File No: EX/132
(STD/1260)

December 2009

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Silane, triethoxy[2-(7-oxabicyclo[4.1.0]hept-3-yl)ethyl]- ('CoatOSil 1770')

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.

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

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Director
NICNAS

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FULL PUBLIC REPORT

This assessment report is for an extension of original assessment certificate for Silane, triethoxy[2-(7-oxabicyclo[4.1.0]hept-3-yl)ethyl]- ('CoatOSil 1770'). Based on the submission of new information by the extension notifier, some sections of the original assessment report have been modified. These modifications have been made under the heading 'Extension Applicant' in the respective sections.

Silane, triethoxy[2-(7-oxabicyclo[4.1.0]hept-3-yl)ethyl]- ('CoatOSil 1770')

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Momentive Performance Products Pty Ltd (ABN 47 105 651 063)
Level 2, 600 Victoria Street
RICHMOND VIC 3121

Applicant for an Extension of the Original Assessment Certificate:
Brenntag Pty Ltd (ABN 24 050 029 000)
Building 25, 270 Ferntree Gully Road
NOTTING HILL VIC 3168

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

Extension Applicant:
Data items and details claimed exempt from publication: Site of Reformulation and Details of Use.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Listed on inventories in USA (TSCA), Canada (NDSL), EU (ELINCS 425-050-4), New Zealand, and China.

2. IDENTITY OF CHEMICAL

CHEMICAL NAME
Silane, triethoxy[2-(7-oxabicyclo[4.1.0]hept-3-yl)ethyl]-

MARKETING NAME(S)
CoatOSil 1770

Extension Applicant:
SILCOLEASE ADD 381 (50% notified chemical)

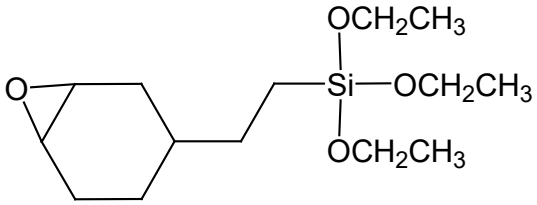
OTHER NAME(S)
2-(3,4-epoxycyclohexyl)ethyltriethoxysilane
7-oxabicyclo[4.1.0]heptane, 3-[2-(triethoxysilyl)ethyl]-
Y-4036
Y-11870

CAS NUMBER
10217-34-2

MOLECULAR FORMULA

$C_{14}H_{28}O_4Si$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
288.5 Da

ANALYTICAL DATA
Reference ^{1}H-NMR, IR and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY 95.5%

HAZARDOUS IMPURITIES

Chemical Name	Silane, triethoxy[1-(7-oxabicyclo[4.1.0]hept-3-yl)ethyl]-		
CAS No.	-	*Weight %*	Unknown
Hazardous Properties	Expected to have similar hazard to the notified chemical (isomer of the notified chemical)		

Chemical Name	3,4-epoxycyclohexylethyldiethoxymethoxysilane		
CAS No.	-	*Weight %*	≤0.5%
Hazardous Properties	Expected to have similar hazard to the notified chemical (structurally related)		

Chemical Name	1,3-bis(3,4-epoxycyclohexylethyl)-1,1,3,3-tetraethoxydisiloxane		
CAS No.	-	*Weight %*	≤0.5%
Hazardous Properties	Expected to have similar hazard to the notified chemical (structurally related)		

Chemical Name	1,3,5-tris(3,4-epoxycyclohexylethyl)-1,1,3,5,5-pentaethoxytrisiloxane		
CAS No.	-	*Weight %*	≤0.5%
Hazardous Properties	Expected to have similar hazard to the notified chemical (structurally related)		

Chemical Name	Ethanol		
CAS No.	64-17-5	*Weight %*	≤1%
Hazardous Properties	F: R11 Highly flammable.		

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)
None.

ADDITIVES/ADJUVANTS
None.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa
Clear, pale, off-white liquid

Property	Value	Data Source/Justification
Freezing Point	<-79°C	Measured

Boiling Point	>295ºC at 101.3 kPa	Measured
Density	1003 kg/m^3 at 25ºC	Measured
Vapour Pressure	$(3.0\pm0.4)\times10^{-4}$ kPa at 20ºC	Measured
Water Solubility	0.86 g/L at 19.5ºC	Measured
Fat Solubility	Miscible in all proportions	Measured
Hydrolysis as a Function of pH	Hydrolytically unstable at pH 4-9	Measured
Partition Coefficient (n-octanol/water)	$logP_{ow}$ = 4.1 at 20ºC	Measured
Surface tension	45.1 mN/m at 20ºC	Measured
Adsorption/Desorption	$logK_{oc}$ = 2.03	Calculated
Dissociation Constant	Not expected to dissociate	Expert statement
Particle Size	Not applicable	The notified chemical is a liquid at room temperature
Flash Point	137.5ºC at 101.3 kPa	Measured
Pyrophoric Properties	Not expected to ignite spontaneously at room temperature	Expert statement
Autoignition Temperature	245ºC	Measured
Explosive Properties	Not expected to be explosive	Expert statement

DISCUSSION OF PROPERTIES
The notified chemical is considered to be surface-active, hydrolytically unstable, and predominantly lipophilic in nature. The notified chemical hydrolyses in contact with water (particularly at low pH), liberating ethanol.

It is not expected to pose a physical hazard on the basis of the physicochemical data provided. For full details of tests on physical and chemical properties, please refer to Appendix A.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as a pure (95.5%) liquid by sea, in shrink-wrapped pallets of 20 L or 200 L closed-head drums.

Extension Applicant:
The notified chemical will be imported at a concentration of 50% in 25 kg jerry cans or 1 kg bottles on pallets.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	1	2	3	4	5
Extension Applicant:					
Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.5	0.5	0.5	0.5	0.5

PORT OF ENTRY
Sydney, Melbourne, and Brisbane

IDENTITY OF MANUFACTURER/RECIPIENTS
The imported drums will be distributed from the notifier's warehouse to industrial coating blending customers. There may be up to three reformulation sites over the next five years.

TRANSPORTATION AND PACKAGING
The pallets of imported chemical will be transported from the dock by road to the notifier's warehouse. Road transport will also be used to transport individual drums from the notifier's warehouse to customer sites.

Extension Applicant:
The imported pallets of cans or bottles of the product containing the notified chemical will be transported by road from the dock to the reformulation site.

USE
The notified chemical is a component for formulation into water-based surface coatings, primarily in surface primers. It functions as an adhesion promoter and bifunctional cross-linker, and will be dispersed in coating formulations at 0.5-5% of total resin solids (typical concentration: 1-2%). It will be consumed during the curing

of applied surface coatings, where the epoxy portion of the notified chemical will react with the resins of coatings, and the alkoxysilanes will form cross-links through condensation to form siloxane bonds.

The coatings formulated using the notified chemical will be used in industrial applications such as on furniture or floors, or for coatings for wooden, masonry, metal, glass, leather, vinyl or plastic surfaces.

Extension Applicant:
The notified chemical will be used as a component of adhesive coatings.

OPERATION DESCRIPTION

Transportation and storage

Dockside workers will transfer the shrink-wrapped pallets loads of drums containing the notified chemical onto trucks, which will carry them to the notifier's warehouse. There, they will be unloaded and unpacked and stored by warehouse workers. These workers will also be involved with loading of trucks for transportation of the drums of the notified chemical to customer sites.

Reformulation

Typically, two batches of coating reformulation would be completed per day of use. The notified chemical will be pumped directly from the imported drums (located on scales) into a closed stainless steel mixing vessel, where it will be blended at high speed with other coating ingredients. After a quality control process, the formulated coatings will be transferred via a closed system into (predominantly) 4 L paint cans via an automated multi-head filling machine. Both the blending and filling-off processes are normally automated, and these units are ventilated to air through a vapour/mist extraction unit. All transfer and sampling operations are claimed to be carried out in areas equipped with local exhaust ventilation.

After emptying, drums will be rinsed with process fluid and the rinsate will be transferred into the blending vessel. Rinsed drums are expected to be sent to a drum recycler. Mixing and filling machinery will be cleaned at the end of a production run.

Application

The notified chemical will be formulated into coating formulations for predominantly brush and roller application. Spray application of coatings containing the notified chemical is not expected. However, if this occurred, it would be likely to be performed in an enclosed and ventilated spray booth, given the industrial setting.

Extension Applicant:
The notified chemical will be added to a mixing vessel using an automated dosing machine and reformulated into a coating.

The coating product containing the notified chemical (< 5%) will be applied to articles by gravure process, heat-cured by passing through an oven and tested for quality control purposes.

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 (days/year)*
Transport and storage	2	0.5	5-10
Process operators	2	1	20
Laboratory technicians	1	0.33	20
Coating appliers/painters	10	6	50

Transportation and storage

Transportation and storage workers might be expected to experience acute dermal and possibly ocular exposure to the notified chemical in the case of a transport emergency where leakage of the imported drums or formulated products occurs. This exposure is likely to be infrequent and accidental in nature. Shrink-wrapping of pallet loads may also restrict the spread of any leakage, reducing the probability of exposure.

