File No: LTD/1832

August 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

4*H*-Indeno[4,5-*d*]-1,3-dioxole, 3a,5,6,7,8,8b-hexahydro-2,2,6,6,7,8,8-heptamethyl-

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

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1832	International Flavours and Fragrances (Australia) Pty Ltd	4*H*-Indeno[4,5-*d*]-1,3-dioxole, 3a,5,6,7,8,8b-hexahydro-2,2,6,6,7,8,8-heptamethyl-	No	1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

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

Based on the available information, when used at 1.8% in fragrances, 0.2% in deodorants or 0.1% in leave-on or rinse-off cosmetic or household products, the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

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

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

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 importation volume exceeds one tonne per annum notified chemical;
- the concentration of the notified chemical is intended to exceed 1.8% in fragrances, 0.2% in deodorants or 0.1% in leave-on or rinse-off cosmetic or household products.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a fragrance ingredient, or is likely to change significantly;
- the amount of chemical being introduced has increased, 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 (M)SDSs of the notified chemical and products containing the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDSs remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
International Flavours and Fragrances (Australia) Pty Ltd (ABN: 77 004 269 658)
310 Frankston-Dandenong Road
DANDENONG VIC 3175

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less 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: flammability and dissociation constant

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Low Volume Permit (NICNAS)

NOTIFICATION IN OTHER COUNTRIES
USA, Canada, EU, China and Philippines

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
IDM Ketal
Operanide

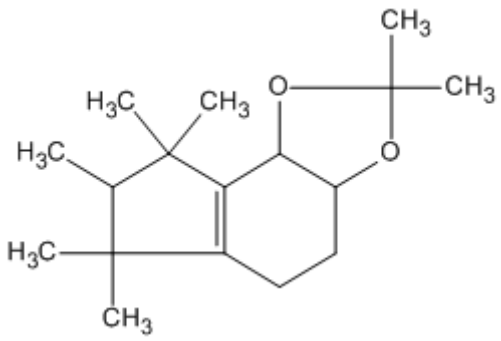
CAS NUMBER
823178-41-2

CHEMICAL NAME
4*H*-Indeno[4,5-*d*]-1,3-dioxole, 3a,5,6,7,8,8b-hexahydro-2,2,6,6,7,8,8-heptamethyl-

OTHER NAME(S)
2,2,6,6,7,8,8-Heptamethyl-4,5,6,7,8,8b-hexahydro-3ah-indeno[4,5-d][1,3]dioxole

MOLECULAR FORMULA
$C_{17}H_{28}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
264.40 Da

ANALYTICAL DATA
Reference NMR, IR, GC, MS, UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 95%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name	4*H*-Inden-4-one, 1,2,3,5,6,7-hexahydro-1,1,2,3,3-pentamethyl-
CAS No.	33704-61-9 *Weight %* < 2
Hazardous Properties	H303 – may be harmful if swallowed, H319 – causes serious eye irritation, H315 – causes skin irritation, H317 – may cause an allergic reaction

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 yellow liquid

Property	Value	Data Source/Justification
Freezing Point	< -20 °C	Measured
Boiling Point	280 °C at 103 kPa	Measured
Density	974 kg/m^3 at 20 °C	Measured
Vapour Pressure	1.1×10^{-3} kPa at 25 °C	Measured
Water Solubility	4.61 × 10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{½}$ < 1 day at pH 4, $t_{½}$ > 1 year at pH 7 and 9	Measured
Partition Coefficient (n-octanol/water)	log Pow = 5.27at 21 °C	Measured
Surface Tension	63 mN/m at 22 °C	Measured
Adsorption/Desorption	log K_{oc} = 4.81	Measured
Dissociation Constant	Not determined	No dissociable functionalities
Flash Point	123 ± 2°C at 101.3 kPa	Measured
Flammability	Not determined	Not expected to be flammable based on measured flash point
Autoignition Temperature	336 ± 5°C	Measured
Explosive Properties	Predicted negative	Based on chemical structure and oxygen balance
Oxidising Properties	Predicted negative	Based on chemical structure

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

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported as a component of fragrance oils at ≤ 5% concentration for reformulation into cosmetic and household products.

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

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

PORT OF ENTRY
Melbourne

IDENTITY OF RECIPIENT
International Flavours and Fragrances (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of fragrance oils at ≤ 5% concentration packaged in polypropylene-lined steel drums (usually in the size of 208 L) for transportation by road. The finished consumer products will be transported primarily by road to retail stores in packages suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient in cosmetic and household products.

