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August 2009

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME
(NICNAS)

FULL PUBLIC REPORT

Ethyl trisiloxane

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

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

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

Street Address:	334 - 336 Illawarra Road MARRICKVILLE NSW 2204, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Momentive Performance Materials Australia Pty Ltd (ABN 47 105 651 063)
175 Hammond Road
Dandenong VIC 3175

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.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: Acute Dermal Toxicity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Japan ENCS No. 7-476; Europe ELINCS No. 469-070-1

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Silsoft ETS
INCI name: Ethyl trisiloxane

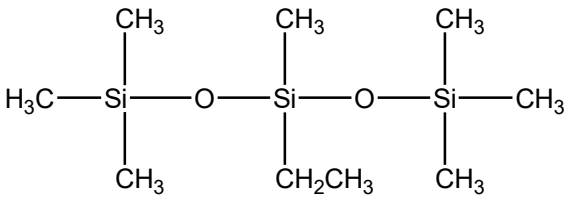
CAS NUMBER
17861-60-8

CHEMICAL NAME
Trisiloxane, 3-ethyl-1,1,1,3,5,5,5-heptamethyl-

OTHER NAME(S)
Y-14877
3-Ethylheptamethyltrisiloxane

MOLECULAR FORMULA
$C_9H_{26}O_2Si_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT

250.56 g/mol

ANALYTICAL DATA
Reference NMR, IR, GC, and UV/Vis spectra were provided.

3. COMPOSITION

DEGREE OF PURITY 98%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)

Chemical Name	Disiloxane, hexamethyl-		
CAS No.	107-46-0	*Weight %*	0.13
Chemical Name	Disiloxane, 1-ethyl-1,1,3,3,3-pentamethyl-		
CAS No.	6231-60-3	*Weight %*	0.06
Chemical Name	Trisiloxane, octamethyl-		
CAS No.	107-51-7	*Weight %*	0.57
Chemical Name	Tetrasiloxane, decamethyl-		
CAS No.	141-62-8	*Weight %*	0.11
Chemical Name	4-Ethylnonamethyltetrasiloxane		
CAS No.		*Weight %*	0.23
Chemical Name	4,6-Diethyloctamethyltetrasiloxane		
CAS No.		*Weight %*	0.12

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Colourless, clear liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -100°C	Measured
Boiling Point	177°C at 101.3 kPa	Measured
Density	828 kg/m^3 at 20°C	Measured
Vapour Pressure	0.170 kPa at 25°C	Measured
Water Solubility	0.016 mg/L at 20°C	Estimated
Hydrolysis as a Function of pH	Hydrolytically stable.	Analogue data
Partition Coefficient (n-octanol/water)	log K_{OW} = 5.84	Estimated
Adsorption/Desorption	log K_{oc} = 3.8	Estimated
Dissociation Constant	Not Applicable	The notified chemical does not contain dissociable functionalities.
Particle Size	Not Applicable	The notified chemical is liquid.
Flash Point	49°C at 101.3kPa	Measured
Flammability	Class 3 Flammable Liquid	MSDS
Autoignition Temperature	305°C	Measured
Explosive Properties	Not Explosive	The notified chemical is not expected to be explosive based on a low decomposition energy (determined to

		be < 500 J/g).
Stability Testing	Thermally stable in the range 25-300°C	Measured
Oxidising Properties	No Oxidising Properties	Measured
Surface Tension	Not determined	Cannot be measured due to low water solubility.

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

Reactivity
The product containing the notified chemical is stable under normal conditions and was determined to be thermally stable in the range 25-300°C and to be non-oxidising.

Dangerous Goods classification
Based on the available data the notified chemical is classified as follows according to the Australian Dangerous Goods Code (FORS, 1998): Class 3 Flammable liquid.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as a component of cosmetic products (1-50% concentration).

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

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

PORT OF ENTRY
Any or all Australian ports.

IDENTITY OF MANUFACTURER/RECIPIENTS
All major personal care product importers are expected to import end-use products containing the notified chemical.

TRANSPORTATION AND PACKAGING
The imported products containing the notified chemical will be packaged in containers suitable for retail sale, the largest of which is expected to be 300 mL.

USE
The notified chemical will be used as a component of personal care products. The notified chemical acts as a vaporisable carrier. The notified chemical will not be used in aerosol applications, but will be used for pumpable spray applications.

Potential products in which the notified chemical (in concentrations of 1-10%, apart from mascara where it will be present at 1-20%) may be used are:
- mascara
- lip liner
- lipstick
- lotions
- foundation
- creams
- eye shadow
- masks
- concealer
- non-aerosol hairspray
- eye liner
- sunless spray tanner

OPERATION DESCRIPTION
There will be no manufacturing or reformulation done in Australia. The marketed product containing the notified chemical will be imported into Australia and transported by road to a central warehouse facility. From the warehouse, the marketed product containing the notified chemical is distributed to retail outlets.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

EXPOSURE DETAILS
Transport and Storage
During transport and storage, workers are unlikely to be exposed to the notified chemical except when packaging is accidentally breached.

Retail
Retail workers are unlikely to be exposed to the notified chemical except when packaging is accidentally breached.

Beauty/Hairdressing
Dermal exposure to the notified chemical is expected to occur during the use of products by beauticians and hairdressers. Due to the nature of the products, no personal protective equipment is expected to be worn, however good hygiene practices are expected to be in place. EASE modelling of the use of the notified chemical by beauticians and hairdressers estimated the dermal exposure as 0.1-0.5 mg/cm^2/day assuming a wide dispersive use, intermittent contact and a maximum concentration of 10%. Assuming a quarter of the hands i.e. fingertips (210 cm^2) are exposed, a dermal absorption of 1% (see section 6.2) and an average body weight of 60 kg, the daily exposure is estimated to be 0.004-0.02 mg/kg bw/day.

Hairdressers may have repeated inhalation exposure to the notified chemical if it is included in non-aerosol hairsprays. The frequency of use and hence exposure is expected to be greater for hairdressers than consumers (i.e. > 0.14 mg/kg bw/day, see Section 6.1.2).

6.1.2. Public exposure
Since the notified chemical will be in products sold to the general public, there will be widespread and repeated exposure of the public to the notified chemical. Exposure will vary depending on the type of cosmetic product and individual use patterns.

Product type	Amount/Use (g)	Retention factor	Concentration (%)	Dermal Exposure (mg/kg bw/day)†
Hair styling preparation	5*	0.1***	10	8 x 10^{-3}
Non-aerosol hairspray	7.81 (2 uses/day)**	0.05**	10	0.013
Body lotions / sunless spray tanner	7.5*	1***	10	0.13
Face creams/foundation	0.8*	1***	10	0.01
Lipstick	0.01 (4 uses/day)**	1***	10	7 x 10^{-4}
Mascara	0.025*	1***	20	8 x 10^{-4}
Eye liner	0.005*	1***	10	8 x 10^{-5}
Eye shadow	0.01*	1***	10	2 x 10^{-4}

* EU TGD (2003)
** SDA (2005)
*** SCCP (2006)
† Systemic exposure after dermal contact assuming an average body weight of 60 kg and a dermal absorption of 1% (see section 6.2)

The main route of exposure is expected to be dermal. Ocular exposure may occur by accident. Due to the use of the notified chemical as a vaporisable carrier and its potential use in non-aerosol spray products, inhalation exposure may also occur. Based on exposure estimation to hairspray (pump) products in North America (SDA, 2005), inhalation exposure to the notified chemical from its use in non-aerosol hairsprays is estimated to be 0.14 mg/kg bw/day, assuming a bodyweight of 60 kg, that the notified chemical is present at a concentration of

10% and uptake is 10% (see section 6.2)

As the finished products will be stored and used in a domestic environment, there is the possibility of accidental ingestion by a child.

