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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Amide #71 in Disparlon 6650

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 and Water Resources.

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.

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Director
NICNAS

TABLE OF CONTENTS

FULL PUBLIC REPORT

Amide #71 in Disparlon 6650

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Chemiplas Australia Pty Ltd (ABN 29 003 056 808) of 3/112 Wellington Pde, East Melbourne VIC 3002

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:

Purity, Spectral Data, Identity of Non-hazardous Impurities, Manufacture/Import Volume, Information on typical products and Methods of Detection and Determination,

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, Partition Co-efficient, Adsorption/Desorption, Dissociation Constant, Induction of Germ Cell Damage, and Bioaccumulation.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
EPA:1995
EU (UK): 1997
KOREA:1998

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Amide #71 in Disparlon 6650

MOLECULAR WEIGHT
>500 $g.mol^{-1}$

ANALYTICAL DATA
A reference IR spectrum was provided.

METHODS OF DETECTION AND DETERMINATION

Remarks For quality control purposes, the composition of the notified chemical is determined from the ratio of reactants added to the starting material.

3. COMPOSITION

DEGREE OF PURITY
>90%

4. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa White powder

Property	Value	Data Source/Justification
Melting Point/Freezing Point	90-123ºC	Measured
Boiling Point	>175ºC	Decomposition occurred before boiling, starting at 175ºC
Density	1,040 kg/m^3 at 20ºC	Measured
Vapour Pressure	$(5.9 \pm 0.5)\times10^{-5}$ kPa at 20ºC	Measured
Water Solubility	$<6.4\times10^{-4}$ g/L at 20ºC	Measured
n-Octanol Solubility	$<2.3\times10^{-2}$ g/L at room temperature	Measured
Hydrolysis as a Function of pH	Not determined	Not expected to hydrolyse in environmental pH range
Partition Coefficient (n-octanol/water)	log P_{ow} = 13.08	Calculated using KOWIN v1.67
Adsorption/Desorption	Not determined	Expected to adsorb to the soil and sediment based on high partition coefficient
Dissociation Constant	Not determined	No expected modes of dissociation
Particle Size	Inhalable fraction (<100 μm): 100% Respirable fraction (<10 μm): >95% MMAD = 2.8 μm	Measured
Flash Point	Not determined	The notified chemical is a solid with a low vapour pressure
Flammability	Not highly flammable	Measured
Autoignition Temperature	>400ºC	Measured
Explosive Properties	Not explosive	Predicted on the basis of the structural formula

Discussion of Observed Effects

For full details of the physical-chemical properties tests please refer to Appendix A.

Reactivity

The chemical is considered stable, based on its structural formula and from experience in use. There are no known hazardous decomposition products. However, the chemical is combustible and it will burn if involved in a fire, evolving noxious fumes (eg oxides of carbon and nitrogen).

Dangerous Goods classification

Based on the available physico-chemical properties the notified chemical is not classified as a Dangerous Good according to the *Australian Dangerous Goods Code* (FORS, 1998).

5. INTRODUCTION AND USE INFORMATION

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

The notified chemical will be imported as a 70-90% preparation, called “Disparlon 6650”.

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

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

PORT OF ENTRY

The notified chemical will be imported through Fremantle, Sydney, Melbourne, Brisbane and/or Adelaide.

IDENTITY OF MANUFACTURER/RECIPIENTS
The notified chemical will be reformulated into paints at 3-4 sites in Australia, located near main ports in Brisbane and Melbourne.

TRANSPORTATION AND PACKAGING
Disparlon 6650, containing 70-90% notified chemical, will be imported in 15 kg fibre bags. Formulated paint products containing <2% notified chemical will be packaged in 200 L drums and transported to their destination (often the site of application) by truck.

USE
The notified chemical is a thixotropic agent, used to enhance the characteristics of paint formulations. It will be imported within Disparlon 6650, and will be blended with other ingredients to form paints, in particular high build anti-corrosive paints, epoxy primers, chlorinated rubber and polyurethane paints. Final paint and primer products will contain <2% notified chemical.

OPERATION DESCRIPTION
The powder of Disparlon 6650 will be weighed using a weighing machine, and it will be tipped from the fibre bags by paint formulation process workers. It will be transferred into a mixing tank, where it will be combined with other ingredients.

The formulated paint preparations will then be ground using a mill base at an activation temperature of 50-70ºC (using a heat generating dispenser such as a sand grind mill or high-speed dissolver). Where it is difficult to achieve an activation temperature in the suggested range, the addition of 1-2% isopropanol to the paint formulation will be used to reduce the activation temperature.

After formulation, the paint will drained from the mixing tanks, and be packaged directly into 200 L drums by process workers. Successive batches will be formulated and packaged, and the equipment will only be cleaned at the end of production. Spillages will be vacuum-cleaned and disposed of to incineration.

Typical applications for paints containing the notified chemical include the painting of bridges and buildings. The paints containing the notified chemical will be applied at the site using either brushes or airless spray (~30%) or rollers (~70%) by end users, who are typically professional painters. Large sized parts (eg steel structures) will be coated at the site of formulation and transported to their destination by marine. Smaller parts may be coated through a dipping process.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure assessment

6.1.1. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration (hrs/day)*	*Exposure Frequency*
Formulation process worker	2	4 hours	Once daily
Maintenance	2	1 hour	Intermittent
Cleaning staff	2	1 hour	Intermittent
End users (professionals)	5-10	1-8 hours	100-150 days/year

Exposure Details

Formulation process workers will experience the most significant levels of exposure to the notified chemical. Significant dermal, ocular and inhalation exposure may occur when opening bags, and during weighing and transfer of the powder containing the notified polymer to the mixer. Airborne dusts of the imported preparation of the notified chemical (70-90%) are likely to be generated. The EASE model predicts a maximum likely atmospheric particulate concentration of 1 mg/m^3 during weighing and addition of powder to the mixer (EASE). However, a lower atmospheric concentration is more likely given that low dust techniques will typically be used and direct handling should be limited (once a day, for only a short period).

Given an hour's exposure to airborne dusts of the notified chemical per day, assuming 100% lung deposition and an estimated respiration rate of an adult male engaged in heavy activity of 3.0 m^3/hr

(EC, 2003), the expected worst-case daily exposure level for a 70 kg worker is estimated as:

$$(1 \times 3.0\ m^3/hr \times 1\ mg/m^3 \times 1\ hr) \div 70\ kg = 0.043\ mg/kg\ bw/day$$

Process workers will wear full personal protective equipment (including an anti-dust respirator) and industrial engineering measures such as local exhaust ventilation will be used to minimise the airborne notified chemical level during weighing and addition. In addition, process workers will wear chemical-resistant clothing, chemical protective gloves and protective eyewear.

Once the notified chemical has been added to the mixing tanks, there will be little further potential for significant exposure of workers, as further steps will occur within a closed system (the mixing tank). Inhalation exposure due to aerosols released during mixing is considered to be unlikely due to the sealed tank and exhaust ventilation systems. It will be formulated into paint products (<2%), and will be packaged from the mixing tanks directly into drums. During packaging, low-level dermal and/or ocular exposure could occur due to drips and spills.

Maintenance and cleaning workers may also experience dermal, inhalation or possibly ocular exposure to the notified chemical during the performance of their duties. This exposure will be either to residual powders of the notified chemical (70-90%) or to the notified chemical bound within paint residues (wet and dry). As any exposure is likely to be only intermittent, it is likely to be minimal overall. These workers may wear some PPE such as safety glasses, gloves and/or coveralls.

End users will consist mainly of professional painters. Dermal and/or ocular exposure to wet and dry paint products containing the notified chemical is expected, during the opening of containers, mixing and applying the paint and during the cleaning of equipment. The only potential for inhalation exposure exists where paint is applied using spray equipment.