The proposed maximum concentrations of the notified chemical in finished consumer products are shown below:

Product Type	***Proposed Maximum Use Concentration (%)***
Deodorant	0.2
Fine fragrances	1.8
Leave-on cosmetic products	0.1
Rinse-off cosmetic products	0.1
Household products	0.1
Air fresheners	0.1

OPERATION DESCRIPTION
The notified chemical will be imported in fragrance oils at ≤ 5% concentration for reformulation into cosmetic and household products.

Reformulation
When reformulated, the notified chemical will be blended into end-use consumer products at customer sites. Procedures will vary depending on the nature of the cosmetic product being formulated. Both manual and automated steps will likely be involved. For example, a chemist will sample and test the notified chemical for QA purposes manually; a compounder will weigh an appropriate amount of the notified chemical into a container then add the amount directly into a flame proof mixing tank, with periodic sampling for quality control purposes also carried out during the manufacturing process. Automated processes may include mixing and filling of end-use containers with products.

End use
Household products
Household products containing the notified chemical (at ≤ 0.1% concentration) will be used by the public and may also be used by professional workers (such as cleaners). The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machine cycles, or open manual processes including rolling, brushing, spraying and dipping.

Cosmetic products
Finished cosmetic products containing the notified chemical at ≤ 1.8% concentration will be used by the public and may also be used by professionals such as hairdressers and workers in beauty salons. Depending on the nature of the product, these are expected to be applied in a number of ways, such as by hand, spray or by using an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse workers	None	Incidental exposure only
Plant operators – Mixing compounding	4	250
Plant operators – Drum handling	1	250
Plant operators – Drum cleaning/washing	2	100
Plant operators – Equipment cleaning/washing	2	250
Plant operators – Quality control	1	250

EXPOSURE DETAILS

Transport and storage

Transport and storage workers may come into contact with the notified chemical as a component of fragrance oils at ≤ 5% concentration, only in the event of unlikely accidental rupture of the containers.

Formulation of end products

During reformulation into cosmetic products, dermal, ocular and inhalation exposure of workers to the notified chemical at ≤ 5% concentration may occur. Exposure is expected to be minimised through the use of exhaust ventilation and/or automated/enclosed systems as well as through the use of personal protective equipment (PPE) such as coveralls, eye protection, impervious gloves and respiratory protection (as appropriate).

End use

Exposure to the notified chemical in end-use products at ≤ 1.8% concentration may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons and cleaners). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical at ≤ 1.8% concentration through the use of a wide range of cosmetic and household products. The principal routes of exposure will be dermal, while ocular and inhalation exposures (e.g., through the use of spray products) are also possible.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2012; Cadby *et al.*, 2002; ACI, 2010; Loretz *et al.,* 2006). For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In the absence of dermal absorption data and based on the low molecular weight of the notified chemical (156.22 Da), a dermal absorption (DA) of 100% was conservatively assumed for the notified chemical (European Commission, 2003). For the inhalation exposure assessment, a 2-zone approach was used (Steiling *et al*., 2014; Rothe *et al*., 2011; Earnest, Jr, 2009). An adult inhalation rate of 20 m^3/day (enHealth, 2012) was used and it was conservatively assumed that the fraction of the notified chemical inhaled is 50%, with the reminder ending up, as intended, on the hair. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes.

Cosmetic products (dermal exposure)

Product type	**Amount** (mg/day)	**C** (%)	**Retention Factor (RF)** (unitless)	**Daily systemic exposure** (mg/kg bw/day)
Body lotion	7820	0.1	1	0.1222
Face cream	1540	0.1	1	0.0241
Hand cream	2160	0.1	1	0.0338
Fine fragrances	750	1.8	1	0.2109

Product type	Amount (mg/day)	C (%)	Retention Factor (RF) (unitless)	Daily systemic exposure (mg/kg bw/day)
Deodorant spray	1430	0.2	1	0.0447
Shampoo	10460	0.1	0.01	0.0016
Conditioner	3920	0.1	0.01	0.0006
Shower gel	18670	0.1	0.01	0.0029
Hand wash soap	20000	0.1	0.01	0.0031
Hair styling products	4000	0.1	0.1	0.0063
Total				0.4502

C = concentration of the notified chemical; RF = retention factor.
Daily systemic exposure = (Amount × C × RF × DA)/BW

Household Products (Indirect dermal exposure – from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.1	0.95	10	0.0034
Fabric softener	90	0.1	0.95	10	0.0013
Total					0.0048

Daily systemic exposure = (Amount × C × PR × PT × DA)/BW

Household products (Direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Usage (g/cm^3)	Film Thickness (cm)	Time Scale Factor (unitless)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.1	1980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.1	1980	0.009	0.01	0.03	0.0003
All-purpose cleaner	1	0.1	1980	1	0.01	0.007	0.0022
Total							0.0024

Daily systemic exposure = Frequency × C × Contact Area × Product Usage × Film Thickness on skin × Time Scale Factor × DA/ BW

Aerosol products (Inhalation exposure)

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone2) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.2	20	1	20	50	1	10	0.006

Daily systemic exposure = [(Amount × C × Inhalation Rate × Fraction Inhaled × 0.1) / BW × 1440)] × [Exposure Duration (Zone 1)/Volume (Zone 1) + Exposure Duration (Zone 2)/Volume (Zone 2)]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 0.4634 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative (screening level) hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposure factors (e.g., air fresheners).

