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June 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Chemical in Liquid Paper®

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 conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment.

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1505	Newell Australia Pty Ltd	Chemical in Liquid Paper®	Yes	< 1 tonne per annum	Component of correction fluid

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified polymer is recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the table below.

Hazard classification	*Hazard statement*
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

Based on the available information, the notified polymer is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrase:

R43: May cause sensitisation by skin contact

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

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

Environmental risk assessment
On the basis of assessed use pattern, the notified polymer is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified polymer should be classified as follows:
  - H317: May cause an allergic skin reaction

The above should be used for products/mixtures containing the notified polymer, if applicable, based on the concentration of the notified polymer present and the intended use/exposure scenario.

CONTROL MEASURES

Occupational Health and Safety

- A copy of the (M)SDS should be easily accessible to employees.
- If products and mixtures containing the notified polymer are classified as hazardous to health in accordance with the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures

consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- The notified polymer should be disposed of to landfill.

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the polymer 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 polymer, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified polymer 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 polymer has changed from a component of correction fluid, or is likely to change significantly;
- the amount of polymer being introduced has increased, 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 (M)SDS of the notified polymer and products containing the notified polymer provided by the notifier were reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Newell Australia Pty Ltd (ABN: 68 075 071 233)
500 Princes Highway
NOBEL PARK VIC 3174

NOTIFICATION CATEGORY
Standard: Synthetic polymer with Mn < 1000 Da (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, polymer constituents, residual monomers, impurities, additives/adjuvants, use details, import volume and identity of recipients.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: hydrolysis as a function of pH, dissociation constant, acute dermal toxicity, and acute inhalation toxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Canada
United States
China

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Liquid Paper® (contains the notified polymer at 1-5% concentration)

MOLECULAR WEIGHT
> 500 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 99%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Light yellow solid

Property	Value	Data Source/Justification
Melting Point	59.3 °C	Measured
Boiling Point	399.8 °C at 101.3 kPa	Measured
Density	1010 kg/m^3 at 20 °C	Measured
Vapour Pressure	< 2.8 × 10^{-7} kPa at 25 °C	Measured
Water Solubility	Overall total extractables = 2 × 10^{-3} g/L Solution concentration ≤ 1.79 × 10^{-3} g/L Per unit mass of polymers ≤ 0.17 × 10^{-3} g/g	Measured

Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionalities.
Partition Coefficient (n-octanol/water)	log Pow > 6.5 at 20 °C	Measured
Adsorption/Desorption	log K_{oc} > 5.6 at 30 °C	Measured
Dissociation Constant	Not determined	Does not contain ionisable functionalities.
Particle Size	Inhalable fraction (< 100 μm): 1.92%	Measured
Flammability	Not highly flammable	Measured
Autoignition Temperature	386 ± 5 °C	Measured
Explosive Properties	Predictive negative	Based on the chemical structure
Oxidising Properties	Predicted negative	Based on the chemical structure

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

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified polymer will be imported into Australia as a component of correction fluid packed in correction pens.

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

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

PORT OF ENTRY
Melbourne

TRANSPORTATION AND PACKAGING
The notified polymer will be imported as a component in finished correction fluid which is packed in correction pens suitable for retail sale and will be transported in the same form in which it is imported.

USE
The notified polymer will be used as a film-forming component in correction fluid at a concentration of 1-5%.

OPERATION DESCRIPTION
The notified polymer will be imported into Australia as a component of finished correction fluid packed in correction pens and will be sold to end-users (the public) in the same form in which it is imported.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure
Worker exposure to the notified polymer at 1-5% concentration is only expected in the unlikely event of accidental rupture of packages.

