File No: LTD/1811

May 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclohexanecarboxylic acid, 3-methyl-, methyl ester

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/1811	International Flavours and Fragrances (Australia) Pty Ltd.	Cyclohexanecarboxylic acid, 3-methyl-, methyl ester	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Flammable Liquids (Category 4)	H227 – Combustible liquid
Acute Toxicity – Oral (Category 4)	H302 – Harmful if swallowed
Skin Irritation (Category 2)	H315 – Causes skin irritation
Serious Eye Irritation (Category 2A)	H319 – Causes serious eye irritation

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

R22: Harmful if swallowed
R38: Irritating to skin
R36: Irritating to eyes

The environmental hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute Category 2	H401 – Toxic to aquatic life

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.

When used in the proposed manner, 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

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Flammable Liquids (Category 4): H227 – Combustible liquid
  - Acute Toxicity - Oral (Category 4): H302 – Harmful if swallowed
  - Skin Irritation (Category 2): H315 – Causes skin irritation
  - Serious Eye Irritation (Category 2A): H319 – Causes serious eye irritation

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

- The Delegate (and/or the Advisory Committee on Chemicals Scheduling) should consider the notified chemical for listing on the SUSMP.

- Due to the hazardous properties of the notified chemical, the notifier should consider their obligations under the Australian Dangerous Goods Code.

(Material) Safety Data Sheet

- The (M)SDS provided by the notifier should be amended as follows:
  - Section 2 of the (M)SDS for the notified chemical should include the eye irritation hazard information.
  - The notifier should consider to disclose the chemical identity in the (M)SDS for the products under Australian OHS legislations.

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Enclosed, automated processes, where possible
  - Adequate general and local exhaust ventilation

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Avoid contact with skin and eyes
  - Avoid breathing in vapours, mists and aerosols if these are present

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Coveralls
  - Impervious gloves
  - Eye protection
  - Respiration protections if inhalation exposure is expected

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

- 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 for the Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures

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

Disposal

- 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.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, physical 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 use concentration exceeds or is intended to exceed 1.3% in fragrance products, 1% in hair care, bathing and showering products, 0.7% in skin care products, 0.2% in deodorants and 1% in other 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)SDS 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 (M)SDS 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)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None for the notified chemical

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Jamunate

CAS NUMBER
72903-23-2

The notified chemical is a racemic mixture of two diastereoisomers:

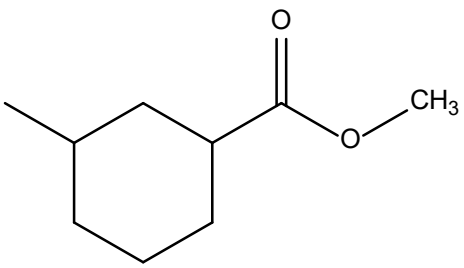
7605-52-9	Cyclohexanecarboxylic acid, 3- methyl-, methyl ester, (1R, 3S)-rel-	80-85%
7605-53-0	Cyclohexanecarboxylic acid, 3-methyl-, methyl ester, (1R, 3R)-rel-	15-20%

CHEMICAL NAME
Cyclohexanecarboxylic acid, 3-methyl-, methyl ester

OTHER NAME(S)
M3MC-carboxylate (test substance of the study reports)

MOLECULAR FORMULA
$C_9H_{16}O_2$

STRUCTURAL FORMULA



The notified chemical is a racemic mixture of two diastereoisomers, Cyclohexanecarboxylic acid, 3- methyl-, methyl ester, (1R, 3S)-rel- and Cyclohexanecarboxylic acid, 3-methyl-, methyl ester, (1R, 3R)-rel-

MOLECULAR WEIGHT
156.22 Da

ANALYTICAL DATA

METHOD	^{1}H NMR
Remarks	Reference spectrum was provided.
TEST FACILITY	IFF R&D

METHOD	IR
Remarks	Reference spectrum was provided. Characteristic absorption peaks were noted.
TEST FACILITY	IFF R&D

METHOD	UV/Visible
Remarks	Reference spectrum was provided. The notified chemical was detected at pH 7 (neutral), 2-3 (acidic) and 9-10 (basic) with absorption peaks at 204, 204 and 206 nm respectively.
TEST FACILITY	IFF R&D

METHOD	GC-MS
Remarks	Reference spectra were provided. Two isomers were detected as main components with GC retention areas covering 82.2% and 17.3% respectively.
TEST FACILITY	IFF R&D