- Professional painters are expected to wear coveralls as a minimum, and may wear a respirator, safety glasses and gloves depending on the characteristics of the paint being used.
- Coating application workers at the notifier's site will wear chemical protective gloves, paint mist respirator, chemical resistant clothing and eye protection, and will operate under adequate ventilation.

Dermal exposure of **all workers** to the notified chemical in cured paint and primer products is likely. However, in this state it is expected to be "trapped" within the matrix of the paint, and thus not be available to cause exposure.

6.1.2. Public exposure

The notified chemical will not be sold to or utilised by the public in the neat form. Paints and primers containing the notified chemical will also not be sold to or made available for use by the public. Therefore, exposure to the notified chemical should not occur under normal use. Although accidental exposure (eg in a transportation spill) is possible, it is considered improbable.

Where paint is professionally applied by spray in a populated area (eg to buildings or bridges), indirect public inhalation exposure cannot be ruled out. The notifier has advised that less efficient methods of spray application (eg airless spray) are not recommended for use in populated areas, but proposes that electrostatic airless spray is suitable provided an electro-conductive mist collector shield is used to prevent the diffusion of the spray mist away from the coating area.

The primary expected public exposure would be dermal, to surfaces coated with paints and primers containing the notified chemical. When paints containing the notified chemical are cured, it is expected to be unavailable to cause exposure.

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		*Assessment Conclusion*
Rat, acute oral toxicity	LD50 >2,000 mg/kg bw *(Study 1)*	Low toxicity
	LD50 >5,000 mg/kg bw *(Study 2)*	
Rat, acute dermal toxicity	LD50 >2,000 mg/kg bw *(Study 1)*	Low toxicity
	LD50 >2,000 mg/kg bw *(Study 2)*	
Rat, acute inhalation toxicity	LC50 >5.08 mg/L/4 hr *(Study 1)*	Low toxicity
	LC50 >5.00 mg/L/4 hr *(Study 2)*	
Rabbit, skin irritation (two studies)		Non-irritating
Rabbit, eye irritation (two studies)		Non-irritating/minimal irritant
Guinea pig, skin sensitisation – adjuvant and non-adjuvant test		Extreme sensitisation
Rat, repeat dose oral toxicity – 28 days		NOAEL = 200 mg/kg bw/day
Genotoxicity – bacterial reverse mutation		Not mutagenic
Genotoxicity – *in vitro* Mammalian Chromosomal Aberration Test		Not clastogenic

Toxicokinetics, metabolism and distribution

The notified chemical is not expected to be readily bioavailable, as it is hydrophobic (log P_{ow} = 13.08) and has a relatively high molecular weight (>500 Da). It has the potential to be absorbed across biological membranes, but the absorption of significant amounts of notified chemical is unlikely. Any dermal absorption would be minimal, given the properties of the notified chemical. No evidence of dermal absorption was observed in the acute dermal toxicity study; however, dermal absorption would be necessary for the sensitisation reactions seen in the guinea pig maximisation study. Sensitisation may also be induced by lower molecular weight impurities that would be more readily absorbed (see below).

Some absorption following oral exposure is probable, given the adverse splenic and haematopoietic effects observed in the in the rat 28-day repeat dose oral toxicity study. Hydrophobic chemicals such as the notified chemical are thought to have a propensity to form micelles in the gastrointestinal tract, which may be taken up by the lymphatic system from the small intestine (EC, 2003). Such lymphatic absorption may explain the relatively selective toxicity to spleen and bone marrow that was observed in the 28-day oral toxicity study, perhaps mediated by the cells of the reticuloendothelial system.

Given the hydrophobic nature of the notified chemical, any absorbed chemical is not expected to distribute significantly throughout the body; rather it would be predisposed to be bound to cellular membranes and to distribute into adipose tissue (EC, 2003). If exposure were continuous, the potential for bioconcentration in these regions could result in more severe effects than would be expected for the given exposure level. Following an oral exposure to the notified chemical, a wider distribution may be possible, as micelles of the notified chemical may be carried to the general circulation through lacteals and the thoracic duct.

The notified chemical may be metabolised by non-specific hydrolase enzymes (eg nonspecific carboxylesterases) to yield smaller species. These species may be quite different to the notified chemical *in vivo*, in terms of their toxicity, distribution and elimination.

Acute toxicity

The notified chemical was found to be non-lethal after an acute dose by any of the oral, dermal and inhalation routes. No treatment-related systemic or local signs of toxicity were observed in oral or skin-treated animals, during the treatment period or at necropsy.

Following inhalation exposure to respirable powders (<10 μm) of the notified chemical, adverse effects on the treated animals included difficult or decreased respiration, piloerection and lethargy. These effects are likely to be induced by the particulate burden on the lungs of treated animals, as all of these effects had reversed by the second day after dosing.

Lung staining and/or discolouration were seen at necropsy in most of the treated test animals of one study. These effects indicated local action of the notified chemical on the lungs, but the observations were variable, indicating that different effects may have been occurring in different animals. No histopathology was performed on these tissues to identify the nature of the observed effects. The hydrophobic nature of the notified chemical and its small particle size may imply a long half-life for any deposition in the lung, as it will not be as readily cleared by mucociliary action (EC, 2003).

Irritation and Sensitisation

The notified chemical was generally found to be non-irritant to eyes and skin. One rabbit acute eye irritation study showed that the notified chemical elicited reversible, minimal irritation (rated 3 on a severity scale of 1 to 8).

A guinea pig maximisation test showed that 9 out of 10 treated animals elicited skin reactions indicative of dermal sensitisation, and thus it is considered an extreme sensitiser. Chemical sensitisation reactions are thought to occur following the reaction of a chemical with cellular material, resulting in the formation of a hapten (Eaton and Klaasen, 1996). In the case of the notified chemical, this might be expected to be the result of activation through metabolism to form a reactive species, but a potential mechanism is not apparent. Analysis of the notified chemical against known structural alerts for skin sensitisers (Barratt *et al*, 1994) showed that it was not homologous to those known sensitisers.

Some component of the sensitising properties of the notified chemical may be related to an impurity - a precursor chemical that is a known human skin sensitiser (SIDS, 2001). This precursor chemical has been reported to be the causative agent in occupational allergic contact dermatoses such as eczema (MS *et al*, 1986; GR and HK, 1990; SS and SMW, 2001). This sensitising species may also be formed *in vivo* as a metabolite.

There is no evidence to exclude the possibility that the notified chemical may induce respiratory sensitisation after repeated inhalation exposure. The probability of such effects may be higher given the potency of the notified chemical to induce skin sensitisation.

Repeated Dose Oral Toxicity (sub acute)

The main effects of the notified chemical observed from a rat 28-day repeat dose toxicity study were spleen enlargement and anaemia. The increased spleen weight of treated animals was thought to be attributable to increased red blood cell sequestration and extramedullary haematopoiesis in the spleen. The NOAEL of 200 mg/kg bw/day was set, despite the increase in spleen weights seen in all treated male animals, on the basis of the absence of haematopoietic effects.

The cause of the observed anaemia is unknown, but may have been due to increased red blood cell sequestration by the spleen. Alternatively, it may have been caused by local effects within bone marrow on haematopoiesis, where the notified chemical had distributed into bone marrow fatty tissue.

The lymphatic and reticuloendothelial systems may be involved in the absorption and distribution of the notified chemical (as speculated above); however, the study did not investigate effects on these systems, nor did it examine lymph nodes for abnormalities.

Mutagenicity/Carcinogenicity

The notified chemical was found to be non-mutagenic in a bacterial reverse mutation test, and non-clastogenic in an *in vitro* human lymphocyte cell tests. Based on this information, it is not considered to have a high potential to be mutagenic or carcinogenic *in vivo*.