6.1.2. Public Exposure
The public is not expected to be exposed to the notified polymer during application of correction fluid containing the notified polymer. In the unlikely event that exposure did occur to the correction fluid during application

exposure to the notified polymer is expected to be negligible given the low concentration of the notified polymer and low volume of correction fluid dispensed per application. The public may come into contact with the correction fluid after application. However, once the correct fluid is dried the notified polymer will form a solid film and will not be bioavailable.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified polymer or an accepted analogue (Analogue 1, identity in Exempt Information) are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity*	LD50 > 5000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity*	LC50 > 0.13 mg/L/4 hour; toxicity not determined
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – local lymph node assay	evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic

* Analogue data

Toxicokinetics.

Based on the relatively high molecular weight (> 500 Da), insolubility in water and high partition coefficient (log Pow > 6.5 at 20 °C), absorption of the notified polymer across biological membranes is expected to be limited. Inhalation exposure to the notified polymer is not expected given the notified polymer has a very low vapour pressure (< 2.8×10^{-7} kPa at 25 °C).

Acute toxicity.

The notified polymer was found to be of low acute oral toxicity in rats.

No acute dermal and inhalation toxicity data for the notified polymer were submitted. An analogue (Analogue 1) of the notified polymer was found to be of low acute dermal toxicity in rats. Acute inhalation toxicity for Analogue 1 cannot be ruled out as the highest concentration tested is within the concentration cut-off for classification under the GHS. However, inhalation exposure is not expected given the very low vapour pressure (< 2.8×10^{-7} kPa at 25 °C) of the notified polymer.

Irritation and sensitisation.

The notified polymer was found to be slightly irritating to the skin and eyes in studies conducted in rabbits.

The notified polymer was found to be a weak skin sensitiser (EC3 > 25%) in a mouse local lymph node assay.

Repeated dose toxicity.

In a 28 day repeated dose oral toxicity study in rats the No-Observed-Effect Level (NOEL) for the notified polymer was established as 1000 mg/kg bw/day based on no test substance-related toxicological significant effects at any of the doses administered.

Mutagenicity/Genotoxicity.

The notified polymer was negative both in a bacterial reverse mutation study and in an *in vitro* chromosome aberration study.

Health hazard classification

Based on the available information, the notified polymer is recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	***Hazard statement***
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

Based on the available information, the notified polymer is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):

R43: May cause sensitisation by skin contact

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

The notified polymer will be imported in finished products at low concentrations without need for repackaging. Only transport, storage and retail workers may come into contact with the notified polymer in the event of accidental rupture of packages. Therefore, the risk to the health of workers is not considered to be unreasonable.

6.3.2. Public Health

The notified polymer is a weak skin sensitiser; however, the public is not expected to be significantly exposed to the notified polymer during application of correction fluid containing the notified polymer. The public may come into contact with the correction fluid after application. However, once the correction fluid is dried the notified polymer will form a thin solid film on the substance and will not be available for exposure. Hence, the risk to public health is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified polymer will be imported as a component of a finished product for use as correction fluid. The notified polymer will not be reformulated in Australia. Therefore, release of the notified polymer from these activities is not expected.

RELEASE OF CHEMICAL FROM USE

According to the notifier, 100% dispense efficiency from each product (correction pen) is expected. When used as correction fluid, the majority of the correction fluid containing the notified polymer is expected to be applied to different papers. Dispensed formulated fluid containing the notified polymer is expected to immediately transform from fluid phase to a solid dry film on papers. Un-dispensed correction fluid, which remains in discarded used correction pens, will remain as a liquid residue until it contacts air and is transformed into a dried mass.

RELEASE OF CHEMICAL FROM DISPOSAL

Following its use, most of the notified polymer is anticipated to share the fate of papers and be disposed of to landfill or subjected to paper recycling processes. Approximately half of the amount of used paper is expected to be recycled. Some of the notified polymer may be released to waste waters during paper recycling processes and be released to sewage treatment plants (STPs). Limited amounts of the notified polymer contained in empty correction pens are expected to be disposed of to landfill.

7.1.2. Environmental Fate

The notified polymer is not readily biodegradable according to the biodegradation study provided. For the details of the environmental fate studies please refer to Appendix C.