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating

Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Human, skin sensitisation – RIPT (5%)	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOEL = 150 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration	non genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus test	non genotoxic

Toxicokinetics.
No toxicokinetic data on the notified chemical were submitted.

Dermal absorption is expected to be limited given the high lipophilicity (Log P_{OW} = 5.27) and low water solubility (4.61×10^{-3} g/L at 20 °C) of the notified chemical limiting penetration of the hydrophilic epidermis.

Acute toxicity.
The notified chemical is of low acute oral and dermal toxicity based on studies conducted in rats.

Irritation.
The notified chemical is slightly irritating to eyes and skin based on studies conducted in rabbits.

In the skin irritation study only very slight erythema was noted that persisted in one animal at the 72-hour observation period. All signs of irritation, except for slight desquamation in one animal, were resolved at the end of the 7-day study period.

In the eye irritation study only minimal conjunctival irritation was observed that was fully resolved in all animals at the 48-hour observation period.

Sensitisation.
The notified chemical was not found to be a skin sensitiser when tested at up to 50% concentration in a local lymph node assay (LLNA) or at 5% concentration in a human repeat insult patch test (HRIPT).

In the LLNA study a 50% test concentration of the notified chemical resulted in a stimulation index (SI) of 2.58. However a linear dose response was not observed in this study as the other two test concentrations of 10% and 25% resulted in a SI of 1.32.

Therefore, on the basis of the available information, the notified chemical is not expected to be sensitising.

Repeated dose toxicity.
A No Observed Effect Level (NOEL) of 150 mg/kg bw/day was established for the notified chemical in a 28-day repeated dose oral gavage toxicity study in rats based on treatment related effects in the kidney, spleen, thyroid, seminal vesicles and bone marrow at the highest dose tested of 1000 mg/kg bw/day. The majority of effects were resolved at the end of the 14 day recovery period, although incidents of marrow hyperplasia and splenic hyperaemia were still evident. In addition, low erythrocyte levels and elevated mean cell volume were still observed.

Mutagenicity/Genotoxicity.
The notified chemical was negative in a bacterial reverse mutation assay and in an *in vitro* chromosomal aberration study in Chinese hamster lung cells. The notified chemical was also negative in an *in vivo* mouse micronucleus assay.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Reformulation
Exposure of workers to the notified chemical at ≤ 5% concentration may occur during blending operations. The notified chemical is a slight skin and eye irritant and may cause systemic toxicity from repeated exposure

(NOEL 150 mg/kg bw/day), although this is expected to be limited by the dermal route. Given the low proposed use concentration, the risk of irritation and systemic effects is not expected. Therefore, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic and household products (at ≤ 1.8% concentration) to clients (e.g. hair dressers, workers in beauty salons and professional cleaners).

Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, the exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the various cosmetic and household products containing the notified chemical.

6.3.2. Public Health
Members of the public are expected to be repeatedly exposed to the notified chemical during the use of cosmetics and household products containing the notified chemical (at ≤ 1.8% in fragrances, ≤ 0.2% in deodorants or ≤ 0.1% in leave-on or rinse-off cosmetic or household products).

Irritation
The notified chemical is slightly irritating to the skin and eyes. However, at the low proposed end use concentrations, skin or eye irritation effects from the normal use of the finished products containing the notified chemical are not expected.

Repeated dose toxicity
The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.4634 mg/kg bw/day (see Section 6.1.2). Using a NOEL of 150 mg/kg bw/day, which was derived from a 28 day repeated dose oral toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 324. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 1.8% in fragrances, ≤ 0.2% in deodorants or ≤ 0.1% in leave-on or rinse-off cosmetic or household products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported as a component of fragrance preparations for local reformulation into a variety of consumer products (cosmetics, household products, fine fragrances). Release during reformulation in Australia is expected to be limited to accidental spills or leaks of drums and residue in import containers. Waste water from reformulation equipment cleaning is expected to be discharged to an on-site and/or local wastewater treatment plant for recycling (no release estimate).