One impurity within the notified chemical may have carcinogenic effects. In an Ames study, this chemical was not found to be mutagenic (MS-R *et al*, 1980). However, in a repeated dose rat carcinogenicity study, where the chemical was administered by subcutaneous injection, a range of tumours was observed (DS *et al*, 1970), and these included distributed subcutaneous sarcomas, pulmonary tumours and lymphomas. The authors of the study only tentatively concluded that this chemical was a “weak carcinogen”, as the incidence of sarcomas was higher at lower doses than with higher doses.

Observations on Human Exposure

Preparations and products containing the notified chemical have been used worldwide for a number of years, and, no evidence of any hazardous effects (including sensitisation) has yet been observed.

Classification

Based on the data from the guinea pig maximisation test, the notified chemical is classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004):

Xi, R43 May cause sensitisation by skin contact.

The imported powdered product Disparlon 6650 (70-90% notified chemical) and any formulated paint products containing >1% notified chemical, also meet the criteria for classification as hazardous substances.

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

General description of risk

Imported formulation: Containing 70-90% notified chemical (Disparlon 6650) and comprised of mainly respirable particles, this material will present the most significant risk to workers. Even low exposure levels are likely to be sufficient to result in sensitisation. This material has the potential to induce dermal and potentially respiratory sensitisation following repeated or prolonged exposure.

Formulated paint products: These products will contain <2% of the notified chemical, and are likely to be viscous liquids containing a variety of other ingredients including pigments and polymers. Many of these paints are additionally likely to be hazardous because of other components of their formulation than the notified chemical. The greatest risk of sensitisation would arise from dermal exposure, as it is the most probable route of exposure. A risk of respiratory sensitisation is also posed by inhalation exposure to sprayed paint droplets.

Formulation process workers

These workers are the only group expected to experience significant exposure to the imported formulation, and thus have the highest risk of respiratory sensitisation to the notified chemical. In addition, while the notified chemical is a dry powder, limiting dermal exposure, there is a high risk of dermal sensitisation.

These workers may also be exposed to the notified chemical formulated into paints during other stages of production, and this exposure may occur more frequently as the paints may be viewed as being of lower hazard, depending on the formulation. Repeated dermal exposure to these paints may precipitate sensitisation to the notified chemical.

These workers perform their duties in an environment where the risks are likely to be minimised according to the hierarchy of controls: exhaust ventilation and appropriate handling procedures are likely. The risk of respiratory and skin sensitisation would also be limited by the proposed PPE: respirator, coveralls, gloves and eyewear. Any risk of other toxic effects would be also be reduced by the use of this PPE (eg irritant effects to the eyes, carcinogenicity).

While the notifier claims that no evidence of sensitisation or other effects have been observed overseas, some workplace health monitoring of these workers for occupational asthma or allergic skin reactions (eg eczema or urticaria) is recommended.

Maintenance and cleaning workers

These workers may experience occasional exposure to the notified chemical, and this may be of concern as this exposure may occur in the absence of the hierarchy of controls that may be applied in other circumstances where exposure to the notified chemical may occur. Any exposure is likely to be low level, but this does not negate the potential risk of skin and/or respiratory sensitisation. This risk is likely to be preventable using PPE, such as that recommended for other at-risk workers: respirator, coveralls, gloves and eyewear.

End users - professional painters

The risk of sensitisation effects for workers involved in the application of the paint by dipping, rollers and brushes is considered acceptable provided good working practices are maintained and suitable PPE is worn, such as coveralls, protective eyewear and impervious gloves.

The potential risk of skin and respiratory sensitisation is significant for workers involved in spray application. The risk to these workers would be reduced by the use of coveralls, impervious gloves,

protective eyewear and a suitable respirator. However, the sensitisation risk for these workers is considered high in situations where higher-level exposure controls (such as isolation of the spray painting process or engineering controls) are absent. Under these circumstances, consideration should be given to practices that isolate workers from any exposure to the notified chemical (eg full-body encapsulation).

6.3.2. Public health

The exposure of the public to the notified chemical is generally expected to be negligible and thus the risk to public health is considered negligible.

The potential for public exposure and risk of sensitisation effects cannot be ruled out where the spray application of paints containing the notified is carried out in a populated area. This risk would be reduced by appropriate spray techniques (eg electrostatic airless spray application), the erection of physical barriers or where an appropriate exclusion zone is established around the spray operation. Electrostatic airless spray application has an expected application efficiency of 40-80%, and this may be considerably less under windy conditions.

It is recommended that where paint containing the notified chemical is intended to be applied in a populated area, that wherever practicable it be applied using means other than spray.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

There will be minimal or no release of the substance during the formulation of the preparation into the paint products. The formulation of the paint products will be performed in a closed system. Residues remaining in the mixing vessels will be incorporated into the next batch. During formulation, both exhausted air and wastewater are filtered before release; hence, exposure of the substance to the aqueous and air compartments from this part of the life cycle will be minimal. Any waste from the process, including the filters will be disposed of as chemical waste by incineration. Residues in the imported bags are estimated to account for <0.1% of the imported chemical.

RELEASE OF CHEMICAL FROM USE

The paints containing the notified chemical will be used by industry as a protective coating/primer for structural steel. Steel surfaces either will be pre-coated with the primer at the formulation sites prior to transportation to the final destination, or will be coated on site for existing structures such as bridges or buildings. The notifier has indicated that the paint will be applied by roller (70%) and by brush (30%). The major potential for environmental exposure for these application methods is through the cleaning of the application equipment. As a worst-case scenario, it will be assumed that this route of exposure will account for 5% of the imported chemical that will be disposed of to the sewer through washing of the equipment. The transfer efficiencies of brushes and rollers is high, particularly for paints of high viscosity, it is estimated that <1% of the notified chemical will be released as a result of application through splashes and drips. It is expected that these releases will be left on the ground, collected with adsorbent and disposed of through industrial waste to landfill.

RELEASE OF CHEMICAL FROM DISPOSAL

Waste notified chemical will be generated annually during the manufacture of the paint, from the cleaning of coating equipment and as residues from the packaging of the products containing the notified chemical (paper bags of the imported product and drums of the formulated paints). Waste from the formulation will be disposed of as chemical waste by incineration.

The bags used import the chemical, containing residual chemical, will be disposed in of to landfill through industrial waste. Residues in paint drums are expected to account for <0.1% of the imported chemical and are expected to be disposed of via incineration.

The majority of the notified chemical will be share the fate of paints into which it has been incorporated. These are expected to share the fate of the surfaces to which they have been applied at the end of their useful life and be recycled.

7.1.2 Environmental fate

The notified chemical is not readily biodegradable according to OECD Guideline 301B. The notified chemical has a molecular weight below 1,000 Da and thus it could potentially cross biological membranes. However, the relatively large molecular weight and predicted partition coefficient of the notified chemical indicate that it would not be expected to bioaccumulate.

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

7.1.3 Predicted Environmental Concentration (PEC)

A PEC has been determined based on the worst case assumption that 5% of the imported chemical will be disposed of to the sewer as a result of the cleaning of application equipment, and assuming that all the chemical remains in the effluent.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	5,000	kg/year
Proportion expected to be released to sewer	5%	
Annual quantity of chemical released to sewer	250	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	0.68	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	20.496	million
Removal within STP	0%	
Daily effluent production:	4,099	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.17	µg/L
PEC - Ocean:	0.02	µg/L

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 > 100 mg/L	The notified chemical is not toxic to carp.
Daphnia Toxicity	EC50 > 0.64 mg/L	The notified chemical is not toxic to *Daphnia* up to the limit of its water solubility. Undissolved material appears to have a physical effect on *Daphnia*.
Algal Toxicity	EC50 > 100 mg/L	The notified chemical is not toxic to algae up to the level of its water solubility. However, undissolved material appears to have an effect on the absorption of light by the algae resulting in a slight effect on growth rate
Inhibition of Bacterial Respiration	IC50 >100 mg/L	The test material is practically non-toxic to sewage microorganisms.