Reformulation
Workers involved in reformulation of coatings are likely to experience dermal, ocular, inhalation and possible accidental oral exposure, during weighing out, mixing and cleaning processes.

Worker exposure during reformulation is most likely to be low-level dermal contact with drips and spills, either from the imported notified chemical solution (at >85%) or from the formulated products containing it (at 0.5-5%).

As the notified chemical has low volatility (i.e. vapour pressure), inhalation exposure is likely to occur primarily through the formation of aerosols. Aerosol formation from solutions containing the notified chemical is possible where rapid mixing or pouring occurs. Aerosol exposures are likely to be high during quality control sampling of enclosed mixers. The viscosity of the notified chemical solution is unknown, but is likely to be lower than that of coatings containing polymeric materials. Therefore, the potential for inhalation exposure of aerosols containing the notified chemical is likely to be highest where the imported solutions (>85%) are handled.

Personal protective equipment (PPE) including gloves, face shields and coveralls is worn during reformulation processes, and local exhaust ventilation (LEV) is claimed to be in use at all sites where the notified chemical is directly handled. All of these measures are expected to mitigate the level of potential exposure of workers to the notified chemical, if used correctly.

Application
Painters and applicators of coatings containing the notified chemical are likely to experience dermal, ocular, and possible accidental oral exposure, during the coating of articles by brush or roller. For these workers, the predominant exposure is likely to be dermal, resulting from drips, spills, over-spray, and from the handling of coated articles before the coatings have cured. The use of gloves and coveralls is expected to reduce the level of dermal exposure to the notified chemical experienced by coatings applicators.

Workers would only experience significant inhalation exposure to the notified chemical if coatings were applied by spray application. Given the use of an appropriate, well maintained spray booth (or similar) and/or respirator, the level of inhalation exposure experienced by these workers is expected to be significantly reduced.

Dried residues and coated articles
Workers may make dermal contact with cured, finished articles (coated with notified chemical-containing coatings) during handling, and may perform these tasks without the use of PPE. Dermal contact with dried residues of coatings around areas where liquid coatings have been handled or processed may also occur. However, as the notified chemical will be consumed during the curing of coatings (forming cross-links within the matrix of the coating), any exposure of workers to the notified chemical is expected to be negligible.

Extension Applicant:
Exposure to workers during reformulation is not expected to be significant given the anticipated use of automated mixing and dosing equipment during the mixing process. Workers are also expected to wear PPE including gloves, face shields and coveralls during reformulation to minimise exposure.

Accidental dermal and ocular exposure to the adhesive coating (< 5% notified chemical) may occur during application to substrates by a gravure process and subsequent curing by heat. However, this is not expected to be significant. Spray application is not anticipated and therefore inhalation exposure is not expected. Once cured, the notified chemical will be bound within the matrix of the coating and will not be available for exposure.

6.1.2. Public exposure
The notified chemical is not intended to be sold to members of the public, either in its imported form or in formulated coatings (e.g. for DIY use). The public will likely experience dermal exposure to cured, coated articles containing the notified chemical. However, given the function of the notified chemical, it is expected to be covalently linked within the cured matrix of a finished coating, and thus be not bioavailable. Public exposure is thus expected to be negligible.

6.2. Human health effects assessment

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

Endpoint	*Result and Assessment Conclusion*

Rat, acute oral toxicity	LD_{50} >5000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD_{50} >2000 mg/kg bw; low toxicity
Rabbit, skin irritation	Slightly irritating
Rabbit, eye irritation	Slightly irritating
Guinea pig, skin sensitisation (modified Buehler test)	Evidence of sensitisation
Guinea pig, skin sensitisation (Maximisation test)	Evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOEL 1000 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days	NOAEL 1000 mg/kg bw/day
Dermal carcinogenicity study	Non-carcinogenic
Genotoxicity – bacterial reverse mutation	Non-mutagenic
Genotoxicity – *in vitro* chromosome aberration test	Genotoxic
Genotoxicity – *in vitro* mutagenicity (three studies on acid-hydrolysed notified chemical)	Non-mutagenic
Genotoxicity – *in vivo* mouse micronucleus test	Non-genotoxic

Toxicokinetics, metabolism and distribution

According to its physicochemical properties (in particular its high $logP_{ow}$ and low molecular weight), absorption might be predicted through the skin, across the gastrointestinal tract, and possibly from the lung (EC, 2003). Given its ability to induce dermal sensitisation, the notified chemical is expected to at least be able to penetrate the stratum corneum.

There is little evidence from the available toxicological studies to suggest that the notified chemical is readily absorbed following an oral dose. The minor effects observed in the 90-day oral study are suggestive, but it is difficult to determine if their lack of severity was due to a lack of toxicity or a lack of significant absorption. One striking finding is that intraperitoneal injection of the notified chemical in the micronucleus study (at doses comparable to those used in the oral toxicity studies) resulted in mortalities and adverse effects that were of greater severity than those observed in other studies. This suggests that gastrointestinal absorption of the notified chemical was generally low, or that hydrolysis occurred in the acidic pH of the stomach (to a species with lower toxicity). Therefore, the extent of absorption or degradation may be a key factor in the interpretation of toxicity data for the notified chemical.

Acute toxicity

The notified chemical has been shown to be of low acute oral and dermal toxicity. However, interpretation of the oral toxicity study results may be hampered by poor gastrointestinal absorption or hydrolysis, as described above. The mortalities seen in the micronucleus study after intraperitoneal administration might support such a hypothesis. The intraperitoneal LD_{50} of an analogous chemical, β-(3,4-epoxycyclohexyl)ethyltrimethoxysilane (EEMS; CAS 3388-04-3) has been reported to be 8- to 12.3-fold lower than that its oral LD_{50} (Daugherty, 1982; RTECS, 2007).

No toxicological data was received to establish the potential of the notified chemical for inducing acute inhalation toxicity. Low molecular weight alkoxysilanes are a known concern for lung toxicity, due to inhalation of vapours or aerosols causing irreversible lung damage at low doses (US EPA, 1994). EEMS, which has a similar acute oral and dermal toxicity profile to the notified chemical (DePass *et al*, 1989; RTECS, 2007), has been shown to be non-toxic in an acute inhalation study, with a lethal concentration of >290 mg/m^3/4 hours (RTECS, 2007). In another study, no signs of toxicity were observed in rats exposed to an EEMS vapour-saturated atmosphere for 8 hours (DePass *et al*, 1989). Given that the notified chemical has a lower probable toxicity than EEMS, due to its ethyl vs methyl alkoxysilane substituents (US EPA, 1994), the notified chemical is expected to have low acute inhalation toxicity.

Repeated dose toxicity

In a 28-day repeat dose study, no treatment-related effects were observed in rats, giving a NOEL of 1000 mg/kg bw/day. Similarly, at the same dose level in the 90-day study, no treatment-related effects were observed that were considered to be adverse. These findings of low toxicity are consistent with those of other epoxy-group bearing alkoxysilanes of similar molecular weight (DePass *et al*, 1989). In addition, after a lifetime of thrice-weekly dermal exposure to the notified chemical (in the dermal carcinogenicity study), the survival of treated mice was similar to those of the negative control; no significant organ effects were noted at the end of the study.

Chemicals containing epoxy functional groups are of concern for reproductive effects, though the concern for epoxy groups with di-substituted carbons (like the notified chemical) is lower than that for singly substituted epoxy groups (US EPA, 1994). The developmental toxicity of the notified chemical is unknown, but has been studied for EEMS (Tyl *et al*, 1988). In this study, pregnant rats and rabbits were dosed with EEMS in corn oil by oral gavage. While maternal toxicity was observed at the highest dose levels (1.0 and 2.5 mL/kg bw/day in rats, and 0.25 and 0.75 mL/kg bw/day in rabbits), no embryotoxicity or teratogenicity was observed in either species

at any dose. Only minimal foetal toxicity (dilated cerebral ventricles and reduced forelimb ossification) was observed in rat offspring at 2.5 mL/kg bw/day. Given that EEMS is expected to be of greater toxicity than the notified chemical, significant developmental toxicity is not expected for the notified chemical.

Given all of these findings, the notified chemical is not expected to cause significant systemic toxicity upon repeated oral or dermal exposure to humans.

Irritation and sensitisation

Slight skin irritation was observed in several tests: in the acute dermal irritation study (rabbit), in the sensitisation studies (guinea pig) and in the acute dermal toxicity study (rat). However, the severity of this effect was insufficient to warrant classification of the notified chemical as a potential skin irritant according to the *Approved Criteria* (NOHSC, 2004).