3. COMPOSITION

DEGREE OF PURITY
>99%

IDENTIFIED IMPURITIES/RESIDUAL MONOMERS

Chemical Name	Cyclohexanecarboxylic acid, methyl ester		
CAS No.	4630-82-4	*Weight %*	< 0.5
Hazardous Properties	H226 – Flammable liquid and vapour*		

* Based on ECHA notified classification

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 liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -25 °C	Measured
Boiling Point	200 °C at 101.3 kPa	Measured
Relative Density (D^{20}_{4})	0.95	Measured
Vapour Pressure	0.27 kPa at 25 °C	Measured
Water Solubility	0.391 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$te_{½}$ > 1 year at pH 4 and 7; $te_{½}$ = 21 days at pH 9	Measured
Partition Coefficient (n-octanol/water)	log Pow = 3.7 at 25 °C	Measured
Surface tension	52.5 mN/m (90% saturated solution)	Measured
Adsorption/Desorption	log K_{oc} = 2.6 at 25 °C	Measured
Dissociation Constant	Not determined	Not expected to dissociate due to hydrolytic stability

Flash Point	72 °C	Measured
Flammability	Not determined	Not applicable. Imported in fragrance oil at ≤ 5% concentration
Autoignition Temperature	324 °C	Measured
Explosive Properties	Not explosive	Theoretically assessed. The notified chemical contains no functional groups characteristic of explosive properties
Oxidising Properties	Non oxidising	Theoretically assessed

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

Hazard classification	***Hazard statement***
Flammable liquids (Category 4)	H227 – Combustible liquid

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 oil (up to ≤ 5% concentration), encased in polypropylene-lined steel drums (usually in the size of 55 gallons, equivalent to approximately 208 L) delivered to the notifier's facility.

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 RECIPIENTS
International Flavours and Fragrances (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical at up to ≤ 5% concentrations will be imported as a component of finished fragrance oil. The finished fragrance oil will be stored in polypropylene-lined steel drums (usually in the size of 55 gallons, equivalent to approximately 208 L), then transported by road to IFF facility.

USE
The notified chemical at concentrations up to 1.3% will be used as a fragrance ingredient and will be incorporated into cosmetics, personal care products and other household products, including soaps, detergents and air fresheners.

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

Product Type	***Proposed Maximum Use Concentration (%)***
Fine fragrances	1.3
Leave-on cosmetics	0.7
Rinse-off cosmetics	1
Household products	1

Product Type	*Proposed Maximum Use Concentration (%)*
Air fresheners	1
Antiperspirant/Deodorant	0.2

OPERATION DESCRIPTION

The notified chemical will not be manufactured within Australia. The notified chemical will be imported in finished fragrance oils at ≤ 5% concentration for reformulation into cosmetics, personal care and household products at concentrations up to 1.3%.

No reformulation or repackaging of the fragrance oil containing the notified chemical will occur at the notifier's facility. The finished fragrance oil will be stored at the notifier's facility until it is further distributed to reformulation facilities.

Reformulation at the customer facility

The procedures for incorporating the fragrance oil containing the notified chemical (at up to 5% concentration) into end-use products will likely vary depending on the nature of the formulated products and may involve both automated and manual transfer steps. A typical end-use operation in the customer facility involves the mixing of the fragrance oil with various other ingredients in a mixing tank to make consumer products.

End use

Household products

Household products containing the notified chemical (at up to 1% concentration) may be used by consumers and 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

The finished leave-on and rinse-off cosmetic products containing the notified chemical at up to 1.3% concentration will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the products, applications could be by hand, spray or through the use of 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 up to 5% concentrations) only in the event of accidental rupture of the drum containers.

At the notifier's facility, the primary work activity undertaken by transport and warehouse workers will include handling, loading and off-loading of drums containing fragrance oils with the notified chemical at up to 5% concentrations. Exposures of these workers will be limited to situations involving products sampling for quality control or, in the event of a discharge, cleaning up from a spill or leaking drum. If such an event occurs, workers may mainly be exposed through dermal and ocular contact. Inhalation exposure to the notified chemical is also possible as the vapour pressure of the chemical at room temperature is relatively high. However, such exposures will be minimised through the use of personal protective equipment (PPE) including protective overalls, hard hats, chemical resistant gloves, safety glasses and appropriate respiratory protections, as proposed by the notifier.