RELEASE OF CHEMICAL FROM USE
The notified chemical is expected to be released to the aquatic compartment through sewers during its use in various cosmetic and domestic end-products.

RELEASE OF CHEMICAL FROM DISPOSAL
It is estimated that a maximum of 1%, or up to 10 kg, of the notified chemical may remain in end-use containers once the consumer products are used up. These will be disposed of through domestic garbage disposal to landfill, or recycled through an approved waste management facility.

7.1.2. Environmental Fate
Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system through its use as a component of cosmetics, household products and fine fragrances, before potential release to surface waters nationwide. The notified chemical is not considered readily biodegradable (2% in 28 days). For

details of the environmental fate studies, please refer to Appendix C. Based on its measured adsorption coefficient (log K_{OC} = 4.81), release to surface waters is unlikely to occur, as the notified chemical is expected to adsorb to soil and sediment. Although it has low water solubility and a high partition coefficient (log P_{OW} = 5.27), the notified chemical is not expected to bioaccumulate due to its low calculated bioconcentration factor (BCF = 1394). Therefore, in surface waters the notified chemical is expected to adsorb to soil and sediment, and eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is expected to be moderately volatile from water (log H = 6.347 Pa/m^3/mol; US EPA, 2011), and may slowly volatilise to air during sewage treatment processes. The half-life of the notified chemical in air is calculated to be 0.937 h, based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, the notified chemical is not expected to persist in the air compartment.

The majority of the notified chemical will be released to sewer after use. A small proportion of the notified chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill as collected spills and empty containers. The notified chemical residues in landfill, soil and sludge are expected to have low mobility based on the reported adsorption coefficient (log K_{OC} = 4.81), and is expected to eventually degrade to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume a worst case scenario, with 100% release of the notified chemical into sewer systems nationwide and no removal within sewage treatment plants (STPs).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.606	µg/L
PEC - Ocean:	0.061	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.606 µg/L may potentially result in a soil concentration of approximately 4.039 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 20.19 µg/kg and 40.39 µg/kg, respectively.

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 h LL50 > 1.3 mg/L (WAF*)	Not harmful to fish up to water solubility limit
Daphnia Toxicity	48 h EL50 > 1.5 mg/L (WAF*)	Not harmful to *Daphnia* up to water solubility limit (acute)
	21 d NOEL = 0.15 mg/L (WAF*)	Not harmful to *Daphnia* up to water solubility limit (chronic)
Algal Toxicity	72 h E_rL50 > 1.6 mg/L (WAF*)	Not harmful to algae up to water solubility limit
Inhibition of Bacterial	3 h IC50 > 1000 mg/L	Not inhibitory to bacterial respiration

Respiration

* Water Accommodated Fraction

Based on the above ecotoxicological endpoints for the notified chemical, it is not considered to be harmful to fish, daphnids, and algae on an acute basis up to the limit of its solubility in water. The notified chemical is not readily biodegradable (2% in 28 days), has low water solubility, and a high partition coefficient (log P_{OW} = 5.27); however, based on the above chronic ecotoxicological endpoint, it is not considered to be harmful to daphnids on a chronic basis up to the limit of its solubility in water. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is not formally classified for acute and chronic toxicities.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for daphnids. A safety factor of 100 was used given acute endpoints for three tropic levels and one chronic endpoint for daphnids are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEL (*Daphnia*, 21 d)	0.15	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	1.5	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated based on the predicted PEC and PNEC.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.606	1.5	**0.404**
Q - Ocean	0.061	1.5	**0.040**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual importation quantity. Whilst the notified chemical is not readily biodegradable, it is expected to adsorb to soil and sludge and have a low potential for bioaccumulation. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic and domestic products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < -20 °C

Method OECD TG 102 Melting Point/Melting Range.
Remarks Cooled in a dry ice/acetone bath. Test material became increasingly viscous during cooling to -21°C.
Test Facility SafePharm (2005a)

Boiling Point 280 °C at 103 kPa

Method EC Directive92/69/EEC A.2 Boiling Temperature.
Remarks Differential scanning calorimetry method
Test Facility SafePharm (2005a)

Density 974 kg/m^3 at 20 °C

Method EC Directive92/69/EEC A.3 Relative Density.
Remarks Pycnometer method
Test Facility SafePharm (2005a)

Vapour Pressure 1.1×10^{-3} kPa at 25 °C

Method EC Directive92/69/EEC A.4 Vapour Pressure.
Remarks Determined using a vapour pressure balance
Test Facility SafePharm (2005b)

Water Solubility 4.61×10^{-3} g/L at 20 °C

Method EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Flask Method
Test Facility SafePharm (2005a)