The notified chemical was found to be sensitising to the skin of guinea pigs in two separate studies. Given the sensitisation rates of 70% in the modified Buehler study and 100% in the Maximisation study, the notified chemical is considered to be a potent sensitiser in Guinea pigs. Therefore, it is considered likely to cause sensitisation reactions in humans upon repeated or prolonged dermal exposure. The capacity of the notified chemical to induce respiratory sensitisation upon inhalation of aerosols is not known, but it should be noted that the class of chemicals has been in use for decades without reports of such effects in the literature.

Mutagenicity and carcinogenicity

Chemicals containing epoxy groups are of concern for cancer effects, though again the concern is lower for epoxy groups with di-substituted carbons (US EPA, 1994). The notified chemical was found negative in a bacterial reverse mutation study, but positive in an *in vitro* chromosome aberration study. However, the ability of the notified chemical to cause chromosome aberrations *in vivo* was also evaluated in a well conducted mouse micronucleus study, in which no chromosome aberrations or aneuploidy were detected (despite significant systemic toxicity and apparent cytotoxicity to the target tissue). In addition, three *in vitro* cultured mammalian cell assays on the acid-hydrolysed notified chemical were found negative, indicating that it is unlikely to be mutagenic in use (or after an oral exposure).

In addition, a lifetime mouse skin-painting study (dermal carcinogenicity study) showed no increased incidence of tumours after long-term dermal treatment with the notified chemical. This result is interesting, as EEMS, under identical experimental conditions, was found to cause fibrosarcomas (2/40 animals tested) and carcinomas (4/40) at higher incidence than found in negative control animals (0/40) (DePass *et al*, 1989). This result highlights the higher reported reactivity and toxicity of the methoxysilane vs. ethoxysilane moieties (US EPA, 1994). The non-neoplastic dermal effects observed in this study are likely to result from the irritant and/or sensitising properties of the notified chemical.

Given the positive chromosome aberration test result, any potential of the notified chemical for mutagenicity cannot be definitively excluded. However, given the weight of evidence from the available animal test data, the possibility of mutagenicity and/or carcinogenicity in exposed humans is not expected.

Classification

Based on the skin sensitisation potential of the notified chemical, it is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004):

Xi: R43 May cause sensitisation by skin contact.

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Given the low potential of the notified chemical to induce systemic toxicity in animal studies following oral or dermal exposure (with acute or repeated dosing), the potential for systemic toxicity in exposed workers is not expected to be significant. The risk of systemic or lung toxicity resulting from inhalation exposure is not known, but data from an analogous chemical would suggest that this risk would be low for acute exposures.

Similarly, acute dermal or ocular exposure is not expected to cause more than mild, transient irritation in exposed workers. Any risk of possible mutagenicity or carcinogenicity of the notified chemical is expected to be low, given the weight of the available evidence—particularly via the predominant dermal route of exposure.

The primary risk to workers will result from repeated (not necessarily frequent) dermal exposure to the notified chemical, resulting in sensitisation. As dermal exposure could occur for all of the expected types of workers (except those only handling cured, coated articles), the risk of sensitisation is considered to be significant. This risk is likely to be lower for transportation and storage workers, due to the smaller probability

of a leak occurring during transport that resulted in dermal exposure.

Given the use of appropriate PPE (i.e. gloves and coveralls) and appropriate ventilation (i.e. a spray booth for spray applicators or otherwise LEV), the level of risk to workers, presented by use of the notified chemical, is expected to be low.

6.3.2. Public health

Given the lack exposure of members of the public to the notified chemical, the risk to public health is considered to be negligible.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured in Australia. Release to the environment during shipping, transport and warehousing will only occur in the unlikely event of accidental spills or leaks from the 20 and 200 L import drums.

After emptying, the import drums will be rinsed with process fluid into the blending vessel and kept for charging as part of the first batch charge in the next campaign. Rinsed and drained import drums are expected to be sent to a drum recycler. The blending and filling-off equipment is expected to be cleaned after the end of the campaign for a given range of common-base products by flushing the system with process fluid. These rinsings are filled out as a heel for charging into the first batch of the next campaign. Hence, no significant losses of the notified chemical to the environment are expected as a result of the reformulation process.

RELEASE OF CHEMICAL FROM USE

The end-use products containing the notified chemical product will be used in water-based resin coatings for printing or for protection of timber products. These coating products will be used predominantly in industrial applications, applied to articles by means of brushes or rollers, but are not expected to be used in spray applicators. Brushes and rollers will be cleaned first by brushing or rolling out excess product on newspaper that will be sent to landfill when the coating is in a dry and cured state. The cleaning process will be completed by rinsing the brushes and rollers with water. As the applications of the end-use products are industrial, these rinsings are expected to pass to the trade waste system where the residual coating product would be filtered out before discharge of the wastewater to the sewer. The release of the notified chemical to the sewer system by this route is not expected to exceed 5% of the total import volume. The residual end-use product in the paint cans will be drained and rinsed with water. The residues of notified chemical remaining in these containers when they are sent for recycling are therefore not expected to be significant.

RELEASE OF CHEMICAL FROM DISPOSAL

The notified chemical irreversibly combines with other components of the resin matrix when the layer of coating applied to articles is dried and cured. Hence, no releases of the notified chemical to the aquatic environment are expected to occur from the disposal of coated articles, which is likely to be to landfill.

7.1.2 Environmental fate

The quantities of notified chemical released to the aquatic environment are limited by the use of this chemical as a component of epoxy resins used in industrial coating applications. However, some releases to the sewer system are conceivable from the disposal of aqueous wastes generated by the application of the end-use products to articles. These quantities of notified chemical released into the sewer are expected to dissipate through a combination of sorption to suspended organic matter and soil, and by hydrolysis, which is rapid in aqueous solution. Thus, although the notified chemical is not readily biodegradable, physical and chemical mechanisms are expected to efficiently remove the chemical from the water compartment before and during sewage treatment. The notified chemical has a theoretical potential to bio-accumulate, but these various dissipation mechanisms are likely to combine to eliminate the chemical from the water column before significant exposure of aquatic organisms occurs.

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

7.1.3 Predicted Environmental Concentration (PEC)

The Predicted Environmental Concentration arising from the industrial use pattern has been modelled for the worst case in which none of the notified chemical released in aqueous wastes from the application of end-use products is removed by or degrades in, on-site waste water treatment and sewage treatment plants. As the notified chemical is to be used in industrial applications at a limited number of sites, it is anticipated that such releases will occur on 260 days per year into only 25% of the total Australian effluent volume. The details of the calculation based on these parameters are presented below:

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	260	days/year
Daily chemical release:	0.96	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
Fraction of population	25	%
Dilution Factor – River	1.0	
Dilution Factor – Ocean	10.0	
PEC - River:	0.94	µg/L
PEC - Ocean:	0.09	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 (96 hours)	LC50 42.3 mg/L	Harmful
Daphnia Toxicity (48 hours)	LC50 58 mg/L	Harmful
Algal Toxicity (72 hours)	E_bC50 36 mg/L	Harmful
Inhibition of Bacterial Respiration (30 mins)	NOEC 100 mg/L	No adverse effects on waste-water bacteria at the test concentration

The notified chemical is harmful to all three trophic levels of the aquatic compartment.

7.2.1 Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated from the algal toxicity of the notified chemical using an assessment factor of 100.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
E_bC50 (Algae)	36	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	360	µg/L

7.3. Environmental risk assessment

Based on the above PECs and PNEC values, the following Risk Quotients (Qs) have been calculated:

Risk Assessment	PEC (µg/L)	PNEC (µg/L)	Q
Q - River:	0.94	360	<< 1
Q - Ocean:	0.09	360	<< 1

The Risk Quotients are much less than 1 for both the river and ocean disposal scenarios. Therefore, the notified chemical is not expected to pose an unacceptable risk to the aquatic environment based on the current use pattern.

8. RISK ASSESSMENT RELATING TO EXTENSION APPLICANT

Extension Applicant:

The proposed use, introduction volume and fate of the notified chemical will not change significantly under the proposed extension. The circumstances in the extension application are not expected to impact on the original human health and environmental risk assessment.

9. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

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

Xi: R43 May cause sensitisation by skin contact

and

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***
Human Health	Skin Sensitisation Category 1	Warning: May cause an allergic skin reaction
Environment	Acute Category 3	Harmful to aquatic life

Human health risk assessment

Under the conditions of the occupational settings described, the notified chemical is not expected to pose an unacceptable risk to the health of workers, given that appropriate control measures are implemented during its reformulation and use.

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

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 proposed use pattern.