The notified polymer in correction fluid is expected to remain fixed to paper for its useful life. The notified polymer is expected to be disposed of to landfill along with papers or released to sewer in recycling wastewaters when papers are recycled. During paper recycling processes, waste paper is repulped using a variety of alkaline, dispersing and wetting agents, water emulsifiable organic solvents and bleaches to improve the detachment of ink from the fibres. Based on its low water extractability (2×10^{-3} g/L), high partition coefficient ($\log P_{ow} > 6.5$) and adsorption coefficient ($\log K_{oc} > 5.6$), the notified polymer is expected to partition to sludge during paper recycling and waste water treatment processes. The sludge is expected to be disposed of to landfill or applied to agricultural soils.

Based on its high n-octanol/water partition coefficient (Log Pow > 6.5), the notified polymer has potential to bioaccumulate. However, due to its low water solubility, it is not likely to be significantly present in the aquatic

system. Hence, it is not expected to be significantly bioavailable to the aquatic organisms. In landfill, soils and water, the notified polymer is expected to degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the Predicted Environmental Concentration (PEC) is summarised in the table below. Based on the reported use in correction fluid, it is assumed as a worst case scenario that 50 % of the total import volume of notified polymer is released to sewer from recycling processes. It is expected that the recycling processes occurs only on working days, which is 260 days per annum. It is conservatively assumed that 0% of the notified polymer will be removed at Sewage Treatment Plants (STPs).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	50%	
Annual quantity of chemical released to sewer	500	kg/year
Days per year where release occurs	260	days/year
Daily chemical release:	1.92	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.43	µg/L
PEC - Ocean:	0.04	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified polymer in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.43 µg/L may potentially result in a soil concentration of approximately 2.8 µg/kg. Assuming accumulation of the notified polymer in soil for 5 and 10 years under repeated irrigation, the concentration of notified polymer in the applied soil in 5 and 10 years may be approximately 14.2 µg/kg and 28.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LL50 (96 hours) > 1000 mg/L*	Not harmful to fish
Daphnia Toxicity	EL50 (48 hours) > 1000 mg/L*	Not harmful to aquatic invertebrates
Algal Toxicity	E_rL50 (72 hours) > 1000 mg/L*	Not harmful to algae

* Filtered Water Accommodated Fraction (WAF)

The notified polymer is not considered to be harmful to aquatic life. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) it is not classified for acute and long term hazard.

7.2.1. Predicted No-Effect Concentration

A Predicted No-Effect Concentration (PNEC) for the aquatic compartment has not been calculated since the notified polymer is not expected to be harmful to aquatic life, up to the limit of its solubility, based on the studies provided by the notifier.

7.3. Environmental Risk Assessment

The risk quotient (RQ = PEC/PNEC) has not been calculated since a PNEC has not been calculated. Although the notified polymer it is not readily biodegradable, it is not harmful to the aquatic organisms. No unacceptable risk to the aquatic environment is expected from the notified polymer based on its reported use pattern and the

absence of any significant acute toxicity effects to aquatic species. Therefore, on the basis of the assessed use pattern, the notified polymer is not expected to pose an unreasonable risk to the aquatic environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 59.3 °C

Method OECD TG 102 Melting Point/Melting Range.
Remarks Determined by differential scanning calorimetry.
Test Facility SafePharm (2007a)

Boiling Point > 400 °C at 101.3 kPa

Method OECD TG 103 Boiling Point.
Remarks Determined by differential scanning calorimetry.
Test Facility SafePharm (2007a)

Density 1010 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids.
Remarks Determined using a gas comparison pycnometer.
Test Facility SafePharm (2007a)

Vapour Pressure < 2.8×10^{-7} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
Remarks Determined using a vapour pressure balance system.
Test Facility SafePharm (2007b)

Water Solubility Overall total extractables = 2×10^{-3} g/L
Solution concentration ≤ 1.79×10^{-3} g/L
Per unit mass of polymers ≤ 0.17×10^{-3} g/g