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	Low toxicity, oral LD50 > 2000 mg/kg bw
Rat, acute inhalation toxicity	Low toxicity, LC50 > 10 mg/L/4 hours
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	No evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 50 mg/kg bw/day
Genotoxicity – bacterial reverse mutation	Non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test with V79 cells	Equivocal
Genotoxicity – *in vitro* mammalian chromosome aberration test with human lymphocytes	Non clastogenic
Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test	Non clastogenic
Genotoxicity – *in vivo* comet assay	Equivocal
Genotoxicity – *in vivo* comet assay	Non genotoxic

Toxicokinetics, metabolism and distribution

The notified chemical may be absorbed across biological membranes, based on the relatively low molecular weight (250.56 g/mol). There was no evidence of absorption of the notified chemical across the gastrointestinal tract after acute oral exposure. However, effects were seen in the repeat dose toxicity study indicating that absorption of the notified chemical across the gastrointestinal tract did take place.

Based on the physicochemical properties of the notified chemical (water solubility < 1 mg/L, log Kow = 5.84, vapour pressure = 0.17 kPa) dermal uptake beyond the stratum corneum is expected to be limited. Octamethylcyclotetrasiloxane (also known as D4, CAS number 556-67-2), a cyclic siloxane which has similar physicochemical properties to the notified chemical (molecular weight = 296.6, log Kow = 5.1, vapour pressure = 0.13 kPa) has been investigated for its dermal absorption properties in a number of in vitro and in vivo studies (Jovanovic *et al,* 2007; SCCP, 2005, SEHSC, 2008). In all studies the majority of the dose applied volatilised from the skin, with the highest dermal absorption measured as 1% of the applied dose. As the notified chemical has similar volatility, partition coefficient and molecular weight to D4 the dermal absorption is expected to also be similar. Therefore the worst case value for the absorption of D4 (1%) will be used in the risk assessment of the notified chemical.

Based on the physicochemical properties of the notified chemical uptake by the lungs is possible. Data from a human inhalation exposure study on D4 showed that the majority (~90%) of the inhaled dose was not absorbed (Hoan-My Do Luu and Hutter, 2001). An estimate of 10% uptake is therefore considered acceptable for the notified chemical.

Based on the physicochemical properties (log Kow >4) daily exposure to the notified chemical could result in build up in the body (EU TGD, 2003). However, potential for build up in the body may be limited as, based on studies on the linear siloxane hexamethyldisiloxane (Varaprath et al, 2003) and PBPK modelling on D4 (Andersen et al, 2005), the notified chemical is expected to be extensively metabolised and excreted.

Acute toxicity

Based on the tests in rats, the notified chemical exhibits low toxicity via the oral and inhalation routes.

Irritation and sensitisation

The notified chemical was non-irritating in rabbits via dermal exposure and was found to be non-sensitising in

guinea pigs. It was found to be only slightly irritating in rabbits via ocular exposure. Slight redness and slight swelling of the conjunctivae were observed in one of the animals tested 1 hour after exposure to the notified chemical. At 24 hours after exposure, the same animal had slight redness of conjunctivae. At 72 hours after exposure, no signs of eye irritation were observed in all of the test animals.

Repeated dose toxicity

An increase in liver weights was seen in all three dose groups in a dose dependent manner. At the mid and high doses these increases were above 10%. No corresponding liver enzyme induction was observed and the reversibility of these effects was not determined. Therefore these liver weight changes were considered to be adverse. In the low dose group (50 mg/kg bw/day) only the male animals showed a statistically significant increase in absolute liver weights (12%). The relative liver weights in the low dose group did not show a significant increase and therefore the effects in this group were determined to be non-adverse. Therefore, the NOAEL for the notified chemical was determined to be 50 mg/kg bw/day.

The effects after repeated inhalation exposure are not known, as no data was available on the notified chemical.

Genotoxicity

The notified chemical contains no structural alerts for mutagenicity and was negative in a bacterial reverse mutation assay (Ames test), conducted both with and without metabolic activation. The notified chemical was also found to be negative in an *in vivo* mammalian erythrocyte micronucleus test. It was unclear from the *in vivo* mammalian erythrocyte micronucleus test whether the notified chemical was reaching the target organ (bone marrow). However, given the effects seen in the repeat dose study systemic exposure is assumed.

Two *in vitro* mammalian chromosome aberration tests were conducted on the notified chemical. One test was conducted with V79 Chinese hamster cells and another using human peripheral blood lymphocytes. The test conducted using V79 Chinese hamster cells showed statistically significant increases in the incidence of cells with chromosomal aberrations while the test conducted using human peripheral blood lymphocytes did not. However, in the test conducted using V79 Chinese hamster cells there was a large difference in the cytotoxic effects between cells treated with S9 metabolic activation and those without it (1750 and 4 µg/mL respectively), and the structure of the notified chemical does not provide a reason for this. The difference in the cytotoxicity between cells treated with S9 and those without was not seen in the study using the human peripheral blood lymphocytes. This may therefore indicate instability in the V79 Chinese hamster cells used. Statistically significant increases in the incidence of V79 Chinese hamster cells with chromosomal aberrations were only seen at concentrations where the test substance was also cytotoxic. This may indicate that the aberration effects seen are unspecific secondary effects. Therefore a false positive in the V79 Chinese hamster cell assay cannot be ruled out.

Two *in vivo* comet assays were also conducted using the notified chemical. The first comet assay looked at skin and liver cells and the test substance was delivered by intraperitoneal injection. Statistically significant ($p < 0.05$) increases were seen in the Olive tail moment (OTM) of the liver hepatocytes and skin fibroblasts for both the male and female animals treated with the test substance in comparison to those animals treated with the negative control in this comet assay. However, based on limitations in this study a false positive could not be ruled out.

A second *in vivo* comet assay was conducted using stomach and liver cells and the test substance was delivered orally. Statistically significant ($p < 0.05$) decreases were seen in the mean OTM for stomach cells with a sample time of 4 hours from animals treated with the test substance in comparison to those animals treated with the negative control. However, the mean OTM for stomach cells were within the historical range (1.75-11.40, mean 4.63) and the mean value for the negative control was higher than the historical mean although still within the historical range.

The second comet assay measured both the olive tail moment as well as the % tail DNA while the first comet assay only measured the OTM. The second comet assay was also conducted at a range of doses including the one dose (2000 mg/kg) that was used in the first comet assay.

Considering the results obtained from all the genotoxicity assays, and the reliability and quality of each of the studies, the notified chemical is not considered to be genotoxic *in vivo*.

Reproductive Toxicity

No data was available on the reproductive toxicity of the notified chemical. Octamethylcyclotetrasiloxane (D4) has been shown to cause reproductive effects in the rat, associated with inhibition of the luteinizing hormone surge. However the relevance of these findings to humans is uncertain, as there are conflicting opinions in this area (SCCP, 2005; European Commission, 2007). The metabolites of linear and cyclic siloxanes have been found to be different (Varaprath et al, 2003) and reproductive effects have not been reported in studies on other siloxanes, including lower molecular weight linear siloxanes, such as hexamethyldisiloxane (SEHSC, 2000).