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- The Safe Work Australia, should consider the following health hazard classification for the notified chemical:
  - *Xi: R43May cause sensitisation by skin contact*
  - *S24 Avoid skin contact*
  - *S36/37 Wear suitable protective clothing/gloves*

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

Health Surveillance

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

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls wherever the imported notified chemical solution is handled, to minimise occupational exposure:
  - *Local exhaust ventilation*

- Employers should implement the following engineering controls during spray application of coating products containing the notified chemical, to minimise occupational exposure:
  - *An appropriate spray booth*

- Employers should implement the following safe work practices to minimise occupational exposure during application of products containing the notified chemical using brushes or rollers:
  - *Avoid skin contact*

- Employers should implement the following safe work practices to minimise occupational exposure during spray application of products containing the notified chemical:
  - *Avoid skin contact*
  - *Avoid breathing 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* Safe Work Australia 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 coating products:
  - *Impermeable gloves, coveralls and face/eye protection (goggles/visor)*
  - *Suitable respirators (where spray application is used)*

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

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

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

Disposal

- The notified chemical should be disposed of by landfill.

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
  - The notified chemical is intended to be used in DIY coating products that are available to the public.

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of industrial coating products, or is likely to change significantly;
  - the amount of chemical being introduced has increased from 5 tonnes, or is likely to increase, significantly;
  - if the chemical has begun to be manufactured in Australia;
  - additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point <-79°C

Method	OECD TG 102 Melting Point/Melting Range. EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	The notified chemical did not solidify at -79°C in a preliminary test. The main study was not performed.
Test Facility	NOTOX (1997a)

Boiling Point >295°C at 101.3 kPa

Method	EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	Performed using a Differential Scanning Calorimeter (DSC). No boiling was observed up to 295°C in a preliminary test, so no main study was performed. Reaction or decomposition of the notified chemical occurred at temperatures greater than ~130°C.
Test Facility	NOTOX (1997b)

Density 1003 kg/m^3 at 25°C

Method	OECD TG 109 Density of Liquids and Solids. EC Directive 92/69/EEC A.3 Relative Density.
Remarks	Pycnometer method.
Test Facility	NOTOX (1997c)

Vapour Pressure $(3.0 \pm 0.4) \times 10^{-4}$ kPa at 20°C

Method	OECD TG 104 Vapour Pressure. EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	The vapour pressure of the notified chemical was measured by a static technique at 24.35°C, 31.49°C, and 37.27°C, using a capacitance manometer. The vapour pressure at 20°C was extrapolated.
Test Facility	NOTOX (1997d)

Water Solubility 0.86 g/L at 19.5°C

Method	OECD TG 105 Water Solubility. EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	The water solubility of the notified chemical was determined by the flask method. The solubility was estimated to be 0.88 g/L based on the results of a preliminary flask test carried out over 3 days at 20°C. In the definitive test, 1-2 g of the notified chemical was stirred in 50 mL of water at 19.5°C for 24, 48, and 72 hours. Additional notified chemical was added to the flasks stirred for 48 and 72 hours to maintain saturation conditions over the period of the test. The notified chemical in the clarified supernatant solution was extracted with toluene, and the concentration determined by gas chromatography. This method resolved two isomers of the notified chemical, and mean concentration of notified chemical in water determined for the major and minor isomers were 0.86 and 0.83 g/L, respectively. The pH of the solutions were a relatively constant 6.5-6.9.
Test Facility	NOTOX (1997e)

Fat (or n-octanol) Solubility Miscible in all proportions

Method	OECD TG 116 Fat Solubility of Solid and Liquid Substances. EC Directive 84/449/EEC A.7 Fat Solubility
Remarks	A simplified flask method was used. Liquefied standard fat was added to the notified chemical (in ratios of 20:1, 1:1, and 1:20) and shaken for 16 hours at 37°C. The formation of a single phase in each flask was established visually.
Test Facility	RCC (2002a)

Hydrolysis as a Function of pH

Method OECD TG 111 Hydrolysis as a Function of pH.
EC Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$ (hours)*
7	65	1.8
7	55	3.3
7	25	28.6*

*Extrapolated from the Arrhenius relationship.

Remarks In a preliminary test at 50°C, 0%, 72%, and 10% of the notified chemical remained after 2.4 hours at pH 4, 7, and 9, respectively. The rate of hydrolysis was then studied in more detail at pH 7 and at test temperatures of 55°C and 65°C. The rate of hydrolysis at 25°C was extrapolated from the pseudo-first order rate constants determined at 55 and 65°C.
Test Facility NOTOX (1997f)

Partition Coefficient (n-octanol/water) $\log P_{ow}$ = 4.1 at 20°C

Method OECD TG 117 Partition Coefficient (n-octanol/water), HPLC Method.
EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks The $\log P_{ow}$ was estimated as >2.7 based on the measured solubility of the notified chemical in water (0.86 g/L) and the observed 1:1 solubility of the notified chemical in n-octanol. A definitive determination was carried out by HPLC.
Test Facility NOTOX (1997g)

Surface Tension 45.1 mN/m at 20°C

Method OECD TG 115 Surface Tension of Aqueous Solutions.
EC Directive 92/69/EEC A.5 Surface Tension.
Remarks The surface tension of a 0.1% solution of the notified chemical at 20°C was measured using the ring tensiometer method. In the initial experiment, no surface equilibrium was reached 17 hours after the test solution was first prepared, indicating a slow reaction of the notified chemical with water. In the second (and definitive) experiment, surface equilibrium was reached ~4 hours after initial dissolution, and 9 minutes after the solution was transferred to the measurement vessel. As the surface tension of the solution was <60 mN/m, the notified chemical is classified as surface active.
Test Facility NOTOX (1997h)

Adsorption/Desorption $\log K_{oc}$ = 2.03

Method Calculation
Remarks The adsorption coefficient was calculated from an established regression correlation between K_{oc} and water solubility (S, in mg/L) of the following functional form:
$\log K_{oc} = -0.55 \log S + 3.64$.
Test Facility RCC (2002b)

Dissociation Constant Not expected to dissociate.

Remarks The notified chemical contains no functional groups that are dissociable in water (expert statement).
Test Facility RCC (2002c)

Flash Point 137.5°C at 101.3 kPa

Method	EC Directive 92/69/EEC A.9 Flash Point.
Remarks	Pensky-Martens closed-cup method. A second flash point value of 129°C was also reported in a technical data sheet for the notified chemical, also determined using the Pensky-Martens closed cup method of ASTM Method D93.
Test Facility	NOTOX (1997i)

Pyrophoric properties Not expected to ignite spontaneously at room temperature

Method	EC Directive 92/69/EEC A.13 Pyrophoric properties of solids and liquids.
Remarks	Expert statement, based on observations during handling.
Test Facility	NOTOX (1997j)

Autoignition Temperature 245ºC

Method	EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	The minimum autoignition temperature was determined for a 0.5 mL injection, with a 45 sec lag time.
Test Facility	NOTOX (1997k)

Explosive Properties Not expected to be explosive

Method	EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks	Expert statement, based on the absence of chemically unstable or highly energetic groups (explosophores) in the structural formula of the notified chemical.
Test Facility	NOTOX (1997m)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Crl: CD BR
- Vehicle: None (dosed undiluted)
- Remarks - Method: A preliminary range-finding study was performed, with dose levels of 500, 1000, 2000, 3500 and 5000 mg/kg bw (1M/1F per dose). No deaths were observed.

RESULTS

Number and Sex of Animals	*Dose (mg/kg bw)*	*Mortality*
5M/5F	5000	0

- LD_{50}: >5000 mg/kg bw
- Signs of Toxicity: Dried red material was observed around the eye(s), nose and/or mouth in seven animals. Six rats had wet and/or dried yellow urogenital and/or ventral abdominal staining. Hypoactivity was observed in five animals. All animals appeared normal on day 4 onwards.
- Effects in Organs: No effects were observed upon gross necropsy.
- Remarks - Results: None.

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

TEST FACILITY: WIL Research Laboratories (1996a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Crl:CD BR
- Vehicle: None (applied undiluted)
- Type of dressing: Semi-occlusive
- Remarks - Method: No significant protocol deviations.
  The dose volume was 2.04 ml/kg (~0.5 mL notified chemical/animal).

RESULTS

Number and Sex of Animals	*Dose (mg/kg bw)*	*Mortality*
5M/5F	2000	0

- LD_{50}: >2000 mg/kg bw
- Signs of Toxicity - Local: Very slight erythema and oedema were observed in 9/10 and 3/10 animals (respectively). Five of ten animals showed desquamation. All signs of irritation had subsided by day 8.
- Signs of Toxicity - Systemic: No clinical findings or remarkable body weight changes were observed.
- Effects in Organs: Reddened cervical lymph node(s) were observed in 7/10 rats upon terminal necropsy.
- Remarks - Results: None.