Hydrolysis as a Function of pH

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

pH	*T (°C)*	*t½*
4	25	< 1 day
7	25	> 1 year
9	25	> 1 year

Remarks After 5 days under the accelerated conditions of 50 °C the rate of hydrolysis of was greater than 50% at pH 4, and less than 10% at pH 7 and 9. This equates to a half-life at 25 °C of $t_{½}$ < 1 day at pH 4, and $t_{½}$ > 1 year at pH 7 and 9. Therefore, it can be concluded that under the conditions of the test, the notified chemical is expected to hydrolyse under acidic conditions, but is hydrolytically stable under neutral and basic conditions.
Test Facility SafePharm (2005a)

Partition Coefficient (n-octanol/water) log Pow = 5.27at 21 °C

Method EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks Shake Flask Method
Test Facility SafePharm (2005a)

Surface Tension 63 mN/m at 22 °C

Method EC Directive92/69/EEC A.5 Surface Tension.

Remarks Concentration: 6.41×10^{-3} g/L
Test Facility SafePharm (2005a)

Adsorption/Desorption – screening test log K_{oc} = 4.81

Method EC Directive 92/69/EEC C.19 Adsorption Coefficient.
Remarks HPLC Screening Method
Test Facility SafePharm (2005a)

Flash Point 123 ± 2°C at 101.3 kPa

Method EC Directive 92/69/EEC A.9 Flash Point.
Remarks Closed cup method
Test Facility SafePharm (2005b)

Autoignition Temperature 336 ± 5°C

Method EC Directive92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility SafePharm (2005b)

Explosive Properties Predicted negative

Method EC Directive92/69/EEC A.14 Explosive Properties.
Remarks Predicted based on the chemical structure and oxygen balance
Test Facility SafePharm (2005b)

Oxidizing Properties Predicted negative

Method EC Directive92/69/EEC A.21 Oxidizing Properties (Liquids).
Remarks Predicted based on the chemical structure
Test Facility SafePharm (2005b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical

METHOD OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain Rat/Sprague Dawley
Vehicle None
Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3F	2000	0/3
2	3F	2000	0/3

LD50 > 2000 mg/kg bw
Signs of Toxicity No signs of systemic toxicity.
Effects in Organs No abnormalities were noted at necropsy.
Remarks - Results All animals showed expected body weight gains over the study period.

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

TEST FACILITY SafePharm (2005c)

B.2. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical

METHOD OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain Rat/Sprague Dawley
Vehicle None
Type of dressing Semi-occlusive
Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M, 5F	2000	0/10

LD50 > 2000 mg/kg bw
Signs of Toxicity - Local No signs of dermal irritation were noted.
Signs of Toxicity - Systemic No signs of systemic toxicity were noted.
Effects in Organs No abnormalities were noted at necropsy.
Remarks - Results All animals showed expected body weight gains over the study period.

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

TEST FACILITY SafePharm (2005d)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3

Vehicle	None
Observation Period	7 days
Type of Dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0.7	1	1	< 7days	0
Oedema	0	0	0	0	-	0

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

Remarks - Results	Very slight erythema was noted at 2 treated skin sites at the 24 and 48-hour observations and at 1 treated skin site at the 72-hour observation. Slight desquamation was noted at 1 treated skin site at the 7-day observation. No oedema was noted in all treated sites.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	SafePharm (2005e)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	72 hours
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.3	0	0	1	< 48h	0
Conjunctiva: chemosis	0	0	0	0	-	0
Conjunctiva: discharge	0.3	0	0	1	< 48h	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks – Results	No corneal effects were noted during the study. Iridial inflammation was noted in 1 treated eye 1 hour after treatment. Minimal conjunctival irritation was noted in all treated eyes 1 hour after treatment and in 1 treated eye at the 24-hour observation. Two treated eyes appeared normal at the 24-hour observation and 1 treated eye appeared normal at the 48-hour observation.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	SafePharm (2005f)

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

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone/olive oil (4:1)
Preliminary study	Yes
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
Remarks - Method	No significant protocol deviations.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5F	2319.78 ± 492.57	-
10%	5F	3064.81 ± 503.75	1.32
25%	5F	3068.08 ± 688.07	1.32
50%	5F	5994.16 ± 764.97	2.58
Positive Control			
5%	5	Not reported	2.76
10%	5	Not reported	3.34
25%	5	Not reported	8.91

EC3	> 50%
Remarks - Results	There were no mortalities or clinical abnormalities. All treated animals gained weight comparable to that of the vehicle control group.
CONCLUSION	There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	SafePharm (2005g)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (5% in vehicle)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 5% test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: 2 weeks Challenge Procedure: A patch was applied to an untreated site. Patches were removed after 24 h. Sites were graded 24h, 48h and 72 h post-application.
Study Group	96 F, 16 M; age range 18-70 years
Vehicle	Diethyl phthalate:ethanol (3:1)
Remarks - Method	Occluded.
RESULTS	
Remarks - Results	104/112 subjects completed the study. No withdrawals were related to the application of the test material. No adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.

