro* Irritancy Score was determined to be 132.6 demonstrating the sensitivity of the assay.

CONCLUSION The notified polymer is not corrosive or severely irritating to the eye under the conditions of the test.

TEST FACILITY Huntingdon (2004a)

B.3. Repeat dose toxicity

TEST SUBSTANCE Notified polymer

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain Rat/Crl:CD(SD)IGSBR
Route of Administration Oral – gavage
Exposure Information Total exposure days: 28 days
Dose regimen: 7 days per week
Vehicle Corn oil
Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0
low dose	5 per sex	15	0
mid dose	5 per sex	150	0
high dose	5 per sex	1000	0

Mortality and Time to Death

No mortalities were reported.

Clinical Observations

Statistically significant decreases in motor activity levels were observed in treated males during the interval between 30 – 36 minutes of the observations. However, the values were within the range of historical data, there was no dosage-relationship and overall activity levels were similar to control animals. As such, these observations were not considered to be toxicologically significant.

Bodyweights and bodyweight gains were unaffected by treatment with the notified polymer. Food consumption values were within the range expected for animals of this age and strain.

Laboratory Findings – Clinical Chemistry, Haematology

A statistically significant decrease in glucose level was observed in females treated with 1000 mg/kg bw/day compared with controls. However, no decreases were reported in the mid or low dose groups.
A statistically significant increase in activated partial thromboplastin time (APTT) was observed in each group of treated female rats. However, the individual values for each group were within the expected range. Variations in APTT in treated females and glucose levels in females treated with 1000 mg/kg bw/day were not considered to be of toxicological significance considering there were no corresponding histopathological findings. No dosage-relationship was observed and similar differences from controls were observed in males.

Effects in Organs

Cortical tubules with hyaline droplets were observed in 2/5 males treated with 150 mg/kg bw/day and 4/5 treated with 1000 mg/kg/day. The observed cortical tubules with hyaline droplets in male rats treated with 150 and 1000 mg/kg bw/day were considered to be treatment-related and toxicologically significant. However, renal tubular hyaline droplet accumulation (characteristic of α2-microglobulin nephropathy) is a phenomenon known to occur only in adult male rats and this finding is not considered to be of toxicological significance to other species.

Statistically significantly higher than control mean brain and adrenal weights were observed for female rats receiving 1000 mg/kg/day. No variations from control were noted in females receiving 15 or 150 mg/kg/day nor in any of the treated males. The increased brain and adrenal weights in females treated with 1000 mg/kg bw/day were not considered to be toxicologically significant given the lack of adverse findings in those organs during histopathological and macroscopic examination.

There were no treatment-related macroscopic abnormalities observed during the post mortem examination.

All other microscopic findings were considered to be incidental and of no toxicological importance.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, given the effects observed in the kidneys of male rats treated with 150 and 1000 mg/kg bw/day were considered unique to the male rat and the lack of any adverse, dose-dependent findings at any dose level.

TEST FACILITY Huntingdon (2004b)

B.4. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Human (male volunteers)
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	Aroclor 1254-induced rat liver S9 fraction
Vehicle	Acetone
Remarks - Method	No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	9.38, 18.75, 37.5, 75, 150, 300*, 600*, 1200*	3 hrs	20 hrs
Test 2	100, 200*, 400*, 600*, 800, 1000, 1200	20 hrs	20 hrs
Present			
Test 1	9.38, 18.75, 37.5, 75, 150, 300*, 600*, 1200*	3 hrs	20 hrs
Test 2	200, 400*, 600*, 800*, 1000, 1200	3 hrs	20 hrs

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 1200	≥ 600	Negative
Test 2	> 400	≥ 1000	Negative
Present			
Test 1	1200	≥ 600	Negative
Test 2	> 800	≥ 600	Negative

Remarks - Results: The test material did not induce any statistically significant increases in the frequency of cells with aberrations, or in the numbers of polyploid cells.

CONCLUSION: The notified polymer was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY: Huntingdon Life Sciences (2003h)

B.3. Skin sensitisation – Buehler Test

TEST SUBSTANCE: Notified polymer

METHOD: OECD TG 406 Skin Sensitisation - Guinea Pig (Buehler Test).

Species/Strain: Guinea pig/Crl:(HA)BR – Hartley

PRELIMINARY STUDY: Maximum Non-irritating Concentration: 50% in acetone

MAIN STUDY

Number of Animals: Test Group: 20 Control Group: 10

Induction phase: Induction Concentration: 50% in olive oil

Signs of Irritation: Slight patchy erythema was observed in 4 treated animals following the first induction, 5 following the second induction and 1 following the third induction.