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

TEST FACILITY: WIL Research Laboratories (1996b)

B.3. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	US EPA TSCA 40 CFR 798.4470
Species/Strain	Rabbit/New Zealand White
Number of Animals	2M/4F
Vehicle	None (applied undiluted)
Observation Period	
Type of Dressing	Semi-occlusive
Remarks - Method	A volume of 0.5 mL notified chemical was applied.
RESULTS	
Remarks - Results	Only one male showed very slight erythema at 72 hours, which had resolved by day 4.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	WIL Research Laboratories (1996c)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	US EPA TSCA 40 CFR 798.4500
Species/Strain	Rabbit/New Zealand White
Number of Animals	3M/3F
Observation Period	72 hours
Remarks - Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0.42	1	48 hours	0
Conjunctiva: chemosis	0	1	1 hour	0
Conjunctiva: discharge	0	1	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	Redness and chemosis of the conjunctivae was observed in all animals at one hour after administration of the test substance.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	WIL Research Laboratories (1996d)

B.5. Skin sensitisation (modified Buehler test)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation – modified Buehler method. EC Directive 96/69/EC B.6 Skin Sensitisation - modified Buehler method.
Species/Strain	Guinea pig/Hartley Crl:(HA)BR
PRELIMINARY STUDY	Maximum Non-irritating Concentration (topical): 25% During the preliminary study, a 50% notified chemical solution (in ethanol) produced slight to moderate (grade 1 to 2) irritation accompanied by focal

eschar on all treated sites. However, as the undiluted test substance caused minimal dermal irritation, it was used for the induction and challenge phases.

MAIN STUDY

Number of Animals: Test Group: 10M/10F; Naïve Control Group: 5M/5F; Positive Control Group: 5M/5F

INDUCTION PHASE

Induction Concentration: 100% (topical only)

Signs of Irritation: Very slight to slight dermal reactions were observed at each of the three application sites used for induction.

CHALLENGE PHASE: In the challenge phase, 100% notified chemical was applied topically to both the test and naïve control groups.

Remarks - Method: No intradermal induction was used. α-Hexylcinnamaldehyde (α-HCA) was used as a positive control substance (undiluted for induction, and a 50% dilution in acetone for challenge).

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 24 h*	*48 h*
Test Group	100%	1 moderate, 11 slight, 8 very slight	14 slight, 6 very slight
Naïve Control Group	100%	9 very slight	6 very slight
Positive Control Group	50% (α-HCA)	2 moderate, 8 slight	1 moderate, 9 slight

Remarks - Results: The sensitisation incidence index was 100% for the positive control, 70% for the test substance, and 0% for the naïve control. The Severity Index was 0.9 for the test substance (at both time points), 1.2 and 1.1 for the positive control, and 0.5 and 0.3 for the naïve control (at the 24- and 48-hour time points for each, respectively).
The irritation observed in the induction phase and the patchy erythema observed in the naïve control animals indicates that the concentration of the test substance was appropriate.
Under the conditions of this test, the test substance was considered to be a mild to moderate skin sensitiser.

CONCLUSION: There was evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: WIL Research Laboratories (2001)

B.6. Skin sensitisation (Maximisation test)

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: Guinea pig/Himalayan

PRELIMINARY STUDY: Maximum Non-irritating Concentration:
intradermal: 20% in corn oil
topical: 100% (undiluted)

MAIN STUDY

Number of Animals: Test Group: 10 males; Control Group: 5 males

INDUCTION PHASE: Induction Concentration:
intradermal: 20% in corn oil
topical: 100% (undiluted)

Signs of Irritation: Mild to well-defined erythema was observed at all intradermal induction sites. Topical induction resulted in slight to severe erythema (10/10), small scab formation (2/10) and oedema (3/10).

CHALLENGE PHASE: A single topical challenge using undiluted (100%) was used.

Remarks - Method: No significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:* *24 h*	*48 h*
Test Group	100%	Moderate and confluent erythema (8/10), discrete erythema (2/10)	Discrete erythema, scaling (10/10)
Control Group	100%	0	0

Remarks - Results: The skin reactions induced by treatment with the test substance during the induction phase were considered to have been enhanced by the pre-treatment of the test site with 10% SDS. This irritation indicates that the test substance concentration was appropriate.
As all animals showed signs of sensitisation, the test substance was considered to have a sensitisation rate of 100%.

CONCLUSION: There was evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: NOTOX (1997n)

B.7. Repeat dose oral toxicity – 28 days

TEST SUBSTANCE: Notified chemical

METHOD: EC Directive 96/54/EC 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
Dose regimen: 7 days per week
Post-exposure observation period: None
Vehicle: Polyethyleneglycol (PEG)
Remarks - Method: Dose levels were selected on the basis of a 5-day dose range finding study (50, 200 and 1000 mg/kg bw/day, with 3 animals/sex/group), in which no significant effects were observed (salivation was noted in 2M/4F).
No recovery group was included in the study design. No urinalysis parameters were examined.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	5M/5F	0 (vehicle)	0
Low dose	5M/5F	50	0
Mid dose	5M/5F	200	0
High dose	5M/5F	1000	0

Mortality and Time to Death
No mortality was observed during the treatment period.

Clinical Observations
Dose-dependent incidences of excessive salivation were observed in both control and treated animals, and this was considered to be a side effect of dosing by gavage rather than a toxic effect. All other observed effects were considered to be within the normal range of biological variability for the test species. No effects on body weight or food consumption were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Significantly decreased serum sodium concentrations (high dose males) and increased serum potassium concentrations (low dose males) were of unknown toxicological significance, due to the lack of obvious causative factors, lack of dose dependency (for potassium). The values were within the normal range of

biological variability.

Effects in Organs

There were no findings observed in treated animals that were not of low incidence and/or within the normal range of biological variability.

Remarks – Results

The lack of a recovery group in the study design was not deemed to be of import, as no treatment-related effects of significance were observed.

CONCLUSION

The No Observed Effect Level (NOEL) was established as 1000 mg/kg bw/day in this study, based on the lack of any significant treatment-related effects observed.

TEST FACILITY NOTOX (1997o)

B.8. Repeat dose oral toxicity – 90 days

TEST SUBSTANCE Notified chemical

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
EC Directive 88/302/EEC B.26 Sub-Chronic Oral Toxicity Test: 90-Day Repeated Oral Dose Study using Rodent Species.
US EPA TSCA 40 CFR 798.2650 Oral Toxicity

Species/Strain	Rat/Wistar Crl:(WI) BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	PEG
Remarks - Method	The dose range was selected on the basis of the results of the 28-day study (above). No recovery group was included in the study design. No urinalysis parameters were examined.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10M/10F	0 (vehicle)	2M
Low dose	10M/10F	100	0
Mid dose	10M/10F	500	1M
High dose	10M/10F	1000	0

Mortality and Time to Death

Two control males died on day 3 of dosing. One died after dosing, and haemorrhagic fluid was noted in the abdominal cavity of this animal upon necropsy. The second died before dosing, after showing hunched posture and piloerection, and necropsy revealed findings in a range of organs. The mid dose animal died on day 5 before dosing, after showing laboured respiration (no macroscopic abnormalities observed on necropsy).

Clinical Observations

There were no clinical signs of toxicity or behavioural changes during the treatment period that were considered to be related to treatment. Dose-dependent excessive salivation and a range of other incidental, dose-independent findings were considered to be either not related to treatment with the test substance and/or within the normal range of biological variability.

No treatment-related effects were observed on body weight, food consumption or on ophthalmoscopic parameters.

Laboratory Findings – Clinical Chemistry and Haematology

Males of the high dose group showed elevated plasma urea levels at the pre-test stage and after 90 days of treatment. However, these levels were minor, and not found to be significantly elevated after 30 days of

treatment in the same animals.
After 30 and 90 days, the red blood cell count and haematocrit values were slightly decreased in high dose females. At 30 days, the serum haemoglobin was also reduced in these animals. Mean corpuscular haemoglobin concentration was decreased in females of the low and mid dose groups at 30 days, but in high dose females this parameter was decreased at 30 days and increased at 90 days.
Total white blood cell count was decreased in high dose females at 30 days, but not at 90 days.
The partial thromboplastin time was slightly increased in mid and high dose females at 90 days, in a dose-dependent fashion.
Any other changes in clinical chemistry or haematology parameters were considered to be either not toxicologically significant, or were not statistically significant.

Effects in Organs
No remarkable macroscopic findings were reported.
One low dose female showed subcutaneous nodules that were found to be mammary adenocarcinoma upon microscopic investigation. Due to its low incidence, this finding was considered by the investigators to be spontaneous and unrelated to treatment.
High dose males showed significantly decreased absolute lung weights; however this significance was considered to be due to an unusually high control value, and was not reflected in the body-weight relative lung weights.
All other microscopic findings were within range for the strain of rat and were common to both control and treated animals.

Remarks – Results
No definitive cause of death could be ascertained for the deaths of the three animals. As these deaths did not occur in the high dose groups, they were not considered to be treatment-related.
The haematological effects noted at 30 days were considered to be due to abnormally high control values, and this is supported by the absence of similar effects in the 28-day study and lesser severities of these effects observed at 90 days.
The increased partial thromboplastin time observed in the mid and high dose females was not considered to be relevant in the absence of corroborative findings.

CONCLUSION
The No Observed (Adverse) Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on the observation of only minor effects, without evidence of organ dysfunction.