Based on the available data the notified chemical is not classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

The highest occupational exposure to the notified chemical is expected to be to beauticians and hairdressers using the finished cosmetic products (≤ 10% notified chemical, apart from mascara where it is present at ≤ 20%).

Local effects

The notified chemical is only a slight eye irritant and no personal protective equipment is expected to be worn by beauticians and hairdressers, however good hygiene practices are expected to be in place. Therefore the risk of irritant effects after exposure to the notified chemical is not considered to be unacceptable.

Systemic effects

The notified chemical was found to have a NOAEL of 50 mg/kg bw/day in the repeat dose 28 day oral toxicity study. Although oral exposure is expected to be low and is likely to be minimised further by good personal hygiene practices, potential for systemic exposure via the dermal route exists given the low molecular weight of the notified chemical. No NOAEL has been determined for the dermal route. EASE modelling for use of the notified chemical by beauticians and hairdressers estimated the dermal exposure to be 0.004-0.02 mg/kg bw/day (assuming 1% dermal absorption). Use of the oral NOAEL results in an MOE (margin of exposure) of ≥ 2500. An MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. This MOE therefore indicates that the risk to workers from dermal exposure to the notified chemical would not be considered unacceptable.

The effects after repeated inhalation exposure are not known. Based on the oral NOAEL (50 mg/kg bw/day) and the assumption that hairdresser inhalation exposure to the notified chemical in non-aerosol hairsprays would be greater than consumer (i.e. > 0.14 mg/kg bw/day), an MOE of < 352 is estimated. For those workers exposed via both the dermal and inhalation routes an MOE of < 314 is estimated (based on the estimated total exposure of > 0.16 mg/kg bw/day). Although an accurate MOE can not be determined it is considered that the exposure values per event used are conservative estimates for occupational use (including a high proportion of respirable droplets) and therefore the risk to hairdressers of adverse effects after inhalation exposure is not considered to be unacceptable.

6.3.2. Public health

The general public will be repeatedly exposed to the notified chemical via a number of different consumer products, applied to the skin.

Local effects

The notified chemical is a slight eye irritant. However, the risk of irritancy in consumers is not considered to constitute an unacceptable risk.

Systemic effects

Based on the NOAEL of 50 mg/kg bw/day, MOEs for a number of likely consumer product categories, using the notified chemical at up to 10%, apart from mascara where it will be used at concentrations up to 20%, are calculated and presented in the table below.

Product type	Exposure (mg/kg bw/day)	MOE
Hair styling preparation	8×10^{-3}	6250
Non-aerosol hairspray*	0.15	323
Body Lotions / sunless	0.13	385

spray tanner		
Face Creams/Foundation	0.01	5000
Lipstick	7×10^{-4}	71,429
Mascara	8×10^{-4}	62,500
Eye liner	8×10^{-5}	625,000
Eye shadow	2×10^{-4}	250,000

*assuming dermal and inhalation exposure

An MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. The above risk estimations were based on the systemic exposure estimation from using one single product listed. In the unlikely event that a consumer would be exposed to all products containing the notified chemical at the highest concentration this exposure (estimated as 0.3 mg/kg bw/day) would still result in a MOE greater than 100. Therefore the risk of adverse systemic effects following exposure via consumer products is not considered to be unacceptable.

Any one off accidental ingestion of the notified chemical is unlikely to pose a risk due to the low acute oral toxicity of the notified chemical.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

No manufacturing will take place in Australia. Small quantities may be lost to waste as an ingredient in personal-care products in the event of leak or spill at the warehouse site. Such waste is expected to evaporate or be absorbed in solid absorbent and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

From consumer use of cosmetic products, the substance is expected to enter sewage treatment plants through domestic waste-water streams. Like other siloxanes, this chemical is expected to be separated from the aqueous stream by about 95% during waste-water treatment. This estimate is supported by the high volatility, low water solubility and high Log Po/w characteristics.

RELEASE OF CHEMICAL FROM DISPOSAL

Following, sale of end-use products to the public, most of the chemical would volatilise or find its way into sewer effluent after being washed from skin or hair. Very diffuse dispersion would be expected across Australia. A very small proportion would be carried from the domestic STP in the aqueous phase and a major proportion would be expected to evaporate or partition to sewage sludge that is normally landfilled or may be incinerated.

The traces of products containing the notified chemical are expected to be disposed of to domestic garbage and thence to landfill.

7.1.2 Environmental fate

Persistence and Ready Biodegradability
Due to its high volatility, the notified chemical's potential for persistence in air and long range transport was assessed using "AOP Program (v1.92)". This estimates the half-life of the notified chemical in air, based on a 12 hour day, as being 57.252 hours, which indicates that the notified chemical has the potential for long-range transport. A single ready biodegradability test report was submitted indicating that the notified chemical is not ready biodegradable. For the details of the environmental fate study, please refer to Appendix C.

Bioconcentration and Bioaccumulation
The notified chemical was assessed for its potential to bioconcentrate using EPISuite's "BCF Program (v2.17)". This calculated a Bioconcentration factor (BCF) of 6247, which indicates that the notified chemical has a high potential to bioconcentrate. Based on the low solubility in water and high K_{OW}, the notified chemical may have the potential to bioaccumulate. However, the diffuse release pattern and high volatility should mitigate this.

7.1.3 Predicted Environmental Concentration (PEC)

Since most of the chemical may be washed into the sewer, under a worst case scenario, with no removal of the notified chemical in the sewage treatment plant, the resultant Predicted Environmental Concentration (PEC) in sewage effluent on a nationwide basis is estimated as follows:

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	5,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	5,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	13.70	kg/day
Water use	200.0	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:	3.34	µg/L
PEC - Ocean:	0.33	µg/L

The PEC was also calculated using the SimpleTREAT model to take into account removal processes within an STP, (Environment Australia, 2003). The SimpleTREAT model indicates partitioning of 27% to air, 69% to sludge, and 4% remaining in effluent. This is shown in the table 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	100%	
Annual quantity of chemical released to sewer	5,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	13.70	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	20.496	million
Removal within STP	96%	Mitigation
Daily effluent production:	4,099	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.13	µg/L
PEC - Ocean:	0.01	µg/L

The mitigated PEC will be used in calculating the risk quotient, as it is more realistic given the high volatility of the notified chemical.

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 (WAF)	Not toxic up to the level of water solubility.
Daphnia Toxicity	EC50 >100 mg/L (WAF)	Not toxic up to the level of water solubility.
Algal Toxicity	I_rC50 >100 mg/L (WAF)	Some toxicity demonstrated at the level of water solubility.
Inhibition of Bacterial Respiration	IC50 >1000 mg/L (WAF)	Not toxic up to the level of water solubility.

The result of the ecotoxicity studies submitted indicated that the notified chemical was not harmful to aquatic organisms, apart from algae, up to its level of solubility in water. The algal ecotoxicity test indicated some growth inhibition at a maximum measured concentration of 0.2 mg/L.

7.2.1 Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated using the maximum measured concentration for the algal NOEC (0.2 mg/L) and a safety factor of 100 as shown below.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (Alga).	0.20	mg/L
Assessment Factor	100.00	
PNEC:	2.00	µg/L

7.3. Environmental risk assessment

Based on the mitigated PEC and PNEC calculated above, the Risk Quotient has been calculated as follows.