As a comparison only, the classification of the notified chemical 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***
Environment: Chronic hazard	4	May cause long lasting harmful effects to aquatic life

7.2.1 Predicted No-Effect Concentration

Aquatic ecotoxicity data were provided for four trophic levels. No effects were observed for fish and sewage microorganisms up to the maximum concentration tested. The effects observed for both *Daphnia* and algae were attributed to the presence of undissolved material due to the low water solubility of the notified chemical. The following Predicted No-Effect Concentration has been calculated based on the lowest EC50 value for *Daphnia* and applying an assessment factor of 100.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50	>0.64	mg/L
Assessment Factor	100	
PNEC	>6.4	µg/L

7.3. Environmental risk assessment

The majority of the notified chemical will be incorporated into industrial paints and applied to metal surfaces as a protective coating/primer. Once incorporated into the cured paint matrix the notified chemical is not expected to be mobile and will share the fate of the metal surface at the end of its useful lifetime. Recycling of the metal surfaces will result in the combustion of the paint containing the notified chemical resulting in its conversion to oxides of carbon and nitrogen and water.

Incineration of the small amounts of the notified chemical (<0.1%) will also occur as a result of the recycling of empty paint drums. A small amount of the notified chemical (<0.1%) will be disposed of to landfill as industrial waste as residuals in the import bags or as cured paint sorbed to absorbent material used to clean spills. In landfill, the notified chemical is not expected to be mobile based on its low water solubility. The inert nature of the cured paint matrix will further diminish any mobility within landfill.

The cleaning of application equipment has the greatest potential for environmental exposure through disposal of the washings to sewer.

Based on the above PEC and PNEC values, the following Risk Quotient has been calculated.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.17	>6.4	<0.026
Q - Ocean	0.02	>6.4	<0.003

The above risk quotients indicate that the proposed import volume and use pattern is expected to pose an acceptable risk to the aquatic environment.

8. CONCLUSIONS – SUMMARY OF RISK ASSESSMENT FOR THE ENVIRONMENT AND HUMAN HEALTH

8.1. Hazard classification

Based on the available data the notified chemical is classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). The classification and labelling details are (for the notified chemical and products containing the notified chemical at >1% concentration):

Xi: R43	May cause sensitisation by skin contact
S22	Do not breathe dust.
S24	Avoid contact with skin
S36/37	Wear suitable protective clothing/gloves

and

As a comparison only, the classification of notified chemical 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 sensitiser	1	May cause allergic skin reaction
Environment: Chronic hazard	4	May cause long lasting harmful effects to aquatic life

8.2. Environmental risk assessment

On the basis of the PEC/PNEC ratio, the notified chemical is not considered to pose a risk to the environment based on its reported use pattern.

8.3. Human health risk assessment

8.3.1. Occupational health and safety

Under the conditions of the occupational settings described, the risk of sensitisation to workers is considered high, but acceptable given the appropriate use of engineering controls and personal protective equipment, as recommended.

8.3.2. Public health

When used in the proposed manner, the risk to public health posed by the notified chemical is considered negligible. However, the risk of a sensitisation response in exposed individuals cannot be ruled out.

9. MATERIAL SAFETY DATA SHEET

The MSDS of the notified chemical provided by the notifier was reviewed by NICNAS and is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant. The MSDS was found to be in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 2003).

10. RECOMMENDATIONS

REGULATORY CONTROLS

Hazard Classification and Labelling

- The Office of the ASCC, Department of Employment and Workplace Relations (DEWR), should consider the following health hazard classification for the notified chemical:
  - *Xi: R43May cause sensitisation by skin contact.*
  - *S22 Do not breathe dust.*
  - *S24 Avoid contact with skin*

- *S36/37 Wear suitable protective clothing/gloves*

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - *>1%: Xi: R43 May cause sensitisation by skin contact.*

- The following safety phrases should appear on the MSDS and label for the notified chemical and those for products containing the notified chemical:
  - *S22 Do not breathe dust.*
  - *S24 Avoid skin contact*
  - *S36/37 Wear suitable protective clothing/gloves*

Health Surveillance

- As the notified chemical is a skin sensitiser and potential respiratory 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 sensitisation. Workers who become sensitised to the notified chemical should be transferred to another workplace and not continue to handle the chemical.

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure wherever powders containing the notified chemical occur:
  - *Low dust techniques*
  - *Local exhaust ventilation*

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced, and in formulated paint products:
  - *Avoid generation of airborne dusts during paint formulation*
  - *Avoid skin contact*
  - *Avoid breathing dusts or sprayed paint containing the notified chemical*
  - *Restrict access to areas where spray painting is being carried out*
  - *Care must be taken to avoid exposure of workers to spray drift*

- Use of spray paints containing the notified chemical should be accordance with the NOHSC National Guidance Material for Spray Painting (NOHSC, 1999) or relevant State and Territory Codes of Practice.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced, and in formulated paint products:
  - *Impermeable gloves*
  - *Coveralls*
  - *Eye protection*
  - *Suitable respirators (where any possibility of inhalation exposure exists)*

  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 NOHSC *Approved Criteria for Classifying Hazardous Substances*, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Public Health

- The employer should implement measures to minimise public exposure to the notified chemical during spray application in populated areas, including:
  - *Avoid spray application if possible;*
  - *Electrostatic airless spray may be used, provided an electro-conductive mist collector shield is used*
  - *Establish appropriate spray paint exclusion zone*
  - *Public access to spray paint application areas should be restricted until the paint is completely dry*
  - *Steps should be taken to minimise spray drift during spray application under windy conditions*

Disposal

- The notified chemical should be disposed of by incineration or landfill.

Emergency procedures

- Spills/release of the notified polymer should be contained (i.e. collect spilled material with an inert absorbent) and the resulting waste disposed of to an authorised landfill.

11. REGULATORY OBLIGATIONS

This risk assessment is based on the information available at the time of notification. If the circumstances under which the notified chemical was assessed change a reassessment may be needed. Under 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 whether or not the notified chemical has been listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of Chemicals Notification and Assessment 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, or is likely to change significantly;
  - the amount of chemical being introduced has increased, or is likely to increase, significantly;
  - in the case of a chemical not manufactured, or proposed to be manufactured, in Australia at the time of assessment – it has begun to be manufactured in Australia;
  - the method of manufacture of the chemical in Australia has changed, or is likely to change, in a way that may result in an increased risk of an adverse effect of the chemical on occupational health and safety, public health, or the environment;
  - 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.

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Appendix A: Physico-Chemical Properties

Melting Point/Freezing Point 90-123ºC

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Measured by differential scanning calorimetry. The temperature at which melting began was unclear, and may have been as low as 32ºC. The range of values indicated were the temperatures at which the majority of the melting occurred. After melting, the liquid sample was light yellow in appearance.
TEST FACILITY Notox (1996*b*)

Boiling Point >175ºC

Remarks In a preliminary melting point test, an exothermic reaction occurred at temperatures >175ºC, probably due to reaction or decomposition of the sample.
TEST FACILITY Notox (1996*b*)

Density 1,040 kg/m^3 at 20ºC

METHOD EC Directive 92/69/EEC A.3 Relative Density.
Remarks Determination was made using the gas comparison method.
TEST FACILITY Notox (1996*c*)

Vapour Pressure $(5.9 \pm 0.5)\times10^{-5}$ kPa at 20ºC

METHOD EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Determination was made using the static technique with a capacitance manometer.
TEST FACILITY Notox (1996*d*)

Water Solubility $<6.4\times10^{-4}$ g/L at 20ºC

METHOD OECD TG 105 Water Solubility.
EC Directive 92/69/EEC A.6 Water Solubility.
Remarks An analytical method that measured the concentration of the notified chemical could not be developed, so no main study was performed. The solubility of the substance in water was determined by visual observation after adding 3.2×10^{-3} g to 5 L of double distilled water and stirring for 167.5 hrs at room temperature.
TEST FACILITY Notox (1997*a*)

n-octanol Solubility $<2.3\times10^{-2}$ g/L n-octanol at room temperature

METHOD OECD TG 117 Partition Coefficient (n-octanol/water).
EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks Analytical Method: Flask method
The n-octanol solubility was determined as a component of the determination of the n-octanol/water partition coefficient by adding 2.3×10^{-3} g to 100 mL of n-octanol and stirring for approximately 25 days at room temperature.
TEST FACILITY Notox (1997*b*)

Hydrolysis as a Function of pH

Remarks Not measured, as substance is a poorly soluble material for which an adequate analytical method could not be developed. The notified chemical contains functionalities that are susceptible to hydrolysis at extreme pH values. Hence, hydrolysis of the notified chemical is not expected to occur within the environmental pH range (4-9).