Formulation of end products
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at up to 5% concentrations) may occur during handling the fragrance oil, intermediate products and finished products containing the notified chemical. The processes may include weighing, transfer, blending, quality control analysis, packaging of materials and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation, local exhaust ventilation and/or enclosed systems, and through the use of PPE such as coveralls, goggles and impervious gloves. Due to the relatively high vapour pressure of the notified chemical, inhalation exposure may be expected. Inhalation exposure is also expected from products where vapours, mists or aerosols of the notified chemical may be generated. The notifier stated that self-contained breathing apparatus will be used if ventilation is inadequate to minimise the inhalation exposure.

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products (at up to 1.3% concentrations) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hair dressers, workers in beauty salons) or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use PPE to minimise repeated exposure, but the use is not always expected. However, good hygiene practices are expected to be in place. If appropriate PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the finished 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 up to 1.3% concentrations) through the use of a wide range of cosmetic, personal care 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 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 20m^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	0.7	1	0.8553
Face cream	1540	0.7	1	0.1684
Hand cream	2160	0.7	1	0.2363
Fine fragrances	750	1.3	1	0.1523
Deodorant spray	1430	0.2	1	0.0447
Shampoo	10460	1	0.01	0.0163
Conditioner	3920	1	0.01	0.0061
Shower gel	18670	1	0.01	0.0292
Hand wash soap	20000	1	0.01	0.0313
Hair styling products	4000	1	0.1	0.0625
Total				1.6024

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	1	0.95	10	0.0341
Fabric softener	90	1	0.95	10	0.0134
Total					0.0475

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	1	1980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	1	1980	0.009	0.01	0.03	0.0025
All-purpose cleaner	1	1	1980	1	0.01	0.007	0.0217
Total							0.0245

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	1	20	1	20	50	1	10	0.0322

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 1.71 mg/kg bw/day. The notified chemical is also used in fragrance creams at 0.7%. According to the notifier, a fragrance cream may be used by consumers instead of a fine fragrance (e.g., eau de toilette or perfume); therefore, exposure to fine fragrance addresses that of fragrance cream as well. As a result, the later product type was not included in the daily systemic exposure calculations. 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	300 < LD50 < 2,000 mg/kg bw; harmful
Rat, acute dermal toxicity	LD50 > 2,000mg/kg bw; low toxicity
Rabbit, skin irritation	irritating
Rabbit, eye irritation	irritating
Mouse, skin sensitisation – Local lymph node assay	inadequate evidence of sensitisation
Human, skin sensitisation – RIPT (5 %)	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 150 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test	non genotoxic

Toxicokinetics, metabolism and distribution
No information on the toxicokinetics of the notified chemical was provided. Based on the low molecular weight (156.22 Da), the potential for the notified chemical to cross the gastrointestinal (GI) tract by passive diffusion or to be dermally absorbed after exposure is possible. However, absorption is expected to be limited, given the relatively high partition coefficient (log Pow = 3.7 at 25 °C) of the notified chemical. The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity
Acute toxicity *via* the oral and dermal routes was studied for the notified chemical. The acute oral study showed various clinical signs of toxicity including death of 2 animals, hunched posture, unsteady gait, piloerection, increased breathing, underactivity, muscle tremors, reduced body temperature, yellow/brown staining of the perigenital area, prominent eyes and thin build at a dose level of 2,000 mg/kg bw. Based on the study findings, the notified chemical was considered harmful via the oral route.

An acute dermal study was conducted on the notified chemical at a dose level of 2,000 mg/kg bw. Macroscopic examination at study termination, on day 15 showed 2 of 5 males with small stomachs, 1 of 5 females with pale liver and kidneys. Another female animal had thinner tissue at the upper part of the stomach. No abnormalities were noted for other test animals. The notified chemical was considered to be of low toxicity via the dermal route.

Irritation and sensitisation
Skin and eye irritation studies showed that the notified chemical is irritating to both the skin and eyes.

A local lymph node assay (LLNA) for skin sensitisation on the notified chemical was provided. The notified chemical was studied at 50% due to the limitation of its physical properties. Stimulation indices (SI) of 0.5, 0.9 and 1.5 were reported for 10%, 25% and 50% of the notified chemical respectively, showing a dose-response. It is also noted that the DPM reading for the vehicle control in the study group was unusually high compared to the readings from the vehicle control in the positive control group, rendering the SI calculations less reliable. It is considered that the study exhibited inadequate evidence for the skin sensitisation properties of the test substance. Therefore, skin sensitisation potential for the notified chemical at high concentrations cannot be ruled out.

A human repeat insult patch test (HRIPT) at 5% concentration of the notified chemical was conducted on 101 subjects. The test substance did not cause skin sensitisation under the conditions of the test.