Method OECD TG 120 Test Guideline.
Remarks The total extractables in each sample was determined gravimetrically. The concentration of polymer in each sample was determined using gel permeation chromatography (GPC).
Test Facility SafePharm (2007a)

Partition Coefficient (n-octanol/water) log Pow > 6.5 at 20 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water) - HPLC Method.
Remarks The test was conducted according to the guidelines above using good laboratory practice (GLP). Testing was performed without pH adjustment to the mobile phase as the test material contained no modes of dissociation.
Test Facility SafePharm (2007a)

Adsorption/Desorption log K_{oc} > 5.6

Method OECD TG 121 Adsorption – Desorption - HPLC Method.
Remarks The test was conducted according to the guidelines above using good laboratory practice (GLP). Testing was performed without pH adjustment to the mobile phase as the test material contained no modes of dissociation.
Test Facility SafePharm (2007a)

Particle Size

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

Range (μm)	*Mass (%)*
< 100 μm	1.92

Remarks Determined using a 100 μm sieve in screening test.

Test Facility SafePharm (2007a)

Flammability Not highly flammable

Method EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks Based on failure to ignite during minutes that Bunsen flame was applied, the notified polymer was determined to be not highly flammable.
Test Facility SafePharm (2007b)

Autoignition Temperature 386 ± 5°C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility SafePharm (2007b)

Autoignition Temperature

Method EC Council Regulation No 440/2008 A.16 Relative Self-Ignition Temperature for Solids.
Remarks Determined not to have a relative self-ignition temperature below melting temperature.
Test Facility SafePharm (2007b)

Explosive Properties Predicted negative

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks Based on the chemical structure the notified polymer was predicted not to have explosive properties.
Test Facility SafePharm (2007b)

Oxidizing Properties Predicted negative

Method EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids).
Remarks Based on the chemical structure the notified polymer was predicted not to have oxidising properties.
Test Facility SafePharm (2007b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified polymer

METHOD: OECD TG 420 Acute Oral Toxicity - Fixed Dose Method.
EC Directive 2004/73/EC B.1 bis Acute Toxicity (Oral) Fixed Dose Method.

Species/Strain	Rat/Sprague-Dawley (Crl:CD(SD) IGS BR)
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations.

RESULTS

Sighting Study

Dose mg/kg bw	*Administered*	*Evident Toxicity*	*Mortality*
2000	1F	no	0/1

Signs of Toxicity	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.

Main Study

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	4F	2000	0/4

Discriminating Dose	2000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	All animals dosed at 2000 mg/kg bw showed expected bodyweight gains.

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

TEST FACILITY: SafePharm (2007c)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Analogue 1

METHOD: Similar to OECD TG 402 Acute Dermal Toxicity – Limit Test.

Species/Strain	Rat/Sprague-Dawley
Vehicle	Corn oil
Type of dressing	Occlusive
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
5000	5 per sex	5000	0

LD50	> 5000 mg/kg bw
Signs of Toxicity - Local	No signs of local toxicity were noted.
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted.
Effects in Organs	The only remarkable funding at necropsy was dark red foci on the lungs of one male animal.

CONCLUSION: Analogue 1 is of low toxicity via the dermal route.

TEST FACILITY PSL (1995)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Analogue 1

METHOD Similar to OECD TG 403 Acute Inhalation Toxicity.
Species/Strain Rat/Sprague-Dawley
Vehicle None
Method of Exposure Whole-body exposure
Exposure Period 4 hours
Physical Form Solid aerosol (particulate)
Particle Size 3.6 µm (MMAD) with a geometric standard deviation of 2.3 µm
Remarks - Method No significant deviations.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <units>*		*Mortality*
		Nominal	*Actual*	
1	10 per sex	1.2	0.13	0/10

LC50 > 0.13 mg/L/4 hours
Signs of Toxicity No signs of test substance related toxicity were noted.
Effects in Organs No test substance related abnormalities were noted at gross necropsy.