TEST FACILITY CRL (2005)

B.7. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain Rat/Sprague Dawley
Route of Administration Oral – gavage
Exposure Information Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: 14 days
Vehicle Arachis oil
Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M, 5F	0	0/10
low dose	5M, 5F	25	0/10
mid dose	5M, 5F	150	0/10
high dose	5M, 5F	1000	0/10
control recovery	5M, 5F	0	0/10
high dose recovery	5M, 5F	0	0/10

Mortality and Time to Death
There were no unscheduled deaths.

Clinical Observations
No clinical signs or adverse effects on body weight gains were noted in the low- and mid-dose groups.

In the high-dose group treatment-related clinical observations included pink staining of the cage tray liners, transient episodes of increased salivation and associated findings of pink/red staining and soiled body fur and generalised fur loss in both male and female animals. The findings were not considered by the study authors to be toxicologically significant. Incidents of hunched posture, pilo-erection and tiptoe gait were also noted during the final week of dosing. In addition, reduced body weight gains were noted in both male and female animals during the treatment period. Recovery was observed during the recovery period for males, but reduced bodyweight gain was still evident during the first week of recovery for females. Reduced food intake and food efficiencies were also evident during the treatment period, with effects more prominent for males.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No treatment-related effects in clinical chemistry, haematology and urinalysis were recorded for animals in the low- and mid-dose groups.

The following findings were recorded for the high-dose group:

Urinalysis
Increased urine volume of reduced specific gravity and pink discolouration of the urine were noted. Reduced urine volume of increased specific gravity was noted prior to the end of the recovery period.

Haematology
Reductions in haemoglobin, erythrocyte count, leucocyte count (specifically in the neutrophil and lymphocyte fractions) and haematocrit were noted in both males and females. The males also showed elevated mean cell volume. Effects were still noted at the end of the recovery period.

Blood chemistry
Elevated urea, total protein, gamma-glutamyltranspeptidase, creatinine, chlolesterol and biliburin were noted in both males and females. Reduced albumin/globulin ratio, glucose and triglyceride levels were detected and

electrolyte changes evident (elevated potassium, sodium and inorganic phosphorus together with a reduction in chloride. Similar effects were observed at the end of the recovery period.

Effects in Organs

No significant changes in organ weights or treatment related macroscopic or microscopic findings were noted in the low- and mid-dose groups.

The following findings were recorded for the high-dose group:

Organ weights

Increased kidney and liver weights were noted in both males and females during the treatment period. These increases were still evident in females at the end of the recovery period. Spleen weights were elevated for males during the treatment period and were higher for recovery females at the end of the recovery period.

Necropsy

Enlarged and pale kidneys, and enlarged and dark spleens, were noted in both males and females. Red contents of the bladder (3 males, 1 female) and enlarged liver (1 male) were also noted.

Histopathology

Liver: glycogen type hepatocyte vacolation (relationship to treatment considered to be unconvincing by the study authors) and centrilobular hepatocyte enlargement (considered to be adaptive in nature by the study authors) were observed in both males and females. The latter condition had regressed at the end of the recovery period.

Spleen: severe extramedullary hematopoiesis, haemosiderin pigment accumulation and splenic hyperaemia were observed in both males and females. Extramedullary hematopoiesis but not pigment accumulation had regressed at the end of the recovery period and a few instances of splenic hyperaemia remained for either sex.

Kidneys: renal tubular basophilia and dilation with underlying focal tubular degeneration and hypertrophy of the epithelium of collecting ducts were observed in both males and females. These effects had largely regressed at the end of the recovery period.

Thyroid: follicular cell hypertrophy was observed in males only. This condition had regressed at the end of the recovery period.

Bone marrow: marrow hyperplasia was observed in both males and females. This effect was observed to have regressed among recovery males but not for females.

Seminal vesicles: seminal vesicles of generally smaller size were noted in males. This condition was observed to have regressed at the end of the recovery period.

Remarks – Results

Treatment related effects were noted in the kidney, spleen, thyroid, seminal vesicles and bone marrow at the highest dose tested of 1000 mg/kg bw/day. Treatment related effects were also noted in the liver but were considered adaptive in nature by the study authors. The majority of effects were resolved at the end of the 14 day recovery period, although incidents of marrow hyperplasia and splenic hyperaemia were still evident. In addition low erythrocyte levels and elevated mean cell volume were still observed.