CHALLENGE PHASE

1st challenge: topical application: 50% in acetone

Remarks – Method: The OECD guidelines recommend the use of 80% ethanol in water for the vehicle during induction. However, this was not suitable for the notified polymer. No other significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	50%	10*	7*
Control Group	50%	7**	4**

* Note: The animals included in the count above only include those with skin reactions of higher severity than slight patchy erythema.
** Slight patchy erythema reactions only

Remarks – Results

The following reactions were noted 24 hrs after challenge application:
- slight patchy erythema in 9 animals,
- slight, confluent or moderate patchy erythema (Grade 1) in 9 animals;
- moderate erythema (Grade 2) in 1 animal; and
- Edema was also evident in the animal with moderate erythema and for 1 of the animals with Grade 1 erythema.

The responses noted at the 48-hour evaluation were:
- slight patchy erythema in 8 animals;
- Grade 1 erythema in 7 animals; and
- Desquamation was evident in 7 animals.

Administration of 50% notified polymer in acetone to 10 control group animals produced slight patchy erythema in 8 animals at the 24 hr evaluation and in 4 animals at the 48 hr evaluation.

2-Mercaptobenzothiazole (MBT) (98%) served as the positive control. For induction MBT was diluted to 25% in peanut oil and for challenge it was diluted to 25% in olive oil. Out of the 10 animals treated with MBT, 6 displayed Grade 1 erythema at the 24 hr and 48 hr evaluations. No incidence of erythema was observed following induction.

Ten animals of the test group (ie. 50%) were considered to have produced sensitisation responses based on the higher incidence and severity of skin responses in these animals, compared to controls.

CONCLUSION

There was evidence of reactions indicative of skin sensitisation to the notified polymer under the conditions of the test.

TEST FACILITY

ExxonMobil Biomedical Science Inc (2004a)

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

TEST SUBSTANCE

Notified polymer (98%)

METHOD

OECD TG 429 Skin Sensitisation: Local Lymph Node Assay

Species/Strain

Female Mouse/CBA/Ca

Vehicle

Acetone:olive oil (4:1 v/v)

Remarks - Method

A preliminary study found that 50% was the maximum concentration of the notified chemical that did not cause irritation. Five female mice were treated at each dosage.

In addition to the standard OECD 429 test protocol, an additional 5 animals in each group that did not receive ^{3}H-thymidine (as per OECD

TG 429), were killed on Day 6. The draining auricular lymph nodes were excised and pooled in 1.0 mL of phosphate buffered saline (PBS). A single cell suspension of lymph node cells (LNC) was prepared from the auricular lymph nodes and diluted to 2 x 10^6 cells/mL in PBS except for 2 animals which had low cell numbers. These animals had suspensions of LNC concentrations of 0.55 and 0.8 x 10^6 cells/mL. Aliquots of each suspension were stained with fluorescently conjugated antibodies recognising CD3, B220, MHC class II and CD69 or other isotype matched controls. The samples were incubated at 4°C for 30 mins away from light and then fixed by adding PBS containing 1.2% formaldehyde. The stained cells were analysed using a flow cytometer for:

- The total number of cells per pair of lymph nodes
- The percentage T lymphocytes (CD3+)
- The percentage B lymphocytes (B220+)
- The ratio of B:T lymphocytes
- The percentage Class II positive B lymphocytes (B220+Ia+)
- The percentage Class II/CD69 positive cells (Ia+CD69+)
- The fluorescent intensity of Class II expression on the B lymphocytes (MnI of B220+Ia+)

RESULTS

OECD TG 429:

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	169.6	1
10	225.5	1.3
25	574.2	3.4*
50	702.7	4.1*
Positive Control		
25% HCA	2682.9	15.8*

* $p \leq 0.001$, HCA = Hexyl cinnamic aldehyde

Flow cytometry method:

Group	**Total cells/pair of lymph nodes**	**T cells ($CD3^+$)**	**B cells ($B220^+$)**	**T:B ratio ($CD3^+$:$B220^+$)**	**Class II^+ B cells ($B220^+/Ia^+$)**		**$Ia^+/CD69^+$**
					(%)	**(MnI)**	**(%)**
Acetone:olive oil (4:1)	3.93 ± 2.07	90.9 ± 1.7	4.36 ± 1.63	20.1 ± 8.4	5.13 ± 1.56	65.3 ± 2.7	2.29 ± 0.78
10% notified polymer	4.79 ± 2.65	89.6 ± 1.9	6.24 ± 2.11	16.4 ± 8.2	6.66 ± 2.12	57.5 ± 4.4	2.03 ± 0.40
25% notified polymer	8.94 ± 6.02	88.0 ± 3.6	8.22 ± 2.88	11.9 ± 4.8	8.88 ± 2.92	66.6 ± 5.1	3.36 ± 0.45
50% notified polymer	7.38 ± 4.07	87.2 ± 2.4	8.80 ± 1.69	10.2 ± 2.3	9.33 ± 1.69	62.3 ± 9.3	2.53 ± 1.04
25% HCA	15.31 ± 3.34	83.8 ± 2.3	11.3 ± 1.38	7.51 ± 1.16	11.9 ± 1.62	80.5 ± 8.6	4.98 ± 1.24

HCA = Hexyl cinnamic aldehyde

Remarks - Results

No signs of systemic toxicity were observed. The stimulation index (SI) for increase in ^{3}H-thymidine incorporation into cells was greater than 3 at concentrations of 25 and 50%.