Partition Coefficient (n-octanol/water) log P_{ow} = 13.08 (calculated)

Remarks Attempts to determine the log P_{ow} experimentally were unsuccessful due to the poor solubility of the test material in both water and n-octanol. QSAR prediction

of the log P_{ow} value was based on fragmentation using KOWIN v1.67.

TEST FACILITY Notox (1997*b*)

Adsorption/Desorption Not determined

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

Remarks Not measured, as the notified chemical is a poorly soluble material. The notified chemical is expected to adsorb strongly to soils and sediments based on the predicted log P_{ow}.

Dissociation Constant Not determined.

Remarks The dissociation constant of the notified chemical was not measured, as it is poorly soluble and has no expected modes of dissociation.

Particle Size

METHOD The particle size was determined according to the method of Lee (Lee, 1972).

Range (μm)	*Mass (%)*
≤ 32.0	100%
≤ 20.5	99.6%
≤ 8.2	95.1%
≤ 5.0	70.0%
≤ 3.1	57.2%
≤ 1.9	28.0%
≤ 1.1	19.2%
≤ 0.7	8.8%
≤ 0.4	4.9%
≤ 0.1	2.6%

Remarks The particle size was determined in the test atmosphere as a part of the acute (4-hour) inhalation toxicity study. The mass median aerodynamic diameter (MMAD) was determined to be 2.8 μm.

TEST FACILITY TNO (1997)

Flash Point Not determined

Remarks The notified chemical is a solid with a low vapour pressure.

Flammability Not highly flammable

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).

Remarks The test sample of the notified chemical could not be ignited, but melted upon contact with the ignition source.

TEST FACILITY Notox (1996*e*)

Autoignition Temperature >400ºC

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.

Remarks No endothermic or exothermic reaction was observed during the test.

TEST FACILITY Notox (1996*f*)

Explosive Properties Not explosive

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.

Remarks Not explosive based on its structural formula (contains no unstable or highly energetic groups), and based on experience in use.

TEST FACILITY Notox (1996*g*)

Appendix B: Toxicological Investigations

B.1.1 Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 401 Acute Oral Toxicity. EC Directive 92/69/EEC B.1 Acute Toxicity (Oral).
Species/Strain	Rat/Wistar Crl:(WI) BR
Vehicle	Corn Oil
Remarks – Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M	2,000 mg/kg	0
2	5F	2,000 mg/kg	0

LD50	>2,000 mg/kg bw
Signs of Toxicity	No clinical signs of toxicity were observed. Body weight gain was considered normal in all groups, relative to historical controls.
Effects in Organs	No abnormalities were found in macroscopic post mortem examinations.
Remarks – Results	None
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Notox (1996*h*)

B.1.2 Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	US EPA Federal Insecticide, Fungicide and Rodenticide Act (FIFRA): Pesticide Assessment Guidelines Subdivision F; Hazard Evaluation Human and Domestic Animals, Section 81-1 "Acute Oral Toxicity Study", Revised November 1984. Toxic Substances Control Act (TSCA): Health Effects Testing Guidelines; Subpart B, Section 798.1175 "Acute Oral Toxicity"
Species/Strain	Rat/Sprague-Dawley
Vehicle	Arachis Oil BP
Remarks - Method	In the range-finding study, animals were observed for deaths or overt signs of toxic effects 30 minutes, 1, 2 and 4 hours after dosing, then subsequently once daily for 5 days. In the main study, animals were observed for deaths or overt signs of toxic effects 30 minutes, 1, 2 and 4 hours after dosing, then subsequently once daily for 14 days.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
Range finding study	1M, 1F	5,000	0
Main study	5M, 5F	5,000	0

LD50	>5,000 mg/kg bw
Signs of Toxicity	No signs of systemic toxicity were observed during the study.
Effects in Organs	No abnormalities were observed at necropsy.
Remarks - Results	None.
CONCLUSION	The notified chemical is of low toxicity via the oral route.

TEST FACILITY	Safepharm (1994*a*)

B.2.1 Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal).
Species/Strain	Rat/ Wistar Crl:(WI) BR
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*
1	5M, 5F	2,000 mg/kg	0

LD50	>2,000 mg/kg bw
Signs of Toxicity - Local	No clinical signs of toxicity were observed.
Signs of Toxicity - Systemic	No clinical signs of toxicity were observed. Some changes in body weight were observed, but these were not considered toxicologically significant as they were within the expected range.
Effects in Organs	No abnormalities were found in the animals at macroscopic post mortem examination.
Remarks – Results	None.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Notox (1996*i*)

B.2.2 Acute toxicity – dermal

TEST SUBSTANCE	Notified Chemical
METHOD	US EPA Federal Insecticide, Fungicide and Rodenticide Act (FIFRA): Pesticide Assessment Guidelines Subdivision F; Hazard Evaluation Human and Domestic Animals, Section 81-2 "Acute Dermal Toxicity Study", Revised November 1984. Toxic Substances Control Act (TSCA): Health Effects Testing Guidelines; Subpart B, Section 798.1100 "Acute Exposure Dermal Toxicity"
Species/Strain	Rat/Sprague-Dawley
Vehicle	Arachis oil BP
Type of dressing	Semi-occlusive.
Remarks - Method	The notified chemical was applied to an area of shorn skin, approximately 10% of total body surface area. The animals were caged individually during the 24-hour treatment period. Animals were observed for deaths or overt signs of toxicity 30 mins, 1, 2 and 4 hours after dosing, and subsequently once daily 14 days.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M, 5F	2,000	0

LD50	>2,000 mg/kg bw
Signs of Toxicity - Local	No signs of skin irritation were observed during the study.
Signs of Toxicity - Systemic	No signs of systemic toxicity were observed during the study.