CONCLUSION

The No Observed Effect Level (NOEL) was established as 150 mg/kg bw/day in this study, based on treatment related effects in the kidney, spleen, thyroid, seminal vesicles and bone marrow at the highest dose tested of 1000 mg/kg bw/day.

TEST FACILITY SafePharm (2006)

B.8. 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 (pKM101)
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 50-5000 µg/plate b) Without metabolic activation: 50-5000 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	Positive controls: With metabolic activation: 2-aminoanthracene; benzo(a)pyrene Without metabolic activation: N-ethyl-N'-nitro-N-nitrosoguanidine [TA1535, TA100, WP2uvrA(pKM101)]; 9-Aminoacridine (TA1537); 4-nitroquinoline-1-oxide (TA98)

RESULTS

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

Remarks - Results	In both tests, no increases in the frequency of revertant colonies were observed in the presence or absence of metabolic activation. No visible thinning of the background lawn of non-revertant cells was observed.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	SafePharm (2005h)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Chinese hamster
Cell Type/Cell Line	Lung cells
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Acetone
Remarks - Method	A dose range-finding study was carried out at 9.69 – 2480 µg/mL which was then narrowed to be 0.31 – 38.75 µg/mL in the without metabolic activation groups due to toxicity. The dose selection for the main experiments was based on toxicity for both short-term exposure groups and the continuous exposure group. Vehicle and positive controls (mitomycin C and cyclophosphamide) were run concurrently with the notified chemical.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	1.21, 2.43, 4.85*, 9.69*, 14.54*, 19.38	6 h	24 h
Test 2	1.21, 2.43*, 4.85*, 7.27, 9.69*, 14.54*	24 h	24 h
Present			
Test 1	9.69, 19.38*, 38.75*, 77.5*, 116.25, 155	6 h	24 h
Test 2	9.69*, 19.38*, 38.75*, 77.5, 96.88, 116.25	6 h	24 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 9.69	> 14.54	> 19.38	negative
Test 2	> 9.69	> 14.54	> 14.54	negative
Present				
Test 1	> 1.21	> 77.5	> 155	negative
Test 2		> 19.38	> 116.25	negative

Remarks - Results: In both main tests, no statistically significant increases in the frequency of cells with structural or numerical chromosome aberrations were observed in the presence or absence of metabolic activation.

The positive and negative controls gave a satisfactory response confirming the validity of the test system.

CONCLUSION: The notified chemical was not clastogenic to Chinese hamster lung cells treated in vitro under the conditions of the test.

TEST FACILITY: SafePharm (2005i)

B.10. Genotoxicity – in vivo

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain: Mouse/Crl:CD-1(ICR)BR
Route of Administration: Oral – gavage
Vehicle: Arachis oil
Remarks - Method: Toxicity was indicated by the percentage polychromatic erythrocytes (%PCEs) per 1000 erythrocytes and mutagenic response was indicated by the relevant increase of micronucleated PCEs.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
vehicle control 1	7M	0	24 h
vehicle control 2	7M	0	48 h
low dose	7M	375	24 h
mid dose	7M	750	24 h
high dose 1	7M	1500	24 h
high dose 2	7M	1500	48 h
positive control, CP	5M	50	24 h

CP=cyclophosphamide

RESULTS
Doses Producing Toxicity: A premature death occurred to 1 animal at 2000 mg/kg in the range-finding test. No mortality was seen in the main test. Clinical signs including hunched posture, ptosis, ataxia and splayed gait were noted at 1500 mg/kg (both 24 h and 48 h groups). There was a marked reduction in the %PCE value in the 48 h group at 1500 mg/kg. This accompanied by the observation of clinical signs was taken to indicate that the test substance had reached the bone marrow.
Genotoxic Effects: There were no statistically significant increases in the frequency of micronucleated PCEs.
Remarks - Results

	The positive and negative controls gave a satisfactory response confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo mammalian erythrocyte micronucleus test.
TEST FACILITY	SafePharm (2005j)

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.
Inoculum	Activated sludge from a local domestic wastewater treatment plant (Leicestershire, UK).
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	No significant deviation in protocol.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	0	7	63
14	2	14	68
28	2	28	70

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, aniline, surpassed the threshold level of 60% by 7 days (63%), and attained 70% degradation by 28 days. Therefore, the test indicates the suitability of the inoculums. The notified chemical attained 2% degradation by 28 days. Therefore, the notified chemical cannot be classified as readily biodegradable according to the OECD (301F) guideline.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	SafePharm (2005k)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static.
Species	*Oncorhynchus mykiss* (rainbow trout)
Exposure Period	96 hours
Auxiliary Solvent	Dimethylformamide
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	No significant deviation in protocol.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*					
Nominal	*Actual*		*3 h*	*6 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	10	0	0	0	0	0	0
2	1.3	10	0	0	0	0	1	1