Repeated dose toxicity
In a preliminary dose range finding study, the notified chemical was tested at 250, 500 and 1,000 mg/kg bw/day. Underactivity, unsteady gait, hunched posture, reddening of the skin, low body weight gain were noted at 1,000 mg/kg bw/day. Post-dose, chin rubbing and salivation were noted in the majority of animals receiving 500 or 1,000 mg/kg bw/day from day 3 and in one male receiving 250 mg/kg bw/day on day 7. Based on the results, a 28 day oral toxicity study was conducted on the notified chemical in rats at the dose levels of 0, 15, 150 and 1,000 mg/kg bw/day. The study showed various treatment-related adverse effects at the highest dose level of 1,000 mg/kg bw/day, including forestomach oedema and depression, elevated liver weight and decreased body weights. Some treatment related disturbances in urinary pH in male animals and increase of forelimb grip strength in female animals were noted in the 150 mg/kg bw/day group; however, these changes were considered by the study authors not to be toxicologically significant. The No Observed Adverse Effect Level (NOAEL) was established by the study authors at 150 mg/kg bw/day and was used for quantitative risk assessment of the notified chemical.

Mutagenicity/Genotoxicity
A bacterial reverse mutation assay and an *in vitro* mammalian chromosome aberration test in human lymphocytes were provided for the notified chemical. Under the conditions of the tests, the notified chemical showed no evidence for mutagenicity and clastogenicity.

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

Hazard classification	*Hazard statement*
Acute Toxicity –Oral (Category 4)	H302 Harmful if swallowed
Skin Irritation (Category 2)	H315 Causes skin irritation
Serious Eye Irritation (Category 2A)	H319 Causes serious eye irritation

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

R22: Harmful if swallowed
R38: Irritating to skin
R36: Irritating to eyes

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Transport and Storage
Workers may experience dermal and accidental ocular exposure to the notified chemical (at up to 5% concentrations) where the fragrance oils are sampled for quality control purposes or in the event of a discharge via spill or drum leakage. The use of PPE (e.g. impervious gloves, goggles, coveralls, hard hats and respiratory protection, if necessary) should minimise the potential for exposure. Provided adequate control measures and safe work practices are in place to minimise worker exposure, including PPE, the risk to workers from the notified chemical is not considered to be unreasonable.

Reformulation
Workers may experience dermal, accidental ocular and perhaps inhalation exposure to the notified chemical (at up to 5% concentrations) during reformulation/blending processes. The exposure may also occur during handling of the drums, cleaning and/or maintenance of the equipment containing the notified chemical. At the reformulation facilities, exposure may also extend to compounders and laboratory staff involved in the formulation of the end products containing the notified chemical and sampling and testing these products for quality control purposes.

As proposed by the notifier, use of enclosed/automated processes, PPE (impervious gloves, goggles, coveralls, hardhats and respiratory protection, if significant inhalation exposure is expected) and deployment of occupational surveillance programs should minimise the potential for exposure. Therefore, provided that adequate control measures are in place to minimise worker exposure, including the use of automated processes and PPE, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Workers involved in professions where the services provided involve the application of cosmetic products to clients (e.g. beauty salon workers) may be exposed to the notified chemical at concentrations up to 1.3%. Hairdressers may also be repetitively exposed to the notified chemical in the application of hair care products including shampoo and hairspray to salon clients. Such professionals may use PPE such as gloves, glasses, face masks and protective clothing to minimise repeated exposure, and good hygiene practices are expected to be in place. For hair salons, good ventilation would be recommended, if hair spray is routinely used in a confined space. If PPE is used and good ventilation is in place, 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 (for details of the public health risk assessment, see Section 6.3.2. below). Based on the information available, the risk to workers associated with use of the notified chemical at ≤ 1.3% concentrations in cosmetic products is not considered to be unreasonable.

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 the proposed concentrations of up to 1.3%.

Local effects on skin
The notified chemical is irritating to the skin and eyes. Skin sensitisation potential of the notified chemical at high concentrations cannot be ruled out. However, at the low proposed end use concentrations, skin or eye irritation effects and skin sensitisation from the normal use of the finished products containing the notified chemical are expected to be unlikely.