CONCLUSION As the test concentration was 0.13 mg/L in this study, the potential for toxicity via the inhalation route for Analogue 1 cannot be ruled out.

TEST FACILITY FDRL (1984)

B.4. Irritation – skin

TEST SUBSTANCE Notified polymer

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 2004/73/EC B.4 Acute Toxicity (Skin Irritation).
Species/Strain Rabbit/New Zealand White
Number of Animals 3
Vehicle Distilled water
Observation Period 72 hours
Type of Dressing Semi-occluded
Remarks - Method Intact skin sites on each animal were tested with 0.5g of the test substance (moistened with 0.5 mL of distilled water) using a 4 hour exposure period. Observations were recorded at 1, 24, 48 and 72 hours after patch removal.

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	0.3	0.3	1	< 48 hours	0
Oedema	0	0	0	0	n/a	0

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

Remarks - Results Very slight erythema was noted at all treated skin sites after 1 hour and at 2 out of 3 treated skin sites after 24 hours. All treated skin sites appeared normal at the 48 hours observation.

CONCLUSION The notified polymer is slightly irritating to the skin.

TEST FACILITY SafePharm (2007d)

B.5. Irritation – eye

TEST SUBSTANCE Notified polymer

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation).
Species/Strain Rabbit/New Zealand White
Number of Animals 3
Observation Period 72 hours
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			
Conjunctiva: redness	0.7	0.7	0.7	1	< 72 hours	0
Conjunctiva: chemosis	0.3	0.7	0.3	1	< 72 hours	0
Conjunctiva: discharge	0	0	0	0	-	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0.3	0.3	0	1	< 48 hours	0

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

Remarks - Results Iridial inflammation was noted for all treated animals 1 hour after treatment and in two treated eyes at the 24-hour observation.

Slight conjunctival redness and chemosis was noted for all treated animals up until the 48-hour observation.

No corneal effects were noted.

CONCLUSION The notified polymer is slightly irritating to the eye.

TEST FACILITY SafePharm (2007e)

B.6. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified polymer

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 A screening study was conducted at 50% concentration in the vehicle with a mouse being treated daily for three consecutive days. The animal was observed twice daily for the first three days and once daily on day 4, 5 and 6. Any signs of toxicity or excessive local irritation noted during this period were recorded. The body weight of the mouse was recorded pre-dose on day 1 and post-dose on day 6. The main study was conducted at 10%, 25% or 50% concentration in the vehicle. Positive control is α-hexylcinnamaldehyde.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	1152.58	-
10	1280.04	1.11
25	1805.79	1.57
50	6109.60	5.30
Positive Control		
5	-	2.50
10	-	4.03
25	-	9.13

Remarks - Results: In the screening study with 50% test substance in the vehicle, no signs of systemic toxicity were observed. Fur loss on the neck and head was noted post-dose on day 3 and for the reminder of the test.

In the main study, neither death nor signs of systemic toxicity were noted in treated or control animals. Body weights were similar in treated and control groups.

CONCLUSION: There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified polymer.

TEST FACILITY: SafePharm (2007f)

B.7. Repeat dose toxicity

TEST SUBSTANCE: Notified polymer

METHOD: OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).

Species/Strain: Rats/Sprague-Dawley
Route of Administration: Oral – gavage
Exposure Information: Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: 28 days
Vehicle: Polyethylene glycol 400
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 unscheduled deaths during the study.

Clinical Observations
No toxicologically important clinical signs were noted during the study.
Incidental findings included increased salivation in each sex of animals and staining around the mouth and noisy respiration in males in the 1000 mg/kg/day group, and one occasion of noisy respiration in 1 male in the 15 mg/kg/day group. These incidents were considered by the study authors to be associated with the gavage administration and/or palatability of the test formulations.