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	0.13	2.00	0.066835
Q - Ocean:	0.01	2.00	0.006684

As the Q value is below 1, the risk to the aquatic environment is considered to be acceptable.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

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

Human health risk assessment

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

When used in the proposed manner at concentrations up to 20%, the notified chemical is not considered to pose an unacceptable risk to public health.

Environmental risk assessment

On the basis of the PEC/PNEC ratio and the reported use pattern, the notified substance is not considered to pose an unacceptable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical in formulated products:
  - Good hygiene practices and good ventilation should be maintained
  - Avoid inhalation of products containing the notified chemical

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

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

Disposal

- The notified chemical should be disposed of to landfill.

Storage

- The following precautions should be taken regarding storage of the notified chemical:
  - Keep away from sources of ignition.

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 imported as the raw material for reformulation in Australia;
  - the notified chemical is imported in personal care products, other than those assessed;
  - information becomes available as to the reproductive effects of the notified chemical.

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of personal care products at concentrations up to 20%, or is likely to change significantly;
  - the amount of chemical being introduced has increased from 5 tonnes, or is likely to increase, significantly;
  - the chemical has begun to be manufactured in Australia;
  - additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

Material Safety Data Sheet

The MSDS of the notified chemical and products containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point < -100ºC

Method OECD TG 102 Melting Point/Melting Range.
EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Differential Scanning Calorimetry (DSC) method was used in the determination of the melting point. Tests showed no endothermic effect (melting) in the temperature range -100 to 50°C and no exothermic effect (freezing) when the test substance was cooled down to-100°C.
Test Facility Siemens (2005a)

Boiling Point 177ºC at 101.3 kPa

Method OECD TG 103 Boiling Point.
EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks The capillary method according to Siwoloboff was used in the determination of the boiling point.
Test Facility IBACON (2005a)

Density 828 kg/m^3 at 20ºC

Method OECD TG 109 Density of Liquids and Solids.
EC Directive 92/69/EEC A.3 Relative Density.
Remarks A glass pycnometer was used in the determination of the density.
Test Facility IBACON (2005b)

Vapour Pressure 0.170 kPa at 25ºC

Method OECD TG 104 Vapour Pressure.
OECD TG 113 Screening Test for Thermal Stability and Stability in Air.
Remarks The dynamic method was used in the range of 47.1-167.4°C for the determination of the vapour pressure. With respect to the environment, the vapour pressure is classified as highly volatile (Mensink *et al.* 1995).
Test Facility Siemens (2005b)

Water Solubility ≤ 0.1 mg/L (OECD A6)
0.016 mg/L WSKOWWIN

Method EEC 92-69, Annex V A.6 (1992): "Water solubility".
OECD 105 (1995): "Water solubility"

WSKOWWIN 1.4, being part of EPI Suite v3.12 © 2000, US Environmental Protection Agency
Remarks Due to the physico-chemical properties of the test item, neither the application of the column elution method nor the shake flask method provided meaningful results.

The high volatility of the test item eliminates a sufficient loading of the carrier material. By evaporation of any solvent the test item was also evaporated. Without using any solvent for loading the test item was observed as clear phase on the water surface. Furthermore, the test item was not disposable because of high adsorption to polar surfaces.

In consequence the shake flask method was applied. Sufficient amount of the test item was shaken in water. However, as a result of this procedure an emulsion of the test item in water was obtained. Although the emulsion was centrifuged several times, the top layer was discarded and the solution occurred clear, the results indicated a high variety. Thus it was assumed that the emulsion could not completely be separated.

A modified shake flask method was applied by slightly stirring an appropriate amount of the test item in water at 22°C. This procedure was chosen to avoid the building of emulsion.
Test Facility IBACON (2006a)
Dr. Knoell Consult GmbH (2006a)

Hydrolysis as a Function of pH Not determined

Remarks Due to the low solubility of the notified chemical in water and the difficulties in the analytical determination of low concentrations of the notified chemical itself, a hydrolysis test was not conducted. However, based on the results for a suitable analogue, the notified chemical is expected to be chemically stable and resist oxidation, reduction, hydrolysis and photodegradation, apart from when in the presence of clay, where it maybe labile, limited by its volatility.
Test Facility IBACON (2006b)

Partition Coefficient (n-octanol/water) Log K_{OW}: 5.84

Method Calculated using KOWWIN v 1.66 (US EPA, 2000)
Remarks The OECD and EC A.8 methods were carried out using the shake flask method. The concentration in the aqueous phase was below the limit of quantification. Therefore, the value for the LOQ was used for calculation of the log K_{OW}. As a result of this procedure, the log K_{OW} is under estimated to be 1.5. The entire amount of the test substance was recovered in the octanol phase which confirms the under estimation. Therefore, the log K_{OW} was estimated using KOWWIN software.
Test Facility IBACON (2006c)
Dr. Knoell Consult GmbH (2006b)

Adsorption/Desorption Log K_{OC} = 3.8

Method Using software PCKOCWIN v1.66 (US EPA, 2000)
Remarks The OECD 121 and C.19 test could not be performed as there was no HPLC signal. Therefore the adsorption/desorption was estimated using PCKOCWIN software.
Test Facility IBACON (2006d)
Dr. Knoell Consult GmbH (2006c)

Flash Point 49°C at 101.3 kPa

Method EC Directive 92/69/EEC A.9 Flash Point.
ISO 2719. Determination of Flash Point Pensky-Martens Cup Method.
Remarks There were no significant deviations from the protocol. Based on the flash point, the notified chemical is classified as a flammable liquid (Class 3 Dangerous Good).
Test Facility IBACON (2005c)

Autoignition Temperature 305°C

Method EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks There were no significant deviations from the protocol.
Test Facility Siemens (2005c)

Explosive Properties Not Explosive

Method EC Directive 92/69/EEC A.14 Explosive Properties.
OECD TG 113 Screening Test for Thermal Stability and Stability in Air.
Remarks The heat of decomposition was investigated using DSC and was found to be below 500 J/g. Therefore, the test on explosion properties was not necessary.
Test Facility Siemens (2005d)

Stability Testing Stable in the range 25-300°C

Method OECD TG 113 Screening Test for Thermal Stability and Stability in Air.
Remarks DSC Method was used in testing for the stability of the test substance.
Test Facility Siemens (2005a)

Oxidizing Properties No Oxidising Properties

Method	EC Directive 92/69/EEC A.21 Oxidizing Properties (Liquids).
Remarks	A 1:1 mass mixture of the test substance and dried cellulose was placed in a pressure vessel where the mixture was heated for at least 60 seconds. The results were assessed on the basis of whether the mixture spontaneously ignites and the comparison with reference substances of the time taken for the pressure to rise from 690 to 2070 kPa. The notified chemical was determined to have no oxidising properties based on the fact that the mean pressure rise time was higher for the notified chemical/cellulose mixture compared to the nitric acid/cellulose mixture.
Test Facility	Siemens (2005e)

Surface Tension Not determined

Remarks	Because the substance is poorly soluble, an effect on surface tension can be excluded. Further, due to the high volatility of the test substance, the concentration in an aqueous phase is hard to maintain constant and the performance of a surface tension test is not practicable.
Test Facility	IBACON (2006b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 96/54/EC, Annex IVB:B.1 Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat / Wistar outbred (Crl:(WI) WV BR)
Vehicle	As supplied
Remarks - Method	The relative humidity of the animal room exceeded the limit mentioned in the OECD guidelines. This deviation is considered not to have adversely influenced the outcome of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	3 females	2000	0
II	3 females	2000	0