Systemic effects
The potential systemic exposure to the public from the use of the notified chemical in cosmetics and household products was estimated to be 1.71 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 150 mg/kg bw/day, which was derived from a 28 day oral repeated dose toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 88. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. However, dermal absorption/bioavailability of 100% for the notified chemical in the use of all the finished consumer products is a conservative assumption, given the relatively high partition coefficient (log Pow = 3.7) of the notified chemical. In addition, the assumption that an adult consumer uses a large number of consumer products on every day, is likely to overestimate the systemic daily exposure to the notified chemical under realistic use scenarios.

Therefore, the risk to the public associated with the use of the notified chemical in fragrance products (≤1.3%), hair care, bathing and showering products (≤ 1%), skin care products (≤ 0.7%), deodorants (≤ 0.2%) and other household products (≤ 1%), 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 fragrance ingredient for local reformulation into a variety of consumer products (cosmetics, consumer products, fine fragrances). Release during reformulation in Australia is expected to be limited to accidental spills or leaks of drums (0.1%) and residue in import containers (0.1%). 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). Therefore, a total of 0.2%, or 2 kg of the import volume, is estimated to be released from reformulation in Australia.

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 3%, or up to 30 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, consumer products and fine fragrances, before potential release to surface waters nationwide. The notified chemical is not considered readily biodegradable, but shows inherent biodegradability (74% in 28 days). For details of the environmental fate studies, please refer to Appendix C. Based on its measured adsorption coefficient (log K_{OC} = 2.6), release to surface waters may occur as only partial partitioning to sludge is expected. The notified chemical is not expected to bioaccumulate due to its n-octanol/water partition coefficient (log P_{OW} = 3.7) and inherent biodegradability. Therefore, in surface waters the notified chemical is expected to disperse and degrade through abiotic and biotic processes to form water and oxides of carbon.

The notified chemical is moderately volatile from water (log H = 2.033 Pa/m^3/mol; European Commission, 2003) and may slowly volatilise to air during sewage treatment. The half-life of the notified chemical in air is calculated to be 12.99 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 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} = 2.6), 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:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 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 1,500 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	96h LC50 = 6.73 mg/L	Toxic to fish (acute)
Daphnia Toxicity	48h EC50 = 21.3 mg/L	Harmful to *Daphnia* (acute)
Algal Toxicity	72h E_rC50 = 27.7 mg/L	Harmful to algae (acute)
Inhibition of Bacterial Respiration	3h EC50 = 210 mg/L	Not inhibitory to bacterial respiration

Based on the ecotoxicological endpoints for the notified chemical, it is expected to be toxic to fish and harmful to daphnids and algae on an acute basis. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as “Acute Category 2; Toxic to aquatic life”. Based on the acute toxicity, inherent biodegradability and low bioaccumulation potential of the notified chemical, it is not expected to be harmful to aquatic life on a long term basis, and is therefore not formally classified under the GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for fish. A safety factor of 10 was used given both acute and chronic endpoints for three tropic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish, 96 h)	6.73	mg/L
Assessment Factor	10	

PNEC:	673	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	673	**0.001**
Q - Ocean	0.06	673	**< 0.0001**

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 considered inherently biodegradable and expected to 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 consumer products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < - 25 °C

Method OECD TG 102 Melting Point/Melting Range.
EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks Test conducted on the notified chemical. The test substance was still a liquid at -25 °C.
Test Facility Huntingdon Life Sciences (2008a)

Boiling Point 200 °C at 101.3 kPa

Method OECD TG 103 Boiling Point.
EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks Siwoloboff method. Test conducted on the notified chemical
Test Facility Huntingdon Life Sciences (2008a)

Relative Density 0.95 at 20 °C

Method OECD TG 109 Density of Liquids and Solids.
EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks Determined on the notified chemical relative to purified water using a pycnometer
Test Facility Huntingdon Life Sciences (2008a)

Vapour Pressure 2.7×10^{-1} kPa at 25 °C

Method OECD TG 104 Vapour Pressure.
EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks The vapour pressure was tested on the notified chemical at temperatures between 50 and 70 °C and extrapolated to 25°C.
Test Facility Huntingdon Life Sciences (2008a)

Water Solubility 0.391 g/L at 20 °C

Method OECD TG 105 Water Solubility.
Remarks Flask Method. 6 mixtures of the notified chemical with distilled water at 50 mg were shaken at 30 °C for 24 to 72 hours. After equilibrating at 20 °C for 24 hours, the mixtures were then centrifuged at 2,500 rpm for 60 minutes. The concentration of the sample solutions was determined by HPLC.
Test Facility Huntingdon Life Sciences (2008a)

Hydrolysis as a Function of pH $te_{½}$ > 1 year at pH 4 and 7, and $te_{½}$ = 21 days at pH 9