Effects in Organs	No abnormalities were observed upon necropsy.
Remarks - Results	None.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Safepharm (1994*b*)

B.3.1 Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity. EC Directive 92/69/EEC B2 Acute Toxicity: Inhalation
Species/Strain	Rat/Wistar Crl:[WI]WU BR
Vehicle	The test material was delivered using a slipstream of air-conditioned room air.
Method of Exposure	Nasal exposure only
Exposure Period	4 hours
Physical Form	Solid aerosol (particulate)
Particle Size	MMAD = 2.8 μm 70% of particles measured in the animals' breathing zone had an aerodynamic diameter ≤5.0 μm, and all were <32 μm.
Remarks – Method	A group of 5 male and 5 female rats was exposed by inhalation to the limit concentration of at least 5 g/m^3 for a single 4-hour period. Animals were secured in plastic animals holders during exposure. The study concluded with necropsy after a 14-day observation period.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (g/m^3)*		*Mortality*
		Nominal	*Actual*	
1	5M	10.0	5.08 ± 0.19	0/5
2	5F	10.0	5.08± 0.19	0/5

LC50	>5.08 mg/L/4 hrs
Signs of Toxicity	Clinical signs during exposure consisted of a slightly decreased breathing rate in all animals that developed in severity from slight in the first hour to moderate during the remainder of the exposure period. In addition, slightly laboured breathing was noted in two male rats in the last two hours of exposure. Clinical signs shortly after exposure consisted of moderately decreased breathing rate, piloerection, hunched posture, blepharospasm and sluggishness, in all animals. During the first day of the observation period, sluggishness could still be seen in three males and in all females. Ruffled fur was noted in two male and in all female animals. All effects had reversed by day 2 after treatment. Less frequent findings on the first day consisted of soiled fur, encrustations around eyes, nasal encrustations and grunting respiration, all of which had resolved by the second day of observation. In the remainder of the 14-day observation period, no exposure related abnormalities were seen. All male rats, except one, showed reduced body weight gain in the first week after exposure. Thereafter, normal body weight gain was observed. Females showed normal body weight gain throughout the observation period.
Effects in Organs	Abnormalities at necropsy were limited to the lungs and consisted of a few white spots on two lobes in three male animals and on one lobe in one female animal. Discolouration of the lungs was observed in two other female animals; pale in one and slightly red/brown in the other.

Remarks – Results	None
CONCLUSION	The notified chemical is of low toxicity via inhalation.
TEST FACILITY	TNO (1997)

B.3.2 Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity. EC Directive 92/69/EEC, 93/21/EEC B.2 Acute Toxicity (Inhalation). US EPA Guidelines 40 CFR 798.1150
Species/Strain	Rat/Sprague-Dawley
Vehicle	
Method of Exposure	Nose-only exposure.
Exposure Period	4 hours
Physical Form	Solid aerosol (particulate).
Particle Size	MMAD = 2.7 μm Respirable fraction <1 μm = 18.3%
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	5M, 5F	15.5	5.00	0/10

LC50	>5.00 mg/L/4 hours.
Signs of Toxicity	Commonly observed abnormalities included wet fur, hunched posture, piloerection, lethargy, ataxia, decreased respiratory rate and ptosis. Incidents of laboured, gasping and noisy respiration and isolated incidents of increased respiratory rate and red/brown staining around the eyes and snout were noted. All effects had resolved by the second day after exposure.
Effects in Organs	No abnormalities were observed upon necropsy.
Remarks - Results	None.
CONCLUSION	The notified chemical is of low toxicity via inhalation.
TEST FACILITY	Safepharm (1994*c*)

B.4.1 Irritation – skin

TEST SUBSTANCE	Notified chemical
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	Three males
Vehicle	Distilled water
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks – Method	Rabbits were exposed to the notified chemical for 4 hours, and observations were made 1, 24, 48 and 72 hours after exposure.

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	0	0	-	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: The dermal application of the notified chemical was non-irritating to the skin of test rabbits. No corrosive effects were observed.

CONCLUSION: The notified chemical is non-irritating to skin.

TEST FACILITY: Notox (1996*j*)

B.4.2 Irritation – skin

TEST SUBSTANCE: Notified chemical

METHOD: US EPA Federal Insecticide, Fungicide and Rodenticide Act (FIFRA): Pesticide Assessment Guidelines Subdivision F; Hazard Evaluation Human and Domestic Animals, Section 81-5 "Primary Dermal Irritation Study", Revised November 1984.
Toxic Substances Control Act (TSCA): Health Effects Testing Guidelines; Subpart B, Section 798.4470 "Primary Dermal Irritation"

Species/Strain: Rabbit/New Zealand White
Number of Animals: Six (5 males, 1 female)
Vehicle: Distilled water
Observation Period: 72 hours
Type of Dressing: Semi-occlusive
Remarks - Method: Rabbits were exposed to the notified chemical for 4 hours, and observations were made 1, 24, 48 and 72 hours after exposure.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema/Eschar	0	1	1 hour	0
Oedema	0	0	-	0

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

Remarks - Results: The dermal application of the notified chemical resulted in a primary irritation index of 0.0 (non-irritating) in the test rabbits. No corrosive effects were observed.

CONCLUSION: The notified chemical is non-irritating to the skin.

TEST FACILITY: Safepharm (1994*d*)

B.5.1 Irritation – eye

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).

Species/Strain: Rabbit/New Zealand White
Number of Animals: Three males
Observation Period: 72 hours
Remarks – Method: 45 mg of the notified chemical (~0.1 mL) were instilled into one eye of each rabbit. Observations were made at 1, 24, 48 and 72 hours after instillation.

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	1	24h	0
Conjunctiva: chemosis	0	0	0	0	-	0
Conjunctiva: discharge	0	0	0	0	-	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks – Results: Remnants of the notified chemical were present in all eyes 1 hour after instillation, and in one animal 24 hours after instillation.

All animals showed redness of the conjunctiva 1 hour after instillation of the notified chemical, but this had resolved by the observation at 24 hours. No evidence of corneal epithelial damage or ocular corrosion was observed.

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

TEST FACILITY: Notox (1996*k*)

B.5.2 Irritation – eye

TEST SUBSTANCE: Notified chemical

METHOD: US EPA Federal Insecticide, Fungicide and Rodenticide Act (FIFRA): Pesticide Assessment Guidelines Subdivision F; Hazard Evaluation Human and Domestic Animals, Section 81-4 "Primary Eye Irritation Study", Revised November 1984.
Toxic Substances Control Act (TSCA): Health Effects Testing Guidelines; Subpart B, Section 798.4500 "Primary Eye Irritation"

Species/Strain: Rabbit/New Zealand White
Number of Animals: Six females
Observation Period: 72 hours
Remarks - Method: 75 mg of the notified chemical (~0.1 mL) were instilled into one eye of each rabbit. Observations were made at ~1, 24, 48 and 72 hours after instillation.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0.50	2	24 hours	0
Conjunctiva: chemosis	0.17	2	24 hours	0
Conjunctiva: discharge	0	2	1 hour	0
Corneal opacity	0	0	-	0
Iridial inflammation	0	1	1 hour	0

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

Remarks - Results: Residual test material was observed around the treated eyes of all test animals 1 hour after treatment.

CONCLUSION: The notified chemical is a minimal irritant to the eye.

TEST FACILITY: Safepharm (1994*e*)

B.6 Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 406 Skin Sensitisation – Maximisation test
EC Directive 96/54/EC B.6 Skin Sensitisation – Maximisation test.

Species/Strain: Albino Guinea pig/Himalayan strain

PRELIMINARY STUDY: Maximum Non-irritating Concentration:
intradermal: 10%
topical: 50%

MAIN STUDY

Number of Animals: Test Group 10 females
Control Group: 5 females

Induction phase: Induction concentration:
intradermal injection (Day 1): 10% in corn oil (± FCA/animal)
epidermal application (Day 8): 50% in corn oil

Signs of Irritation: The reactions noted in the experimental and control animals after the epidermal induction exposure were enhanced by SDS treatment.

CHALLENGE PHASE

1st challenge: Challenge concentration:
topical application (Day 22): 50% in corn oil

Remarks – Method: Induction was carried out by intradermal injection into the scapular region. Any dermal reactions were assessed 24 and 48 hours later.

Epidermal induction was carried out ~24 hours after treatment of the scapular region application site with 10% SDS in Vaseline (which induced a mild inflammatory reaction). The site was cleaned after treatment with the notified chemical).

Challenge was carried out by epidermal exposure for 24 hours on the clipped flank of each animal, and any skin reactions were assessed 24 and 48 hours after exposure.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge:*	
		24 h	*48 h*
Test Group	50%	9*	8
Control Group	50%	0	0

* Two animals exhibited no erythema, but displayed scaliness which was scored as positive.