LD50	>2000 mg/kg bw
Signs of Toxicity	Tremors were observed in 3 animals (2 in Group I and 1 in Group II) at 1 hour after dosing only. No other clinical signs were observed during the observation period.
Effects in Organs	Necropsy findings did not reveal distinct treatment-related gross alterations.
Remarks - Results	All animals gained weight during the observation period.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	TNO (2003a)

B.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).
Species/Strain	SPF-reared / Wistar-derived (CRl:[WI]WU BR)
Vehicle	As supplied
Method of Exposure	Oro-nasal exposure.
Exposure Period	4 hours
Physical Form	Vapour
Remarks - Method	The actual concentration was measured using ICP-AES (inductively coupled plasma absorption emission spectroscopy) instead of using the results of infrared absorption analysis or total carbon analysis. These deviations were not considered to have influenced the validity of the study. The notified chemical reached a saturated concentration of approximately 10.0 ± 0.4 mg/L at 21.6°C, and therefore the limit value of 20 mg/L could not be reached.

RESULTS

Group	*Number and Sex of Animals*	*Concentration mg/L/4 hours*		*Mortality*
		Nominal	*Actual*	
I	5 males	10.6	10	0
II	5 females	10.6	10	0

LC50	> 10 mg/L/4 hours
Signs of Toxicity	A slightly decreased breathing rate was observed in all animals at all four hourly observation times during exposure and slight laboured breathing was observed at the last two hourly observation times during exposure. Shortly after exposure, clinical signs consisted of red/brown discoloration of the fur at the head of all Group II animals. No abnormalities were seen in the Group I animals. During the 14-day observation period, no other abnormalities were observed and no mortality occurred.
Effects in Organs	At necropsy, macroscopic abnormalities consisted of petechiae on the lobes of the lungs in three Group I animals.
Remarks - Results	Overall, body weight gain was considered within the limits expected of the test animals in consideration of their species strain and age. The test substance was not tested at sufficient concentration to determine that it is of low toxicity via inhalation, due to it forming a saturated concentration. However, as no mortalities occurred at or up to the concentration where the notified chemical reached a saturated vapour it is considered likely to be of low toxicity via inhalation.
CONCLUSION	The notified chemical is considered to be of low toxicity via inhalation.
TEST FACILITY	TNO (2003b)

B.3. 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 SPF-bred
Number of Animals	3
Vehicle	As supplied
Observation Period	3 days
Type of Dressing	Semi-occlusive
Remarks - Method	The relative humidity of the animal room exceeded the limit mentioned in the OECD guidelines. This deviation is considered not to have adversely influenced the outcome of the study.
RESULTS	
Remarks - Results	There were no signs of skin irritation observed in all of the test animals.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	TNO (2003c)

B.4. 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 3
Observation Period 3 days
Remarks - Method The relative humidity of the animal room exceeded the limit mentioned in the OECD guidelines. This deviation is considered not to have adversely influenced the outcome of the study.

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	0.33	0	0	1	< 48 hours	0
Conjunctiva: chemosis	0	0	0	0	0	0
Conjunctiva: discharge	0	0	0	0	0	0
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results After 1 hour of exposure, slight redness and slight swelling of the conjunctivae were observed in one of the animals. At 24 hours after exposure, the same animal had slight redness of conjunctivae. After 72 hours of exposure, no signs of eye irritation were observed in all of the test animals.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY TNO (2003d)

B.5. Skin sensitisation

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 406 Skin Sensitisation – Magnusson & Kligman Maximization Test.
EC Directive 96/54/EC B.6 Skin Sensitisation.

Species/Strain Guinea pig / Dunkin Hartley SPF-bred
PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: None (all treatments were irritating)
topical: 30% dilution of the test substance in maize oil
Minimal irritating concentration:
intradermal: 10%
topical: 100%
MAIN STUDY
Number of Animals Test Group: 10 Control Group: 5
INDUCTION PHASE Induction Concentration:
intradermal: 10% dilution of the test substance in maize oil
topical: Undiluted as supplied
Signs of Irritation No change to moderate erythema was observed at the intradermal induction sites of all control group animals. Moderate erythema was observed at all the intradermal induction sites of all test animals. Slight erythema was observed at the topical induction sites of all test animals.
CHALLENGE PHASE
1st challenge topical: 30% dilution of the test substance in maize oil
topical: Vehicle (maize oil)

Remarks - Method

The relative humidity of the animal room exceeded the limit mentioned in the OECD guidelines. This deviation is considered not to have adversely influenced the outcome of the study.

The body weights of the test and control animals were not weighed during the induction phase of a positive control study with alpha-hexylcinnamaldehyde (HCA).

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	0%	2	0
	30%	2	0
Control Group	0%	2	0
	30%	2	0

Remarks - Results

Two control animals and two test animals showed discrete patchy erythema 24 hours after the challenge phase. Therefore the degree and incidence of reactions were comparable to test and control animals and were considered to be signs of irritation not sensitisation.

The sensitivity of the system was checked by means of a simultaneous positive control study with HCA. The challenge treatment with a 20% and 10% test dilutions of HCA in saline induced positive reactions in all test animals.

CONCLUSION

There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY

TNO (2003e)

B.6. Repeat dose toxicity

TEST SUBSTANCE

Notified Chemical

METHOD

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

Species/Strain: Rat / Wistar
Route of Administration: Oral – gavage
Exposure Information: Total exposure days: 28 days
Dose regimen: 7 days per week
Post exposure observation: Not conducted
Vehicle: Corn oil
Physical Form: Liquid
Remarks - Method: There were no significant deviations from the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5/sex	0	0
low dose	5/sex	50	0
medium dose	5/sex	250	0
high dose	5/sex	1000	0

Mortality and Time to Death
All test animals survived the test throughout the test period.

Clinical Observations
There were no unusual clinical symptoms found in any of the test animals in all groups. No differences were observed concerning functional and behavioural examination prior to application and during the last week of dosing, respectively. No abnormalities were recorded concerning posture, gait, palpebral closure, lacrimation, piloerection, arousal and vocalization. There were no significant changes in the food consumption and the body weight of the treated animals apart from male animals in the low dose group which showed a significant increase in the mean body weight.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
There was a dose related decrease in the % mean haematology values aPTT and PTT which were significant for female animals in the high dose group. There was also a dose related decrease in the procentual mean biochemistry values CHOL and TP which were significant for animals of both sexes in the high dose group and female animals in the medium dose group.

Effects in Organs
A statistically significant increase in liver weight (both absolute and relative) was found in both sexes with a relative weight increase of 2, 25 and 68% in male animals and 9, 38 and 95% in female animals at the low, medium and high doses respectively.
A statistically significant and dose related increase in the absolute kidney weight was seen in male animals in the medium and high dose groups. The relative kidney weight increase in male animals is also dose related but is only significant in the high dose. There was a significant decrease in the absolute weight in the low dose group for female animals that was not dose related.
Both absolute and relative thymus weights were decreased in both sexes in the high dose group, but it was only significant for female animals. A statistically significant increase in the absolute thymus weight of male animals in the low dose group was also seen. The toxicological significance of weight changes in the thymus is questionable.
Other significant organ weight changes were either isolated or not dose related and so are not considered toxicologically significant.