TEST FACILITY NOTOX (1998)

B.9. Dermal carcinogenicity study

TEST SUBSTANCE	Notified chemical	
METHOD	In-house skin-painting method (no standard test method available at the time of testing).	
Species/Strain	Mice/C3H/HeJ	
Route of Administration	Dermal – non-occluded.	
Exposure Information	Total exposure:	Lifetime (~500-550 days on average)
	Dose regimen:	3 days per week
	Duration of exposure:	24 hours/day.
Vehicle	Acetone	
Remarks - Method	The dose levels were determined from the results of a pre-test, in which groups of 5 mice each were dosed ('painting' on the animal's back) for 10 days with 25 µL of 100%, 80%, 50%, 25%, 15% or 10% (v/v) test substance in acetone. A 10% solution was found to be sufficiently non-irritating and non-toxic to be used in the main study (equivalent to ~2 mg/mouse). Acetone was used as a negative control, and 3-methylcholanthrene (0.1% in acetone) was used as a positive control. Besides histological investigation of the treatment site, only lesions that were visible at gross necropsy underwent histological examination.	

RESULTS

Group	Mean survival (days)	Number and Sex of Animals	Conc. (% v/v)	Animals with:		
				Papillomas	Carcinomas	Subcutaneous sarcomas
Test substance	545	40M	10	0	0	0
Positive control	204	40M	0.1	2	37	0
Negative control	502	40M	100	0	0	2

Mortality and Time to Death

The survival curve and the mean survival time for animals treated with the test substance were not significantly different from that of control animals.

Effects in Organs – General

Dermal effects observed in test substance-treated mice (at greater incidence compared with vehicle treatment) were surface alteration (2/40), mast cell infiltration (1/40), hyperkeratosis (5/40), epidermal necrosis (1/40), and dermal fibrosis (5/40). No other effects were observed, either gross or histological, which were significantly different from the negative control group (and thus considered to be treatment-related).

Effects in Organs – Tumours

No skin or subcutaneous tumours were observed in the test substance-treated animals. Liver tumours (hepatocellular carcinoma in 9/10 animals with gross liver lesions) were observed in test-substance treated animals. However, this tumour is common in the strain of mice, and appeared with a similar incidence in negative control animals (though not in positive control animals, due to their early deaths).

The two tumours (a lymphosarcoma and a fibrosarcoma) observed in the negative control animals were considered to be historically uncommon. The tumours observed in the positive control animals were either papillomas (2/40) or squamous cell carcinomas (33/40 animals; four additional mice with gross carcinomas were not examined due to cannibalism).

Remarks – Results

The results obtained with the positive control substance confirms the sensitivity of the test system to detect a known skin carcinogen.

CONCLUSION

The notified chemical was not considered to be carcinogenic to the skin of treated mice under the conditions of this study. Note that this study has also been published as part of a scientific paper (DePass *et al*, 1989).

TEST FACILITY Bushy Run Research Centre (1982)

B.10. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD

	OECD TG 471 Bacterial Reverse Mutation Test.
	EC Directive 92/69/EEC B.13/14
	Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100,
	E. coli: WP2uvrA (pKM101), WP2 (pKM101)
Metabolic Activation System	Aroclor-1254 induced rat liver S9-mix
Concentration Range in Main Test	a) With metabolic activation: 10-5000 µg/plate b) Without metabolic activation: 10-5000 µg/plate
Vehicle	Acetone
Remarks - Method	No significant protocol deviations. A preliminary toxicity assay, using ten doses (6.7-5000 µg/plate) tested against the cultures TA100 and WP2uvrA (pKM101), was used to determine the dose-range for the main test. There were a number of technical problems including contamination and unacceptable positive control values. The experiments were repeated so

that two acceptable tests were achieved for each tester strain.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥333	≥333	>5000	Negative
Test 2		≥333	>5000	Negative
Present				
Test 1	≥667	≥333	>5000	Negative
Test 2		≥333	>5000	Negative

Remarks - Results: The test substance did not lead to an increase in the number of revertant colonies, either with or without S9 mix. Positive controls confirmed the sensitivity of the test system.

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

TEST FACILITY: Microbiological Associates (1995)

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

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 92/69/EEC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Human
Cell Type/Cell Line: Peripheral lymphocytes
Metabolic Activation System: Aroclor-1254 induced rat liver S9-mix
Vehicle: Dimethylsulphoxide
Remarks - Method: No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period (hours)*	*Harvest Time (hours)*
Absent			
Test 1A	33, 100, 133*, 180*, 240*, 333	24	24
Test 1B	133*, 180*, 240*, 333	48	48
Test 2	33, 100*, 133, 180*, 240*, 333	24	24
Present			
Test 1A	33*, 100*, 333*	3	24
Test 1B	333*	3	48
Test 2	33*, 100*, 333*	3	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 1A	333[p]	≥240	333	Negative
Test 1B		333	333	Positive
Test 2		≥240	333	Negative
Present				
Test 1A	333[p]	>333	333	Negative

Test 1B	>333	333	Negative
Test 2	>333	333	Negative

p = precipitation

Remarks - Results: In Test 1B (48 h treatment time with 48 h fixation time), in the absence of metabolic activation, the notified chemical induced statistically and biologically significant increases in the number of chromosome aberrations in the presence of a clear dose-response relationship. No statistically significant increases in aberration rates were seen in any of the other tests. Positive controls confirmed the sensitivity of the test system.

CONCLUSION: The notified chemical was clastogenic to human peripheral lymphocytes treated in vitro in the absence of metabolic activation under the conditions of this test.

TEST FACILITY: NOTOX (1997p)

B.12. Genotoxicity – *in vitro* Mammalian Cell Gene Mutation Test

TEST SUBSTANCE: Notified chemical, hydrolysed in water

METHOD: In-house procedure
Cell Type/Cell Line: CHO/K1-BH4-subclone D1
Metabolic Activation System: Aroclor-1254 induced rat liver S9-mix
Vehicle: Ethanol
Remarks - Method: The in-house procedure used is similar to OECD Guideline 476 – *In vitro* Mammalian Cell Gene Mutation Test. The notified chemical was hydrolysed in water (pH 3.2-3.4, adjusted with acetic acid) to simulate the conditions of its typical use in aqueous solutions.
The test with S9 activation was repeated because several dosed cultures were lost to contamination in the incubator.

Metabolic Activation	*Test Substance Concentration (% v/v)*	*Exposure Period (hours)*	*Expression Time (days)*	*Selection Time (days)*
Absent				
Test 1	0.012*, 0.015*, 0.018*, 0.021*, 0.024*	5	7-10	6-8
Test 2	-	-	-	-
Present				
Test 1	0.02*, 0.04†, 0.06†, 0.08†, 0.10*, 0.20*	5	7-10	6-8
Test 2	0.03*, 0.06*, 0.10*, 0.13*, 0.16*, 0.20*	5	7-10	6-8

*Cultures selected for analysis.
† Contaminated tests

RESULTS

Metabolic Activation	*Test Substance Concentration (% v/v) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	0.07%	0.024	> 0.024	Negative
Test 2		-	-	-
Present				
Test 1	0.14%	0.20	> 0.20	Weak positive
Test 2		0.20	> 0.20	Negative

Remarks - Results: In the first test in the presence of metabolic activation one concentration of the test agent produced a small, but statistically significant increase in

mutation frequency. However, this result was not reproduced in the second test, which used a similar but narrower range of doses. No other statistically significant increases in mutation frequency were observed for any treated cultures. Positive controls confirmed the sensitivity of the test system.

CONCLUSION The hydrolysed notified chemical was not mutagenic to CHO cells treated in vitro under the conditions of the test.

TEST FACILITY Bushy Run Research Center (1983)

B.13. Genotoxicity – *in vitro* sister chromatid exchange test

TEST SUBSTANCE Notified chemical, hydrolysed in water

METHOD In-house procedure
Cell Type/Cell Line CHO/K1-BH4-subclone D1
Metabolic Activation System Aroclor-1254 induced rat liver S9-mix
Vehicle Ethanol
Remarks - Method The in-house procedure used is similar to OECD Guideline 479 – *In vitro* Sister Chromatid Exchange Assay in Mammalian Cells. The cells were exposed to both BrdU and the test substance during the exposure period. The dose range was established from the cytotoxicity study undertaken as part of the CHO mutagenicity assay above.
The notified chemical was hydrolysed in water (pH 3.2-3.4, adjusted with acetic acid) to simulate the conditions of its typical use in aqueous solutions.