LL50	> 1.3 mg/L (WAF) at 96 hours.
NOEL	1.3 mg/L (WAF) at 96 hours.
Remarks – Results	The temperature of the test conditions was 13.9-15.2 °C, which was

	outside the range reported in the study (14 ± 1 °C); however, this was not deemed to have had a significant impact on the validity or the integrity of the study. All other validity criteria for the test were met and satisfied. The test solutions were renewed every 24 hours during the 96 h test period. The 96 h LL50 and NOEL for fish were determined to be > 1.3 mg/L and 1.3 mg/L, respectively, based on measured concentrations.
CONCLUSION	Under the study conditions, the notified chemical is not considered to be toxic to fish up to the limit of its water solubility.
TEST FACILITY	SafePharm (2005l)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Dimethylformamide
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	No significant deviation in protocol.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
80	1.5	20	0	0

EL50	> 1.5 mg/L (WAF; 95% CL 1.2-1.7 mg/L) at 48 hours
NOEL	1.5 mg/L (WAF) at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were not renewed during the 48 h test period. The 48 h EL50 and NOEL for daphnids were determined to be > 1.5 mg/L and 1.5 mg/L, respectively, based on measured concentrations.
CONCLUSION	Under the study conditions, the notified chemical is not considered to be harmful to daphnids up to the limit of its water solubility.
TEST FACILITY	SafePharm (2005m)

C.2.3. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 211 *Daphnia magna* Reproduction Test.
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	Dimethylformamide
Water Hardness	250-264 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	No significant deviation in protocol.

	Test Concentration mg/L		
	Control	Solvent Control	0.2
Total no. Offspring released by survived *Daphnia*	842	835	778

Survival (%)	100	100	90

EL50	0.15-0.44 mg/L (WAF) at 21 days
NOEL	0.15 mg/L (WAF) at 21 days
Remarks - Results	The temperatures of some of the test conditions were marginally outside the range reported in the study (20 ± 1 °C); however, this was not deemed to have had a significant impact on the validity or the integrity of the study. All other validity criteria for the test were met and satisfied. The 21 d EL50 and NOEL for daphnids were determined to be 0.15-0.44 mg/L and 0.15 mg/L, respectively, based on measured concentrations.
CONCLUSION	Under the study conditions, the notified chemical is not considered to be harmful to daphnids on a chronic basis up to the limit of its water solubility.
TEST FACILITY	SafePharm (2005n)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test.
Species	*Scenedesmus subspicatus* (green alga)
Exposure Period	72 hours
Concentration Range	Nominal: 0.2-2 mg/L Actual: 0.16-1.75 mg/L
Auxiliary Solvent	Dimethylformamide
Water Hardness	Not reported
Analytical Monitoring	GC
Remarks - Method	No significant deviation in protocol.

RESULTS

Biomass		*Growth*	
E_bL50	*NOE_bL*	*E_rL50*	*NOE_rL*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
> 1.6	Not determined	> 1.6	1.6

Remarks - Results	All validity criteria for the test were satisfied. The 72 h E_bL50 and E_rL50 were both determined to be > 1.6 mg/L, based on measured concentrations. The 72 h NOE_rL was determined to be 1.6 mg/L.
CONCLUSION	Under the study conditions, the notified chemical is not considered to be harmful to algae up to the limit of its water solubility.
TEST FACILITY	SafePharm (2005o)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Aerated activated sludge from a synthetic sewage feed.
Exposure Period	3 hours
Concentration Range	Nominal: 100-1000 mg/L Actual: Not determined
Auxiliary Solvent	Dimethylformamide
Water Hardness	100 mg $CaCO_3$/L
Remarks – Method	No significant deviation in protocol. Chemical 3,5-dichlorophenol was

	used as the reference control. The respiration rate was determined by measurement of Biochemical Oxygen Demand during the test after 3 hours of exposure.
RESULTS	
IC50	> 1000 mg/L at 3 hours
Remarks – Results	All validity criteria for the test were satisfied. No significant inhibition of respiration rates were observed at 1000 mg/L. The 3 h EC50 was determined to be > 1000 mg/L, based on nominal concentrations. The notified chemical is not considered to be inhibitory to sludge microbial activity.
CONCLUSION	The notified chemical is not inhibitory to microbial activity.
TEST FACILITY	SafePharm (2005p)

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