Centrilobular hypertrophy in the liver was noted in all treated animals and contributed to the increase in the weight. Scattered vacuolation was seen in three female rats in the high dose group.
Cortical tubular eosinophilic droplets and a higher incidence of basophilic tubules in the kidneys were noted in all treated male groups, only accompanied by granular casts in the medium and high dose groups. Unilateral hydronephrosis was seen in 2 male rats in the high dose group.
Follicular epithelial hypertrophy in the thyroids was seen in 1, 2 and 3 male animals in the low, medium and high dose groups respectively and in 1 and 2 female animals in the medium and high dose groups respectively.
Diffuse acanthosis of the forestomach was noted in 1 male animal in the medium dose group and 3 male and 4 female animals in the high dose group.

Remarks – Results
No recovery period observations were conducted and therefore the reversibility of the liver effects could not be determined. No liver enzyme increases or degenerative changes were associated with the centrilobular hypertrophy, which is possibly due to P450 enzyme induction. However, given the magnitude of the liver weight changes and the absence of data to support this mechanism the changes are considered to be adverse. Follicular epithelial hypertrophy in the thyroids may be secondary to the liver changes. Diffuse acanthosis of the forestomach is possibly due to a minimally irritant effect.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 50 mg/kg bw/day in this study, based on the findings and weight changes seen in the liver.

TEST FACILITY BSL Bioservice (2005a)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Aroclor 1254-induced rat S9 liver homogenate
Concentration Range in Main Test	a) With metabolic activation: 62 to 5,000 µg/plate b) Without metabolic activation: 62 to 5,000 µg/plate
Vehicle	Ethanol
Remarks - Method	Ethanol was chosen as the vehicle since the test substance did not mix with the preferred solvent dimethyl sulfoxide (DMSO). The background spontaneous reversion rate observed in the *S. typhimurium* TA98 strain in the presence of the S9-mix was outside the acceptable ranges for negative control data. Thus, the assay was repeated with only the TA98 strain in the presence of S9-mix. The actual concentrations of the test substance in the test solutions were not determined, thus, reported concentrations are nominal concentrations.

RESULTS

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

Remarks - Results	The test substance did not cause a marked increase in the number of revertant colonies in any of the tester strains either in the presence or absence of metabolic activation. The positive, vehicle and non-treated controls gave satisfactory responses, confirming the validity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	TNO (2003f)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Chinese hamster
Cell Type/Cell Line	V79
Metabolic Activation System	S-9 fraction from Phenobarbitone and β-Naphtoflavone induced rat liver
Vehicle	Ethanol
Remarks - Method	The positive controls used were as follows: with metabolic activation – cyclophosphamide (CP) at 0.83 µg/mL; and without metabolic activation – ethyl methanesulfonate (EMS) at 600µg/mL. A pre-experiment to test for toxicity was carried out both with and without metabolic activation at the following concentrations: 0.008, 0.016, 0.03, 0.06, 0.13, 0.25, 0.5, 1, 2.5 and 5 µL/mL. The notified chemical was cytotoxic at all concentration ranges tested without

metabolic activation but only cytotoxic at 0.008 μL/mL with metabolic activation. Precipitation of the test item was noted at concentrations 0.25 μL/mL.

Metabolic Activation	*Test Substance Concentration (μL/mL)*	*Exposure Period*	*Harvest Time*
Absent	0.0005, 0.001*, 0.002*, 0.004*, 0.008*, 0.016*, 0.03, 0.06, 0.18, 0.36, 0.75, 1.75, 5	4 hours	20 hours
Present	0.0005, 0.001, 0.002, 0.004, 0.008, 0.016, 0.03, 0.06, 0.18, 0.36, 0.75*, 1.75*, 5*	4 hours	20 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (μL/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	0.008	0.004	0.060	0.016
Present	0.008*	1.75	0.060	1.75

*However all tested concentrations above this showed no evidence of cytotoxicity (up to the maximum dose tested).

Remarks – Results

The test substance caused statistically significant increases in the incidence of cells with chromosomal aberrations, both in the presence and absence of metabolic activation.

In the absence of metabolic activation, the aberration rates of the lower dose groups were within the historical control data of the negative control. A statistically significant aberration rate of 7.6% was noted at the 0.016 μL/mL dose, a dose at which significant cytotoxicity (decrease in relative mitotic index down to 28%) was also seen. In the presence of metabolic activation, the aberration rate values of the higher dose groups (1.75 μL/mL and 5 μL/mL) evaluated were significantly above the historical control data of the negative control. Cytotoxicity (decrease in relative mitotic index down to 58%) was also seen at the higher doses. With this increase in aberration rates, no dose-response relationship was indicated.

There was a large difference in the cytotoxic effects between treatments with S9 metabolic activation and those without it. Cytotoxicity was seen at 4 μg/mL in the absence of metabolic activation and at 1.75 μL/mL in the presence of metabolic activation. This difference is not explained in the report, and is not easily explained by the structure of the notified chemical, it may point to instabilities in the test system. Statistically significant increases in the incidence of cells with chromosomal aberrations were only seen at concentrations where the test substance was also cytotoxic. In addition a clear dose response was not established. The positive effects at cytotoxic levels may be due to unspecific secondary effects.

There was no biologically relevant increase in the frequencies of polyploid cells after treatment with the test substance. The positive controls used induced distinct and biologically relevant increases in cells with structural chromosomal aberration. Positive controls confirmed the sensitivity of the test.

CONCLUSION

The test results were equivocal, and therefore the clastogenicity of the notified chemical can not be established based on this study.

TEST FACILITY

BSL Bioservice (2005b)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test.
Species/Strain	Human (One female donor)
Cell Type/Cell Line	Peripheral blood lymphocytes
Metabolic Activation System	S9 fraction derived from Aroclor 1254 induced rat liver
Vehicle	Ethanol
Remarks - Method	The positive controls used were as follows: with metabolic activation – cyclophosphamide (CP) at 20 µg/mL; and without metabolic activation – mitomycin C at 0.6 and 0.3 µg/mL for the 4 and 20 hour treatment times respectively. A pre-experiment to test for toxicity was carried out both with and without metabolic activation at the following concentrations: 0.0005, 0.0015, 0.005, 0.015, 0.05, 0.15, 0.5, 1.5, 5 µL/mL. In the absence of metabolic activation two tests were run with exposure periods of 4 and 20 hours and harvest times for both of 20 hours. In the presence of metabolic activation the exposure time was 4 hours and the harvest time was 20 hours. The notified chemical was cytotoxic at concentrations of 0.05 µL/mL and above in the absence of metabolic activation apart from at 5 µL/mL with a 20 hour exposure time where the decrease in the mitotic index was 13%. In the presence of metabolic activation the notified chemical was cytotoxic at concentrations above 0.15 µL/mL.