Metabolic Activation	*Test Substance Concentration (% v/v)*	*Exposure Period (hours)*	*Harvest Time (hours)*
Absent			
Test 1	0.008*, 0.010*, 0.012*	5	29
Test 2	0.010*, 0.012*		
Present			
Test 1	0.008*, 0.010*, 0.012*	2	30-40
Test 2	-	-	-

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (% v/v) Resulting in:*			
	Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	0.012	0.012	>0.012	Weakly positive
Test 2		0.012	>0.012	Negative
Present				
Test 1	0.014	0.012	>0.012	Negative
Test 2		-	-	-

* Cytotoxicity = < 50% survival

Remarks - Results In the first test in the absence of metabolic activation the highest concentration of the test agent produced a small, but statistically significant increase in the SCE frequency. However, this result was not reproduced in the second test, which retested the two highest doses. No other statistically significant increases in SCE frequency were observed for any treated cultures. Positive controls confirmed the sensitivity of the test system.

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

TEST FACILITY Bushy Run Research Center (1983)

B.14. Genotoxicity – *in vitro* unscheduled DNA synthesis (UDS) test

TEST SUBSTANCE Notified chemical, hydrolysed in water

METHOD In-house procedure
Cell Type/Cell Line Primary rat hepatocytes isolated from Hilltop/Wistar albino rats
Metabolic Activation System None (primary cells used)
Vehicle Ethanol
Remarks - Method The in-house procedure used is similar to OECD Guideline 482 – DNA damage and repair/unscheduled DNA synthesis in mammalian cells *in vitro.* Each test concentration was run in duplicate, rather than the six cell cultures per experimental point recommended in the Guideline. The radioactivity in both nuclei and DNA was quantitated for each experimental concentration.
The notified chemical was hydrolysed in water (pH 3.2-3.4, adjusted with acetic acid) to simulate the conditions of its typical use in aqueous solutions.
In the preliminary toxicity test a range of concentrations from 0.3% to 0.0003% were tested.

Test Substance Concentration (% v/v)	*Exposure Period (hours)*	*Harvest time (hours)*
0.0003, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3	2	2

RESULTS

Test Substance Concentration (v/v) Resulting in:			
Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
>0.3%	>0.3%	>0.3%	Negative

Remarks - Results The test substance did not stimulate a significant increase in the incorporation of radioactive thymidine in treated cells. The ^{3}H-thymidine incorporation values for the treated cells were lower than the solvent controls and comparisons to historical controls suggested that the test substance might have inhibited uptake or incorporation of ^{3}H-thymidine. However there was no evidence for a dose-related treatment effect on UDS. Positive controls confirmed the sensitivity of the test system.

CONCLUSION The hydrolysed notified chemical was not mutagenic to primary rat hepatocytes treated *in vitro* under the conditions of the test.

TEST FACILITY Bushy Run Research Center (1983)

B.15. Genotoxicity – *in vivo*

TEST SUBSTANCE Notified chemical

METHOD In-house procedure
Species/Strain Mouse/ICR
Route of Administration Intraperitoneal injection
Vehicle PEG 400
Remarks - Method The method used was consistent with the OECD Guideline 473 -

Mammalian Erythrocyte Micronucleus Test. A preliminary toxicity study was used to determine appropriate doses for the micronucleus assay.
In the micronucleus assay an additional 5 animals/sex was dosed at 2000 mg/kg bw as a replacement group in case of mortalities.

Dose (mg/kg bw)	*Number and Sex of Animals*	*Sacrifice Time (hours)*
0	5M, 5F	24
0	5M, 5F	48
500	5M, 5F	24
1000	5M, 5F	24
2000	5M, 5F	24
2000	5M, 5F	48
50 (CP)	5M, 5F	24

CP=cyclophosphamide

RESULTS

Doses Producing Toxicity

Mortality was observed in 2/15 male and 4/15 female mice dosed at 2000 mg/kg bw. Clinical signs observed included piloerection in male and female mice at all test article dose levels, as well as irregular breathing, crusty eyes, tremors and hunched position in male and female mice at 2000 mg/kg bw. Significantly low excreta was observed with male and female mice dosed with 1000 and 2000 mg/kg bw.
Reductions in the PCE/NCE ratio were observed in male and female dose groups 48 hours after treatment with 2000 mg/kg bw, and in female mice 24 hours after treatment with 1000 and 2000 mg/kg bw.

Genotoxic Effects

No increase in micronucleated PCEs was observed in the bone marrow of treated animals, regardless of dose level or treatment time. The positive control showed a significant increase in the frequency of induced micronuclei, confirming the sensitivity of the test system.

Remarks - Results

The reduction in the PCE/NCE ratio indicates that the notified chemical reached the bone marrow target tissue.

CONCLUSION

The notified chemical was not clastogenic under the conditions of this *in vivo* mouse micronucleus test.

TEST FACILITY

MA BioServices (1998)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test EC Directive 92/69/EEC C.4 Biodegradation: Determination of the 'Ready' Biodegradability, C.4-E: Closed Bottle Test.
Inoculum	Secondary effluent from a municipal sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	The dissolved oxygen concentration was determined by means of an oxygen electrode.
Remarks - Method	The biodegradation of the notified chemical was evaluated at nominal test concentrations of 2 and 5 mg/L. The theoretical oxygen demand calculated for the notified chemical is 2.11 mg O_2/mg. The toxicity control test was performed on test solutions containing 2 mg/L (nominal) of both the notified chemical and the sodium acetate reference.

RESULTS

Test substance		*Sodium acetate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	15	7	84
14	28	14	74
21	28	21	81
28	28	28	75

Remarks - Results	The degradation of the reference substance reached the pass value within 7 days of test initiation and the degradation in the toxicity control was 31% of the nominal maximum within 14 days of test initiation. The test was therefore valid. The measured biodegradation of the notified chemical at both nominal test concentrations was similar at each time point. As the biodegradation reached a limiting value of only 28% of the nominal maximum 14 days after test initiation, the notified chemical is not classified as readily biodegradable according to the test guidelines.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	NOTOX (1997q)

C.1.2. Bioaccumulation

Remarks	The notified chemical does have a theoretical potential to bioaccumulate based on its high logP_{ow} and the complete miscibility of the chemical with fat. However, it also undergoes rapid hydrolysis in water, particularly at the limits of the pH range that are accessible in the aquatic environment. The notified chemical is therefore expected to undergo rapid abiotic degradation before bioaccumulation occurs in aquatic organisms.

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test (Flow-Through) EC Directive 92/69/EEC C.1 Acute Toxicity for Fish (Flow-Through).
Species	Common carp (*Cyprinus carpio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	The solutions for the flow-through tests were prepared from analysed tap water with a measured hardness of 1.9 mmol/L.
Analytical Monitoring	Gas chromatography was used to analyse toluene extracts of the aqueous test medium diluted with acetonitrile (< 10% v/v).
Remarks – Method	A preliminary 96-hour range-finding toxicity test was carried out at nominal test concentrations of 0.1, 1.0, 10, and 100 mg/L in ISO-medium. This test was carried out under static conditions using 3 fish per test concentration. The concentration of the notified chemical was determined for the medium with a nominal 10 mg/L test concentration at the 0-, 24-, and 96-hour time points. The concentration of the notified chemical in the test medium at each nominal concentration was measured at test initiation for the definitive study carried out under flow-through conditions. The concentration was redetermined for nominal concentrations in the range 10-100 mg/L at 48 hours, and 10-56 mg/L at 96 hours. The positive control, pentachlorophenol, was used to check the sensitivity of the test organism to toxic substances at nominal concentrations of 0.10, 0.15, 0.22, 0.32, and 0.46 mg/L in ISO-medium under static conditions. A total of 5 fish were used per test concentration.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control		7	0	0	0	0	0
10	11	7	0	0	0	0	0
18	20	7	0	0	0	0	0
32	35	7	0	0	0	0	0
56	61	7	0	0	5	5	7*
100	100	7	7	7	7	7	7
180	180	7	7	7	7	7	7

* One fish moribund.

LC50	42.3 mg/L at 96 hours.
LOEC	10 mg/L at 96 hours.
Remarks – Results	The static positive control test resulted in no mortalities in fish at a nominal reference substance concentration of 0.1 mg/L, 60% mortality after 96 hours at 0.15 mg/L, and 100% mortality at nominal concentrations ≥ 0.22 mg/L after 24 hours. The 96-hour LC50 for fish exposed to the reference substance is 0.14 mg/L (95% CI: 0.13-0.18 mg/L), which confirmed the sensitivity of the test organism to toxic substances. The static range-finding test demonstrated 100% mortality in fish after 24 hours when exposed to the notified chemical at a nominal concentration of 100 mg/L. No mortality occurred at lower test concentrations in 96-hours. The analysis of the nominal 10 mg/L test solution showed that under static test conditions, the concentration of the notified chemical had declined by 30% after 24 hours and 60% after 96 hours relative to the

nominal level. This result confirmed the need for flow-through conditions for the definitive fish toxicity test.

The measured concentration of the notified chemical under flow-through conditions was within a range of 101-116% of the nominal value when tested, except for one outlier, attributed to a sampling error.

The fish exposed to the lowest test concentration (10 mg/L) were hypoactive at the top and bottom of the test vessel after 96 hours. Fish exposed to higher concentrations of notified chemical in the range 18-56 mg/L displayed other non-lethal toxic effects including immobility and loss of equilibrium, which were manifest less than 96 hours after test initiation. The 96-hour LOEC based on these observations is 10 mg/L.