Remarks – Results: Skin reactions varying between grades 1 and 3 were observed in nine

experimental animals in response to the 50% test substance concentration. According to the allergenicity rating of A.M. Kligman, such a sensitisation rate (90%) ranks the notified chemical as having extremely sensitising properties (Kligman, 1966).

No mortality or signs of systemic toxicity were observed in the treated experimental animals during the main study.

No skin reactions were evident in the control animals. Small scabs, scaliness and white staining of the skin were seen in some treated skin sites of the experimental animals.

CONCLUSION — Reactions indicative of strong skin sensitisation to the notified chemical were observed under the conditions of the test.

TEST FACILITY — Notox (1996*m*)

B.7 Repeat dose toxicity

TEST SUBSTANCE — Notified chemical

METHOD — EC Directive 92/69/EEC B.7 Repeated Dose (28 Days) Toxicity (Oral).

Species/Strain	Rat/Wistar Crl:(WI) BR
Route of Administration	Oral – gavage.
Exposure Information	Total exposure days: 28 days; 7 days per week
Vehicle	Corn oil
Remarks – Method	No satellite (control or high-dose) groups were examined to establish the reversibility of observed effects after a recovery period.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5M, 5F	0	0
II (low dose)	5M, 5F	50	0
III (mid dose)	5M, 5F	200	0
IV (high dose)	5M, 5F	1,000	0

Mortality and Time to Death

No mortality occurred during the study period.

Clinical Observations

There were no treatment-related clinical signs of toxicity or behavioural changes over the 28-day observation period. Incidental observations (in both control and treated animals) included alopecia, red staining around the eye, and scabs.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were no treatment-related differences in clinical biochemistry test results noted between control and treated rats. Some changes in alanine aminotransferase, aspartate aminotransferase, total protein, sodium, chloride, and inorganic phosphate were observed, but these findings did not appear to be related to treatment.

Red blood cell counts and haematocrit were decreased (anaemia) with statistical significance in males of the 1,000 mg/kg bw/day dose group. In addition, haemoglobin was slightly decreased and mean corpuscular volume was slightly increased in these high dose males.

Effects in Organs

Absolute and relative spleen weights were increased in males receiving 1,000 mg/kg bw/day. Statistical significance was reached for the relative spleen weights of all treated males, but only in 50 mg/kg bw/day treated males when absolute values were considered. In females receiving 1,000 mg/kg bw/day, absolute spleen weights and spleen: body weight ratios were slightly increased, although the increases were not statistically significant. The spleens of all male and most of the female rats of the 1,000 mg/kg

bw/day dose group showed an increase in severity of extramedullary haematopoiesis.

A small number of other findings were observed, but these were within the normal background range of untreated rats of this age and strain.

Remarks – Results

It was considered that the slight anaemia observed in high dose animals led to the spleen functioning as an additional site for red blood cell formation and explains the increased spleen weights and extramedullary haematopoiesis.

At 200 mg/kg bw/day, the relative spleen weights were increased, but no changes in blood cell parameters or microscopic changes were observed at this dose and this was not, therefore, considered to be adverse.

CONCLUSION

A No Observed (Adverse) Effect Level (NO(A)EL) of 200 mg/kg bw/day was established in this study, based on minor effects at this dose level.

TEST FACILITY

Notox (1997*c*)

B.8 Genotoxicity – bacteria

TEST SUBSTANCE

Notified chemical

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
Metabolic Activation System	Aroclor 1254-induced rat liver S9 microsome mix
Concentration Range in Main Test	a) With metabolic activation: 3, 10, 33, 100, 333 µg/plate. b) Without metabolic activation: 3, 10, 33, 100, 333 µg/plate.
Vehicle	DMSO
Remarks – Method	A preliminary study (Test 1) showed that precipitation of the notified chemical occurred in the agar at concentrations ≥333 µg/plate. On this basis, the upper concentration used in the main test (Test 2) was 333 µg/plate. No cytotoxicity was observed in the preliminary study.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Present				
Test 1	>5000	-	≥333	None
Test 2	-	>333	≥333	None
Absent				
Test 1	>5000	-	≥333	None
Test 2	-	>333	≥333	None

Remarks – Results

The positive controls used showed the expected increases in the number of revertant colonies, verifying the integrity of the test.

CONCLUSION

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

TEST FACILITY

Notox (1996*n*)

B.9 Genotoxicity – *in vitro*

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 *In vitro* Mammalian Chromosomal Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Human
Cell Type/Cell Line	Cultured human peripheral lymphocytes
Metabolic Activation System	Aroclor 1254-induced rat liver S9 microsome mix
Vehicle	DMSO
Remarks – Method	A dose range finding test was carried out (0.1, 0.3, 1.0, 3.0, and 10.0 µg/mL) and the concentrations for use in the main test were determined by the solubility of the notified chemical in the culture media (precipitation occurred at ≥10.0 µg/mL). No cytotoxicity was observed in the preliminary study. Positive controls: Mitomycin C (-S9) and cyclophosphamide (+S9)

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Present			
Test 1A	1*, 3*, 10*	3 hours	24 hours
Test 1B	10*	3 hours	48 hours
Test 2	1*, 3*, 10*	3 hours	24 hours
Absent			
Test 1A	1*, 3*, 10*	24 hours	24 hours
Test 1B	10*	48 hours	48 hours
Test 2	1*, 3*, 10*	24 hours	24 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Present			
Test 1A	>10	10	None
Test 1B	>10	10	None
Test 2	>10	10	None
Absent			
Test 1A	>10	10	None
Test 1B	>10	10	None
Test 2	>10	10	None

Remarks – Results	A small increase in chromosomal aberrations was observed in all concentrations and treatment conditions without S9 in Test 1. However, this was not statistically significant, and was not reproducible in Test 2.
CONCLUSION	The notified chemical was not clastogenic to cultured peripheral human lymphocytes treated *in vitro* under the conditions of the test.
TEST FACILITY	Notox (1997*d*)

Appendix C: Environmental Fate and Ecotoxicological Investigations

ENVIRONMENTAL FATE

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test. EC Directive 92/69/EEC C.4-C Biodegradation: Determination of the "Ready" Biodegradability: Carbon Dioxide Evolution Test
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	CO_2 production via back titration of the $Ba(OH)_2$ traps.
Remarks - Method	Test material was dispersed directly in the culture medium. Bottles were sealed and CO_2-free air bubbled into the stirred solutions and maintained in the dark. Initial test material concentration was 32.2 mg/L. Titrations were made every second or third day during the first 10 days, and thereafter at least every fifth day until the 28th day. Test temperature 20-22°C. Test solutions pH range: 7.5-7.7.

RESULTS

Test substance		*Sodium acetate*	
Day	*% Degradation*	*Day*	*% Degradation*
2	0.1	2	17.0
14	2.4	14	73.8
29	5.4	29	87.2

Remarks - Results	All test validation criteria were met. The reference substance (sodium acetate) degraded by 87.2% after 29 days confirming the suitability of the inoculum and test conditions. In the toxicity control, the test material attained 40% degradation by day 14 confirming that the test substance was not toxic to the sewage microorganisms used in the study.
CONCLUSION	The notified chemical cannot be classed as ready biodegradable.
TEST FACILITY	Notox (1996*p*)

C.1.2. Bioaccumulation

A bioaccumulation study has not been performed on the substance because it has an extremely low water and n-octanol solubility. The calculated log P_{ow} gives a very high value. The Bioconcentration Factor (BFC) that is calculated from such a high log P_{ow} value will be low as a parabolic relationship exists between BCF and P_{ow} for substances with $P_{ow} > 6$. Furthermore, the relatively high molecular weight of the substance precludes significant accumulation in body tissues, as does the low water solubility that limits bioavailability.