Laboratory Findings – Blood Chemistry, Haematology
There was only 1 slight but statistically significant increase in plasma levels of alkaline phosphatase in 1000

mg/kg/day group. However, this isolated increase was considered fortuitous by the study authors based on that individual animal values were all within the normally expected ranges for rats of the strain and age used and there were no histopathological correlates to suggest tissue damage.

Effects in Organs
No test substance related abnormalities were noted in the organ weights measured or in the necropsy or in the histopathology.

CONCLUSION
The No Observed Effect Level (NOEL) was established by the study authors as 1000 mg/kg bw/day in rats, based on the absence of test substance related toxicological significant effects at any of the doses administered.

TEST FACILITY SafePharm (2007g)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified polymer

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure

Species/Strain *S. typhimurium*: TA1535, TA1537, TA98, TA100
E. coli: WP2uvrA

Metabolic Activation System S9 preparation

Concentration Range in Main Test a) With metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate
b) Without metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate

Vehicle Tetrahydrofuran

Remarks - Method A preliminary toxicity test (0-5000 µg/plate) was performed to determine the toxicity of the test substance (TA100 or WP2uvrA).

In the mutation studies, aliquots of 0.025 mL of either test substance or negative control solution, or 0.1 mL of positive control solution were used at 5 concentrations up to 5000 µg/plate. The negative control was tetrahydrofuran and positive controls were N-ethyl-N'-nitro-N-nitrosoguanidine, 9-aminoacridine, and 4-nitroquinoline-1-oxide in the absence of S9 mix and 2-aminoanthracene and benzo[a]pyrene in the presence of S9 mix.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5000	> 5000	≥ 5000	Negative
Test 2		> 5000	≥ 1500	Negative
Present				
Test 1	> 5000	> 5000	≥ 5000	Negative
Test 2		> 5000	≥ 1500	Negative

Remarks - Results No toxicologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

All the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION The notified polymer was not mutagenic to bacteria under the conditions

of the test.

TEST FACILITY SafePharm (2007h)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified polymer

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
Cell Type/Cell Line Lymphocytes
Metabolic Activation System S9 fraction from phenobarbitone/β-naphthoquinone induced rat livers
Vehicle Dimethyl sulfoxide (DMSO)
Remarks - Method Doses up to 1000 µg/mL were chosen based on the maximum practical level with the exception of chromosome aberration test 1 in the presence of S9 (doses up to 750 µg/mL) where toxicity (although limited i.e. < 20% mitotic inhibition) was the deciding factor.

The negative control was DMSO and positive controls were mitomycin C in the absence of S9 mix and cyclophosphamide in the presence of S9 mix.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	62.5, 125, 250, 500*, 750*, 1000*	4	24
Test 2	62.5, 125, 250, 500*, 750*, 1000*	24	24
Present			
Test 1	62.5, 125, 250, 375*, 500*, 750*	4	24
Test 2	62.5, 125, 250, 500*, 750*, 1000	4	24

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 1000	> 1000	≥ 500	Negative
Test 2	> 1000	> 1000	≥ 500	Negative
Present				
Test 1	> 1000	> 750	≥ 500	Negative
Test 2		> 1000	≥ 500	Negative

Remarks – Results The test substance did not induce any statistically significant increases in the frequency of cells with aberrations in any of the exposure groups. The test substance showed some evidence of toxicity to the human lymphocytes in vitro at and above 500 µg/mL.

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

TEST FACILITY SafePharm (2007i)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE: Notified polymer

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.

Inoculum	Activated Sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	TOC-5050A Total Organic Carbon (TOC) Analyser
Remarks - Method	The test was conducted according to the guidelines above using good laboratory practice (GLP). No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation ($ThCO_2$)*	*Day*	*% Degradation ($ThCO_2$)*
1	6	1	30
2	10	2	77
10	22	10	105
28	39	28	103

Remarks - Results: All validity criteria for the test were satisfied. The reference compound, sodium benzoate, reached the 60% pass level by day 2 indicating the suitability of the inoculum. The toxicity control exceeded 25% biodegradation within 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified polymer after the cultivation period was 39%. Therefore, the test substance is classified as not readily biodegradable according to the OECD (301 B) guideline.