The 96-hour LC50 for the notified chemical was estimated from the geometric mean of the 96-hour LC0 (32 mg/L) and LC100 (56 mg/L) end points.

CONCLUSION The notified chemical is harmful to fish.

TEST FACILITY NOTOX (1997r)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp., Acute Immobilisation Test (Flow-Through)
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia (Flow-Through).

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	The solutions for the flow-through test were prepared from analysed tap water with a measured hardness of 1.9 mmol/L.
Analytical Monitoring	As for the fish test (above).
Remarks - Method	A preliminary 48 hour range-finding toxicity test was carried out on 10 daphnids at nominal test concentrations of 0.1, 1.0, 10, and 100 mg/L in M7-medium. This test was carried out under static conditions on 10 daphnids per test concentration. The concentration of the notified chemical was determined for the medium with a nominal 10 mg/L test concentration at the 0- and 24-hour time points. The definitive toxicity test for this organism was carried out under flow-through conditions simultaneously with the fish toxicity test (above). The daphnids were therefore exposed to the same nominal test concentrations as for the fish test (10-180 mg/L). The concentration of the notified chemical in the test medium was measured for all test concentrations (except the 18 mg/L test solution) at the 0- and 48-hour time points. The positive control, potassium dichromate, was used to check the sensitivity of the test organism to toxic substances at nominal concentrations of 0.10, 0.18, 0.32, 0.56, 1.0, and 1.8 mg/L in ISO-medium under static conditions. A total of 10 daphnids were used for each test concentration.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control		2 x 10	0	0
10	11	2 x 10	0	0
18	20	2 x 10	0	0
32	33	2 x 10	0	0

56	60	2 x 10	0	4(A), 3(B)*
100	109	2 x 10	9(A), 8(B)*	10
180	293	2 x 10	10	10

* The descriptors (A) and (B) refer to duplicate test vessels, which initially contained 10 daphnids each.

LC50	82 mg/L at 24 hours (95% CI: 77-91 mg/L) 58 mg/L at 48 hours (95% CI: 53-68 mg/L)
NOEC	32 mg/L at 48 hours
Remarks - Results	The positive control test resulted in no mortality to daphnids at nominal concentrations ≤0.56 mg/L after 48 hours, and 100% mortality at nominal concentrations ≥1.0 mg/L after 48 hours. The 48-hour EC50 for daphnids exposed to the reference substance is therefore estimated as 0.75 mg/L. The static range-finding test resulted in immobilisation of 1 daphnid at each of the two highest nominal test concentrations (10 and 100 mg/L) after 48 hours. The measured concentration of the notified chemical was 65% of the nominal value after 24 hours in the nominal 10 mg/L test solution, which confirmed the need for the use of flow-through conditions in the definitive test. The measured concentration of the notified chemical under flow-through conditions was within ±20% of the nominal value, except at the highest nominal concentration of 180 mg/L, where measured concentrations were up to 181% of the nominal value at test initiation (for reasons not resolved). The daphnids exposed to nominal concentrations of ≤32 mg/L showed no signs of non-lethal toxic effects over the period of the test. However, after 24 hours exposed to 56 mg/L, ≤9 daphnids were observed trapped at the surface of the solution. At the next highest test concentration (100 mg/L), all 10 daphnids in each test chamber were trapped at the surface and most were immobile. Based on these observations, both the 24- and 48-hour NOECs are 32 mg/L. The 24-hour and 48-hour EC50 end-points for the notified chemical were calculated by means of probit analysis using nominal concentrations.
CONCLUSION	The notified chemical is harmful to aquatic invertebrates.
TEST FACILITY	NOTOX (1997s)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	Freshwater green algae (*Pseudokirchneriella subcapitata*)
Exposure Period	72 hours
Concentration Range	Nominal: 10, 18, 32, 56, 100, and 180 mg/L Actual: 6, 11, 19, 34, 60, and 108 mg/L
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	As for the fish test.
Remarks - Method	A preliminary 72-hour range-finding toxicity test was carried out at nominal test concentrations of 0.1, 1.0, 10, and 100 mg/L (actual concentrations not determined). The cell densities in the test solutions could not be determined spectrophotometrically because of excessive turbidity. The cell densities in this study were therefore determined microscopically. These determinations were made at the 48- and 72-hour time points for the definitive test. In the definitive test, the concentration of the notified chemical in test solutions with nominal concentrations of 10 and 180 mg/L was

determined at the 0-, 24-, and 72-hour time points.

The sensitivity of the test system to toxic substances was tested with potassium dichromate at nominal concentrations of 0.18, 0.32, 0.56, 1.0, 1.8, and 3.2 mg/L in standard algal growth test media.

RESULTS

Biomass		*Growth*	
E_bL50 mg/L at 72 h	*NOE_bC mg/L*	*E_rL50 mg/L at 72 h*	*NOE_rC mg/L*
60 (nominal) (95% CI: 46-84 mg/L) 36 (actual)	10 (nominal) 6 (actual)	72 h: Not determined 48 h: 56-100 (nominal)	18 (nominal) 11 (actual)

Remarks - Results

The positive control test resulted in 96.2% inhibition of growth and 73.2% inhibition of growth rate in algae after 72 hours at the highest nominal test concentration of 3.2 mg/L. The 72-hour EC50s for growth inhibition and growth rate derived from this test are 1.0 and 1.6 mg/L, respectively. These toxicity end-points are within the historical ranges for this reference substance.

The results of the range-finding test appeared to show a significant reduction in cell densities after 72 hours relative to controls only at the highest nominal test concentration, although only one measurement was made at this time point for this concentration.

The measured concentration of the notified chemical at test initiation was 92-94% of the nominal concentration. However, after 24 hours the measured concentration had declined to 66-73% of the nominal level and, at test completion, the measured concentration was 30-39% of nominal. The decline in concentration was comparable between samples with and without added algae and was attributed to hydrolysis of the notified chemical. The actual exposure concentration in the test solutions over the 72-hour test period was therefore calculated as a weighted average of the geometric means of the concentrations measured for the intervals 0-24 hours and 24-72 hours. Thus, the 72-hour average exposure concentration in each test solution was 60% of the respective nominal value.

The cumulative inhibition of cell growth over 72 hours increased monotonically with increasing concentration of the notified chemical up to a maximum of 85% for the highest tested concentration. The nominal EC50 for growth inhibition and the 95% confidence interval was interpolated from a plot of the percentage inhibition against the logarithm of the nominal concentration. The E_bC50 based on actual exposure concentrations of the notified chemical was estimated as 60% of the end-point derived from the analysis based on nominal concentrations.

There was no growth of algae after 48 hours (100% rate reduction) when they were exposed to the two highest nominal test concentrations. However, after a further 24 hours, the algae grew in these media such that the reduction in cumulative growth rate after 72 hours had *declined* to 17.4% and 30.1% for nominal test concentrations of 100 and 180 mg/L, respectively. The onset of growth in the interval between 48 and 72 hours is correlated with a significant decline in the actual concentration of notified chemical in the test solution in this interval from approximately 70% of the nominal level to 30-40% of nominal. Based on the available data, a 48-hour nominal E_rC50 was estimated as 56-100 mg/L.

The inhibition of algal cell growth was statistically significant at all nominal test concentrations >10 mg/L. The 72-hour NOE_bC is therefore 10 mg/L based on nominal levels of the notified chemical and 6 mg/L based on the average exposure concentration. The cumulative reduction in growth rate over 72 hours was statistically significant at nominal

	concentrations ≥32 mg/L. Therefore, the 72-hour NOE_rC was 18 mg/L based on nominal concentrations and 11 mg/L based on the average exposure concentration.
CONCLUSION	The notified chemical is classified as harmful to algae based on the 72-hour EC50 for growth inhibition.
TEST FACILITY	NOTOX (1997t)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test.
Inoculum	Activated sludge from a municipal sewage treatment plant
Exposure Period	0.5 hours
Concentration Range	Nominal: 100 mg/L
Remarks – Method	A limit test (one nominal concentration) was used to assess the potential inhibitory effects of the notified chemical on sewage microbe activity. The sensitivity of the sewage sludge microorganisms used in the test was assessed using the reference substance, 3,5-dichlorophenol, at nominal concentrations of 3.2, 10, and 32 mg/L.
RESULTS	The 30-minute EC50 for inhibition of microbial respiration for the reference substance is 7.3 mg/L and the difference between the respiration rates for the controls was < 10%. The test is therefore valid. There was no significant inhibition of microbial respiration in duplicate test solutions of the notified chemical after 30 minutes of contact time.
IC50	>100 mg/L
NOEC	100 mg/L
CONCLUSION	The notified chemical does not adversely affect waste-water bacteria at a nominal concentration of 100 mg/L.
TEST FACILITY	NOTOX (1997u)

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