ECOTOXICOLOGICAL INVESTIGATIONS

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – static conditions. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish - static conditions.
Species	Carp - *Cyprinus carpio*
Exposure Period	96 hours

Auxiliary Solvent	Tween 80
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	TOC analysis
Remarks – Method	Two limit tests were performed with carp. In the first test, carp were exposed to 100 mg/L (filtered as well as unfiltered) in a static system and the test solution was prepared using Tween 80 as a dispersant. In the second test, carp were also exposed to 100 mg/L. No additive was used in the preparations of the test solution and the solutions were unfiltered. Samples for analysis were taken at the start and the end of the second test and analysed for determination of Total Organic Carbon (TOC). Oxygen content fluctuated throughout the experiment (see below) with aeration being commenced on Day 2 for solutions in the first test. The pH (7.2 to 8.3 in both control and test solutions) and temperature (20.8 to 21.5°C in both control and test solutions) were all satisfactorily maintained.

Test Solution	Dissolved Oxygen (mg/L)				
	Day 0	Day 1	Day 2	Day 3	Day 4
			Test 1		
Blank-control	9.0	8.7	6.8	9.1	9.0
Tween-Control	8.9	8.6	5.0	9.0	9.0
100 (5µm filt.)	8.9	8.5	5.9	9.3	9.1
100 (unfiltered)	8.9	8.6	4.8	9.0	9.0
			Test 2		
Blank-control	9.2	8.9	6.6	6.4	6.6
100 (unfiltered)	9.1	8.8	6.2	6.1	6.4

RESULTS

Concentration mg/L Nominal	*Number of Fish*	*Mortality*				
		1 h	*24 h*	*48 h*	*72 h*	*96 h*
Test 1						
Blank Control	7	0	0	0	0	0
Tween Control	7	0	0	0	0	0
100 (5 µm filtered)	7	0	0	0	0	0
100 (unfiltered)	7	0	0	0	0	0
Test 2						
Blank Control	7	0	0	0	0	0
100 (unfiltered)	7	0	0	0	0	0

LC50	>100 mg/L at 96 hours.
NOEC	100 mg/L at 96 hours.
Remarks – Results	The results quoted above are based on nominal test concentrations, which were well in excess of the water solubility of the test substance. Hence, it can be said that the 96 h LC50 of the test substance is well beyond its water solubility. The study reports TOC analysis of the test media that showed recoveries of 74% and 41% for the beginning and the end of the test, respectively. The report concludes that dispersions of the chemical in the test medium appeared to be relatively stable. The fish in the first test were observed to be hypoactive in both the filtered and unfiltered test solutions. The effect was more pronounced in the unfiltered solutions and the hypoactivity was only observed between 24-48 h in the filtered solutions.
CONCLUSION	The notified chemical is not toxic to carp up to the limit of its water solubility.
TEST FACILITY	Notox (1996*q*)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 92/69/EEC C.2 Acute Toxicity for *Daphnia* – 48h/static conditions.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Tween 80
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	TOC analysis
Remarks - Method	After a limit test performed using the solutions prepared in the fish study above, two full tests were performed with daphnids exposed to 4.5 to 100 mg/L (Test 1) and 0.1 to 4.5 mg/L (Test 2), respectively. In the limit test, the test solution was prepared using Tween 80 as a dispersant. No additives were used in the full tests. The test concentrations were prepared by diluting stock solutions (100 mg/L for Test 1 and 20 mg/L for Test 2). Turbidity was observed in solutions at concentrations of ~4.5 mg/L or greater. Test solutions were unfiltered. The test consisted of two vessels per group containing 10 daphnids per vessel. Samples for analysis were taken at the start and the end of the full tests and analysed for determination of Total Organic Carbon (TOC). In Test 1 TOC analysis of the highest and lowest concentrations at the start of the test showed 61 and 74% recoveries, respectively. At the end of the test, the recoveries were less than the control and 8%, respectively. TOC analysis of the 4.5 mg/L test media in Test 2 showed recoveries of 97 and 27% for the beginning and the end of the test, respectively. Oxygen content (8.1-9.2 mg/L in both control and test substance solutions for Test 1 and 8.3-9.3 mg/L for Test 2), pH (8.0-8.3 in both control and test solutions for Test 1 and 8.0-8.2 in Test 2) and temperature (21.0-21.5°C in control and test solutions for the Test 1 and 20.0-20.4°C for Test 2) were satisfactorily maintained.

RESULTS

Concentration mg/L Nominal	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
Limit Test			
0 (Blank Control)	20	0	0
0 (Tween 80 Control)	20	0	0
100 (5µm filt.)	20	0	10
100 (unfiltered)	20	0	14*
Test 1			
0 (Control)	20	0	0
4.5	20	0	8
10	20	0	11*
22	20	0	9*
45	20	0	9*
100	20	0	15*
Test 2			
0 (Control)	20	0	0
0.10	20	0	0
0.22	20	0	0
0.45	20	0	0
1.0	20	0	0
4.5	20	0	0

*Substance deposits were observed on the bottom of the vessel.

EC50	>4.5 mg/L at 48 hours based on test 2
LOEC	4.5 mg/L at 48 hours
Remarks - Results	The effects observed in Test 1 did not follow a dose response.

	Concentrations of the test substance that induced effects on Daphnia exceeded the maximum solubility of the test substance (assumed to be 4.5 mg/L for this test based on the observation of clear test solution at this test level and high recoveries for TOC analysis at this test concentration) These effects do not appear to be related to test concentration. The report indicates that the effects are probably due to physical damage to or mechanical obstruction of the swimming apparatus of the exposed organisms caused by flocculation of the undissolved fraction of the test substance.
CONCLUSION	The test substance is not toxic to Daphnia up to the limit of its water solubility of ~4.5 mg/L in this test. Undissolved material appears to have a physical effect on Daphnia.
TEST FACILITY	Notox (1996*q*)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Selenastrum capricornutum*, strain: CCAP 278/4
Exposure Period	72 hours
Concentration Range Nominal	10, 18, 32, 56 and 100 mg/L
Concentration Range Actual	Not determined
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Remarks - Method	After a range-finding test, a final test was performed exposing exponentially growing algal cultures to the nominal test substance concentrations of 10, 18, 32, 56 and 100 mg/L. The initial cell density was 10^4 cells/ml. The total test period was 72 hours. Samples for analysis were taken at the start and the end of the second test and analysed for determination of Total Organic Carbon (TOC).

RESULTS

Biomass		*Growth*	
EC_b50 (mg/L at 72 h)	*NOEC (mg/L)*	*EC_r50 (mg/L at 72 h)*	*NOEC (mg/L)*
>100	10	>100	10

Remarks - Results	The test substance only slightly affected cell growth of the freshwater algae species at nominal concentrations of 32 mg/L and above. This minor effect on algal growth was attributed to the presence of undissolved test material at these concentrations absorbing part of the light needed for algal growth. The EC50 values for both cell growth inhibition and growth rate reduction were beyond the range tested (i.e. greater than the nominal concentration of 100 mg/L which corresponds to an average measured concentration by TOC of 71 mg/L).
CONCLUSION	The test material is not toxic to algae up to the level of its water solubility. However, undissolved material appears to have an effect on the absorption of light by the algae resulting in a slight effect on growth rate.
TEST FACILITY	Notox (1996*s*)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical

METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sludge
Exposure Period	0.5 hours
Concentration Range Nominal	100 mg/L
Remarks – Method	The test substance was insoluble in water and was added quantitatively to the test vessels at a concentration of 100 mg/L. This concentration was tested in duplicate.
RESULTS	
0.5 h IC50	Not determined
NOEC	100 mg/L
Remarks – Results	No significant inhibition in respiration rate of the sludge was recorded at 100 mg/L (significant: >10%). The duplicate measurement confirmed the result of the first measurement. Results for the reference substance were within the expected range. Therefore, no further testing was needed.
CONCLUSION	The test material is practically non-toxic to sewage microorganisms.
TEST FACILITY	Notox (1996*t*)