Metabolic Activation	*Test Substance Concentration (µL/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0, 0.005, 0.01*, 0.025*, 0.05, 0.075, 0.1*, 0.2	4 hours	20 hours
Test 2	0, 0.005, 0.01*, 0.025*, 0.05*, 0.075, 0.1, 0.2	20 hours	20 hours
Present			
Test 1	0, 0.01, 0.025*, 0.05*, 0.1*, 0.15, 0.2	4 hours	20 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µL/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	0.05	0.1	> 0.2	Negative
Test 2		0.05	> 0.2	Negative
Present				
Test 1	0.15	0.1	> 0.2	Negative

Remarks – Results	There was no significant increase in chromosomal aberrations in the test-article treated groups relative to the control treated groups. The positive controls used induced distinct and biologically relevant increases in cells with structural chromosomal aberration, and therefore confirmed the sensitivity of the test.
CONCLUSION	The notified chemical was not clastogenic to human peripheral blood lymphocytes treated *in vitro* under the conditions of the test.
TEST FACILITY	BioReliance (2008a)

B.10. Genotoxicity – in vivo

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test. EC Directive 2000/32/EC B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mouse / NMRI strain
Route of Administration	Oral – gavage
Vehicle	Cottonseed oil
Physical Form	Liquid
Remarks - Method	With regard to animal husbandry: instead of granulated, soft wood bedding, lignocel bedding was used; and instead of the standard pelleted diet, the totally pathogen free ssniff R/m-H, 10mm V1534-000 complete diet for rats/mice was given. These variations are not expected to affect the quality or validity of the study.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
vehicle/negative control	5 males, 5 females	0	24, 48
test article treated	5 males, 5 females	2000	24, 48
positive control, CP	5 males, 5 females	40	24

CP=cyclophosphamide.

RESULTS	
Doses Producing Toxicity	The dose range finding study was conducted and since all the animals (2 males and 2 females) showed no signs of toxicity, the limit test at 2000 mg/kg bw with the test substance was used in the main test. No systemic toxicity was observed in the main experiment.
Genotoxic Effects	No biologically relevant increase of micronuclei was found.
Remarks - Results	There was no statistically significant change in the PCE/NCE ratio, and therefore the notified chemical did not cause cytotoxicity of the bone marrow cells. It is unclear from this study whether the notified chemical was reaching the target organ, the bone marrow. The positive control (cyclophosphamide) induced a statistically significant increase of induced micronucleus frequency. This demonstrates the validity of the assay.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo mammalian erythrocyte micronucleus test.
TEST FACILITY	BSL Bioservice (2005c)

B.11. Genotoxicity – in vivo

TEST SUBSTANCE	Notified Chemical
METHOD	Single Cell Gel/Comet Assay *in vivo* The comet assay was based upon the methods described by Tice *et al.* (2000) and Hartmann *et al*. (2003).
Species/Strain	Rat/HsdBrlHan: Wist (SPF)
Route of Administration	Intraperitoneal (ip)
Vehicle	Cottonseed Oil
Remarks - Method	No standard test guideline is available for conducting an *in vivo* comet assay.

Pre-Experiment
A preceding study on acute toxicity was performed based on the OECD guidelines 420 and 423. Three males and three females were treated. A single dose of 2000 mg/kg bw was administered ip. The volume administered was 10 mL/kg bw.

Main Experiment
Liver hepatocytes and skin fibroblasts were used in the Comet assay.
Hartmann et al. (2003) recommend that the intraperitoneal route is not used when examining tissues such as the liver that could be exposed directly to the test substance rather than via the circulatory system. In addition no justification was provided for the choice of skin as a tissue given the route of administration i.e. it is not the tissue of first contact.

At least 200 cells/animal were used in the Comet assay. The volume administered was 10 mL/kg bw. Animals were administered the test substance once.

Methylmethanesulfonate (MMS, CAS number 66-27-3) was used as the positive control. Cottonseed oil was used for the negative control.
The DNA damage was quantified by measuring the Olive tail moment (OTM).

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sample time hours*
I (vehicle control)	4 per sex	0	4
II (test substance)	4 per sex	2000	4
III (test substance)	4 per sex	2000	24
IV (positive control, MMS)	4 per sex	50	4

RESULTS

Liver hepatocytes	*Mean OTM, Male Animals*	*Mean OTM, Female Animals*
I (vehicle control)	2.53	2.84
II (test substance)	8.04*	8.16*
III (test substance)	7.63*	7.85*
IV (positive control MMS)	46.66*	36.11*

* Indicates results that were a statistically significant ($p < 0.05$) change relative to the negative control.

Skin fibroblasts	*Mean OTM Male, Animals*	*Mean OTM, Female Animals*
I (vehicle control)	6.75	4.66
II (test substance)	10.03*	11.94*
III (test substance)	10.87*	14.32*
IV (positive control MMS)	68.74*	44.16*

* Indicates results that were a statistically significant ($p < 0.05$) change relative to the negative control.

Doses Producing Toxicity

No significant irreversible toxic effects of the test item were noted in the pre-experiment. All male rats and one female rat showed a reduction of spontaneous activity. One male rat also had a constricted abdomen after 10 min.
The toxicity in the main test was equivalent to that seen in the preliminary test as the same volume and dose rates were used.

Genotoxic Effects

Statistically significant ($p < 0.05$) increases were seen in the OTM of the liver hepatocytes and skin fibroblasts for both the male and female animals treated with the test substance in comparison to those animals treated with the negative control.

Remarks - Results

The % viability of cells as determined by the trypan blue dye exclusion test was substantially lower for the liver cells (52%) compared to skin

cells (92%) for animals of both sexes dosed with the test article. The % viability of cells for the vehicle control for animals of both sexes combined was 82 and 95 % for the liver and skin cells respectively.

It is important to distinguish DNA damage that may be a direct consequence of genotoxic insult from DNA degradation resulting from cell death. Therefore, a histopathological examination is recommended when positive results are seen in an *in vivo* comet assay (Smith et al., 2008). No histopathological examination was conducted in this *in vivo* comet assay and the extent of necrosis or apoptosis in the tissues was not determined.

As only a limit dose was tested a dose response could not be observed. Positive responses at multiple levels reinforce the biological relevance of a result (Burlinson et al., 2007)

CONCLUSION

Based on the increases in the mean OTM in animals treated with the test substance in comparison to the negative control, the notified chemical induced DNA damage under the conditions of this in vivo Single Cell Gel/Comet Assay. However, based on limitations in this study a false positive could not be ruled out.

TEST FACILITY BSL Bioservice (2007a)

B.12. Genotoxicity – in vivo

TEST SUBSTANCE Notified Chemical

METHOD Single Cell Gel/Comet Assay *in vivo*
The comet assay was based upon the methods described by Tice *et al.* (2000) and Hartmann *et al*. (2003).

Species/Strain	Rat/Sprague Dawley (Hsd:SD), all male
Route of Administration	Oral
Vehicle	Corn Oil
Remarks - Method	No standard test guideline is available for conducting an *in vivo* comet assay.

Main Experiment
Liver and stomach cells were used in the Comet assay.
100 cells/animal were used in the Comet assay. The volume administered was 10 mL/kg bw. Animals were administered the test substance once.
Methylmethanesulfonate (MMS, CAS number 66-27-3) was used as the positive control. Corn oil was used for the negative control.
The DNA damage was quantified by measuring the Olive tail moment (OTM), % of tail DNA and Comet tail migration.

The minimum recommended number of cells were scored (Hartman et al. (2003), however an increased number of slides increases sensitivity. The use of six animals is recommended to investigate responses in the stomach (Smith et al. 2008).

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sample time hours*
I (vehicle control)	5 male	0	4
II (vehicle control)	5 male	0	24
III (test substance)	5 male	1000	4
IV (test substance)	5 male	1000	24
V (test substance)	5 male	1500	4

VI (test substance)	5 male	1500	24
VII (test substance)	10* male	2000	4
VIII (test substance)	5 male	2000	24
IX (positive control, MMS)	5 male	50	4

*An additional 5 animals were included as replacements to be used in the event of mortality.