CONCLUSION: The notified polymer is not readily biodegradable.

TEST FACILITY: SafePharm (2007j)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified polymer

METHOD: OECD TG 203 Fish Acute Toxicity Test – Semi Static Test

Species	Rainbow Trout (*Oncorhynkus mykiss*)
Exposure Period	96 hours
Auxiliary Solvent	Not reported
Water Hardness	Not reported
Analytical Monitoring	HPLC method
Remarks – Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported. A Water Accommodated Fractions (WAF) of a single loading rate (1000 mg/L) containing the test substance was prepared in dechlorinated tap water. The mixture was stirred for 48 hours and the mixture was allowed to stand for 1 hour. The aqueous phase was removed by filtering

three times though Postlip BW/S filter paper (10 µm retention size) to give the WAF treatment solution. Microscopic inspection of the WAF after filtration showed no micro-dispersions or particles of test material to be present. The toxicity test was conducted as a limit test.

RESULTS

Concentration (mg/L) Nominal	*Number of Fish*	*Mortality*				
		3 h	*24 h*	*48 h*	*72 h*	*96 h*
Control	20	0	0	0	0	0
1000	20	0	0	0	0	0

LL50	> 1000 mg/L at 96 hours (filtered WAF)
NOEL	≥ 1000 mg/L at 96 hours (filtered WAF)
Remarks – Results	All validity criteria for the test were satisfied. There were no sub-lethal effects of exposure observed in any of the fish exposed to the treatment concentration during the 96 hour exposure period.

CONCLUSION The notified polymer is not harmful to fish.

TEST FACILITY SafePharm (2007k)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified polymer

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

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None reported
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC method
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported. A Water Accommodated Fractions (WAF) of a single loading rate (1000 mg/L) containing the test substance was prepared in reconstituted water. The mixture was stirred for 48 hours and the mixture was allowed to stand for 1 hour. The aqueous phase was removed by filtering three times though Postlip BW/S filter paper (10 µm retention size) to give the WAF treatment solution. Microscopic inspection of the WAF after filtration showed no micro-dispersions or particles of test material to be present. The toxicity test was conducted as a limit test.

RESULTS

Nominal Concentration (mg/L)	*Number of D. magna*	*Cumulative % Immobilised*	
		24 h	*48 h*
Control	20	0	0
1000	20	0	0

EL50	> 1000 mg/L at 48 hours (filtered WAF)
NOEL	≥1000 mg/L at 48 hours (filtered WAF)
Remarks - Results	All validity criteria for the test were satisfied. The 48 hour EL50 was greater than 1000 mg/L.

CONCLUSION The notified polymer is not harmful to aquatic invertebrates.

TEST FACILITY SafePharm (2007l)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified polymer
METHOD	OECD TG 201 Alga, Growth Inhibition Test
Species	*Desmodesmus subcapitatus*
Exposure Period	72 hours
Concentration Range	Nominal: 1000 mg/L
Auxiliary Solvent	Not reported
Water Hardness	Not reported
Analytical Monitoring	Not reported
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported. A Water Accommodated Fractions (WAF) of a single loading rate (1000 mg/L) containing the test substance was prepared in the culture medium. The mixture was stirred for 47 hours and the mixture was allowed to stand for 1 hour. The aqueous phase was removed by filtering three times though Postlip BW/S filter paper (10 µm retention size) to give the WAF treatment solution. Microscopic inspection of the WAF after filtration showed no micro-dispersions or particles of test material to be present. The toxicity test was conducted as a limit test.

RESULTS

Growth (72 h)	
E_rL50 (mg/L)	*NOE_rL*
> 1000	≥ 1000

Remarks - Results	All validity criteria for the test were satisfied.
CONCLUSION	The notified polymer is not harmful to algae.
TEST FACILITY	SafePharm (2007m)

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