Flow cytometry analysis of the draining lymph nodes also indicated that the notified polymer at 25 and 50% induced modest activation of the immune system when administered topically. There was a significant increase in the percent B lymphocytes in the groups treated with 25 and 50% notified polymer, causing a significant reduction in the T:B cell ratio

	in the high dose group compared with the vehicle control. The degree of immune stimulation was clearly less than that seen with the positive control HCA (25% v/v), where there was a greater expansion of leucocytes expressing an activation phenotype.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified polymer.
TEST FACILITY	Huntingdon (2004c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified polymer
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test
Inoculum	Activated sludge from Oakley sewage treatment works
Exposure Period	29 days
Auxiliary Solvent	None
Analytical Monitoring	Acid titration of residual barium hydroxide after precipitation.
Remarks - Method	The test substance (40.8 mg in each 3 L culture bottle) was added on Teflon discs.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	0	7	67
29	1	29	85

Remarks - Results	The test substance did not inhibit the biodegradation of sodium benzoate. The rate of biodegradation of the test substance is limited by the low aqueous solubility.
CONCLUSION	The notified polymer is not readily biodegradable.
TEST FACILITY	Huntingdon (2004d)

C.1.2. Bioaccumulation

Remarks	The bioaccumulation potential of the notified polymer in fish is considered to be low based on the molecular size and properties, but this has not been confirmed experimentally.

C.1. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified polymer
METHOD	OECD TG 203 Fish, Acute Toxicity Test – semi static. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish – semi static.
Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	None (water accommodated fractions (WAFs) were used).
Water Hardness	176 mg $CaCO_3$/L
Analytical Monitoring	HPLC (first five chromatographic peaks).
Remarks – Method	The test substance was introduced on a Teflon slide. WAFs were obtained by siphoning after 40 hours stirring and a 4 hour settling period. Test media were renewed at 24 hour intervals.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
1000	0.179	10	0	0	0	0	0

LC50	> 0.179 mg/L at 96 hours.
NOEC	0.179 mg/L at 96 hours.
Remarks – Results	Measured concentrations ranged from 0.150 to 0.163 mg/L in fresh media and 0.163 to 0.221 mg/L in expired (24 hour old) media.
CONCLUSION	The notified polymer is not toxic to fish, up to the limit of water solubility.
TEST FACILITY	Huntingdon (2004e)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified polymer
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - static. EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None (WAFs were used).
Water Hardness	260 mg $CaCO_3$/L
Analytical Monitoring	HPLC (first five chromatographic peaks).
Remarks – Method	The test substance was introduced on a Teflon slide. WAFs were obtained by siphoning after 40 hours stirring and a 4 hour settling period.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h]*	*48 h*
1000	0.265	20	0	0

LC50	> 0.265 mg/L at 48 hours
NOEC	0.265 mg/L at 48 hours
Remarks – Results	The measured concentrations declined from 0.297 mg/L at the start of the test to 0.234 mg/L after 48 hours.
CONCLUSION	The notified polymer is not toxic to daphnids, up to the limit of water solubility.
TEST FACILITY	Huntingdon (2004f)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified polymer
METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Selenastrum capricornutum*
Exposure Period	72 hours
Concentration Range	Nominal: 1000 mg/L Actual: 0.093 mg/L
Auxiliary Solvent	None (WAFs were used).

Water Hardness	OECD algal nutrient medium (soft water)
Analytical Monitoring	HPLC (first five chromatographic peaks).
Remarks – Method	The test substance was introduced on a Teflon slide. WAFs were obtained by siphoning after 40 hours stirring and a 4 hour settling period.

RESULTS

Biomass		*Growth*	
E_bC50	*NOEC*	*E_rC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
> 0.093	0.093	>0.093	0.093

Remarks - Results	The measured concentrations declined from 0.156 mg/L at the start of the test to 0.056 mg/L after 72 hours.

CONCLUSION The notified polymer is not toxic to green algae, up to the limit of water solubility.

TEST FACILITY Huntingdon (2004g)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified polymer

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.
EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test

Inoculum	Activated sludge collected from the Oakley Sewage Treatment Works
Exposure Period	3 hours
Concentration Range	Nominal: 25, 50, 100, 200, 400 mg/L
Remarks – Method	The rate of oxygen consumption was measured with a dissolved oxygen meter. 3,5-Dichlorophenol was used as positive control.

RESULTS

IC50	> 400 mg/L
NOEC	400 mg/L
Remarks – Results	The response to the positive control (IC50 10.9 mg/L) indicated that the test was valid and that the sample of activated sludge employed was sensitive to inhibition.

CONCLUSION The notified polymer is not inhibitory to the respiration of activated sludge.

TEST FACILITY Huntingdon (2003i)

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