RESULTS

Liver	*Mean % tail DNA*	*Mean OTM*
I (vehicle control)	1.89(1.18)	0.42(0.23)
II (vehicle control)	0.70(0.41)	0.15(0.08)
III (test substance)	1.71(1.71)	0.39(0.20)
IV (test substance)	1.07(0.82)	0.23(0.13)
V (test substance)	3.42(1.84)	0.62(0.32)
VI (test substance)	0.7(0.25)	0.17(0.04)
VII (test substance)	1.90(1.18)	0.40(0.22)
VIII (test substance)	1.38(0.42)	0.30(0.1)
IX (positive control MMS)	60.74(4.46)*	23.13(4.30)*

* Indicates results that were a statistically significant ($p < 0.05$) change relative to the negative control for that particular sampling time.
The standard deviation for the values is shown in brackets.

Stomach	*Mean % tail DNA*	*Mean OTM*
I (vehicle control)	24.37(3.90)	7.54(1.41
II (vehicle control)	5.83(2.18)	1.39(0.51)
III (test substance)	17.55(3.62)	4.89(1.14)*
IV (test substance)	12.45(12.39)	3.57(4.06)
V (test substance)	15.44(1.63)	3.94(0.61)*
VI (test substance)	10.00(5.03)	2.32(1.09)
VII (test substance)	17.47(6.02)	4.42(1.69)*
VIII (test substance)	6.48(1.75)	1.61(0.35)
IX (positive control MMS)	77.59(4.47)*	40.80(5.26)*

* Indicates results that were statistically significant ($p < 0.05$) change relative to the negative control for that particular sampling time.
The standard deviation for the values is shown in brackets.

Doses Producing Toxicity	No significant irreversible toxic effects of the test item were noted in the experiment.
Genotoxic Effects	Statistically significant ($p < 0.05$) decreases were seen in the mean OTM for stomach cells with a sample time of 4 hours from animals treated with the test substance in comparison to those animals treated with the negative control. However, the mean OTM for stomach cells were within the historical range (1.75-11.40, mean 4.63) and the mean value for the negative control was higher than the historical mean although still within the historical range.
Remarks - Results	
CONCLUSION	The notified chemical did not induce DNA damage under the conditions of this in vivo Single Cell Gel/Comet Assay.
TEST FACILITY	BioReliance (2008b)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test. EC Directive 92/69/EEC C.4-D Biodegradation: Determination of the " Ready" Biodegradability: Manometric Respirometry Test
Inoculum	Activated STP sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Oxygen uptake
Remarks – Method	The amounts of test item and reference item were directly weighting into the test flasks and were dispersed by stirring to achieve a homogenous solution. No significant protocol deviations were recorded.

RESULTS

Test substance		*Aniline*	
Day	*% degradation*	*Day*	*% degradation*
7	0	7	61
10	0	10	87
14	2	14	105
21	2	21	109
28	0	28	109

Remarks – Results	The degradation rate did not reach 60% in the 10-day window or after 28 days incubation. The toxicity control degraded 53% after 28 days and the test substance was assumed not to be inhibitory to sewage microorganisms. All test validity criteria were satisfied.
CONCLUSION	The notified chemical cannot be classed as ready biodegradable.
TEST FACILITY	IBACON (2005d)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 203 Fish, Acute Toxicity Test -Rainbow Trout 96-hr semi-static EC Directive 92/69/EEC C.1 Acute Toxicity for Fish-Rainbow Trout 96-hr semi-static
Species	*Oncorhyncus mykiss*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	A pre-test was performed, but not to GLP. The test medium was prepared by dissolving 1500 mg test item into 15000 mL test water by intense stirring for 5 days in a closed system (to prevent evaporation of the test item from the test media) to obtain a saturated solution of the poorly water soluble test item in the test media. The test media were prepared just before each 24 h test medium renewal. Significant deviations from the test

protocol were not reported.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*			
Nominal	*Actual*		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	0	7		0	0	0	0
100	<LOD	7		0	0	0	0

LC50	>100 mg/L at 96 hours (WAF).
NOEC	=100 mg/L at 96 hours (WAF).
Remarks – Results	The test validity criteria were satisfied. Freshly prepared test medium was analysed and test the concentration of test substance was less than the LOD = 0.1 mg/L. No sub-lethal effects were noted.

CONCLUSION The notified chemical is not toxic to *Oncorhyncus mykiss* up to the limit of its solubility in water.

TEST FACILITY IBACON (2006e)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – semi-static
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia – semi-static

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	The test medium was prepared by dissolving 200 mg of test substance into 2000 mL test water by stirring for 6 days. During range-finding tests, it was noted that after 96 hours of stirring, the test item was not visible in the test media (ie very small particles homogenously dispersed with no turbidity). Consequently, no additional filtration was performed after stirring. Significant deviations to the study protocol were not reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	0	20	0	0
100	<LOD	20	0	0

EC50	>100 mg/L at 48 hours (WAF)
NOEC	=100 mg/L at 48 hours (WAF)
Remarks – Results	Test validity criteria were satisfied. Freshly prepared test medium was analysed and test the concentration of test substance was less than the LOD = 0.1 mg/L. No sub-lethal effects were noted.

CONCLUSION The notified chemical is not toxic to *Daphnia magna* up to its limit of solubility in water.

TEST FACILITY IBACON (2006f)

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	*Desmodesmus subspicata*
Exposure Period	72 hours
Concentration Range Nominal	0.0, 0.95, 3.05, 9.77, 31.25 & 100 mg/L
Concentration Range Actual	0 – 9.77 mg/L <LOD; 31.25 mg/L <LOQ; 100 mg/L = 0.2 mg/L
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	The test medium was prepared by dissolving 300 mg of test substance into 3000 mL test water by stirring for 6 days in a closed system (to prevent evaporation of the test item from the test media) to obtain a saturated solution of the poorly water soluble test item in the test media. This was directly diluted further to produce the final test concentrations.

RESULTS

Biomass		*Growth*	
E_bC50	*NOE_bC*	*E_rC50*	*NOE_rC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
>100 (WAF)	31.25 (WAF)	>100 (WAF)	31.25 (WAF)

Remarks – Results	A significant inhibitory effect was noted at the 100 mg/L nominal concentration after 72 hours. Test validity criteria were satisfied. Freshly prepared test medium was analysed and test the concentration of test substance detected, but at a concentration less than the LOQ = 0.2 mg/L. The pH ranged from 8.0-8.2 at the start of the test and ranged from 9.7-10.1 at the end of the test. This is common for rapidly growing algae.
CONCLUSION	The notified chemical shows some toxicity at its level of solubility in water.
TEST FACILITY	IBACON (2006g)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Y-14877
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC L133/118 Activated Sludge Respiration Inhibition Test.
Inoculum	Activated STP sludge
Exposure Period	3 hours
Concentration Range Nominal	10, 32, 320, 1000 mg/L
Remarks – Method	Reference substance was 3,5-dichlorophenol. There were no deviations to the study protocol.
RESULTS	
IC50	>1000 mg/L
EC20	>1000 mg/L
Remarks – Results	Test validity criteria were satisfied. Less than 20% inhibition was noted after three hours incubation.

CONCLUSION	The test item is not toxic to sewage microorganisms.
TEST FACILITY	IBACON (2005e)

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