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	$t_{½}$
4	25	> 1 year
7	25	> 1 year
9	50	~ 30 hours
9	60	~ 7 hours
9	70	~ 3.5 hours

Remarks The stability of the notified chemical was determined at pH values from 4-9 under accelerated conditions of 50 °C. Less than 10% of the notified chemical underwent hydrolysis after 120 hours (5 days) at pH 4 and 7 at 50 °C, equivalent of an environmental half-life ($te_{½}$, at 25 °C) of > 1year. No further testing at these pH values were deemed necessary. At pH 9 and 50 °C, greater than 10% hydrolysis had occurred after 120 hours, but less than 50% after 2.4 hours, equivalent of 1 day < $te_{½}$, < 1 year. The stability of the notified chemical at pH 9 was further tested at 60 °C and 70 °C. It can be concluded that the notified chemical is hydrolytically stable under acidic and neutral conditions, but hydrolysed under basic conditions.

Test Facility Huntingdon Life Sciences (2009b)

Partition Coefficient (n-octanol/water) log Pow = 3.7 at 25 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks HPLC Method
Test Facility Huntingdon Life Sciences (2008a)

Surface Tension 52.5 mN/m at 20 °C

Method OECD TG 115 Surface Tension of Aqueous Solutions.
EC Council Regulation No 440/2008 A.5 Surface Tension.
Remarks Concentration: 90% saturated aqueous solution. Test conducted on the notified chemical
Test Facility Huntingdon Life Sciences (2008a)

Adsorption/Desorption log K_{oc} = 2.6 at 25 °C

Method OECD TG 121 Estimation of the Adsorption Coefficient (K_{OC}) on Soil using High Performance Liquid Chromatography (HPLC).
Remarks HPLC screening method was employed using a column temperature of 25 °C and a mobile phase of methanol/water (55/45 v/v). The dead time was determined to be 3.205 minutes (formamide). A single peak was detected with a retention time of 4.096 minutes.
Test Facility Huntingdon Life Sciences (2009a)

Flash Point 72 °C at 99.8 kPa

Method EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks Pensky-Martens closed cup method. Test conducted on the notified chemical
Test Facility Huntingdon Life Sciences (2008a)

Autoignition Temperature 324 °C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases)
Remarks BS 4056 method. Test conducted on the notified chemical at 99.6 kPa
Test Facility Huntingdon Life Sciences (2008a)

Explosive Properties Not explosive

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks An assessment was made using a theoretical consideration of the structure of the notified chemical. The notified chemical contains no functional groups characteristic of explosive properties.
Test Facility Huntingdon Life Sciences (2009a)

Oxidizing Properties Not oxidising

Method EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).
Remarks An assessment was made using a theoretical consideration of the structure of the notified chemical. The notified chemical was confirmed to contain oxygen only chemically bonded to carbon and would not be expected to possess oxidising properties.
Test Facility Huntingdon Life Sciences (2009a)

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/CD (Crl:CD 'SD')
- Vehicle: Corn oil
- Remarks - Method: No significant protocol deviations were noted. The purity of the test substance was recorded as 99.5%

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3F	300	0/3
2	3F	300	0/3
3	3F	2000	0/3
4	3F	2000	2/3

LD50: > 300 but < 2,000 mg/kg bw

Signs of Toxicity: Two test animals dosed at 2,000 mg/kg bw from Group 4 were found dead on day 2. Clinical signs noted prior to death in both animals included hunched posture, unsteady gait, piloerection, increased shallow and irregular breathing, reduced body tone, underactivity, flat and prostate postures, lachrymation, reduced body temperature and partially closed eyelids. One animal showed red staining in urine, while the other animal showed yellow/brown staining of the perigenital area, along with uncoordinated gait. Loss of bodyweight was noted for both of the decedents.

Clinical signs of reaction to treatment in the surviving animals treated at 2,000 mg/kg bw included hunched posture, unsteady gait, piloerection, increased breathing, underactivity, muscle tremors, reduced body temperature, yellow/brown staining of the perigenital area, prominent eyes and thin build. All of these signs had resolved by day 10.

Clinical signs in animals dosed at 300 mg/kg bw included unsteady gait (seen in five animals) and loose faeces (noted in two animals). These signs had resolved by day 2.

Low bodyweight gain was recorded for all but one animals treated at 2,000 mg/kg bw and for one animal treated at 300 mg/kg bw.

Effects in Organs: Macroscopic examination of the two deceased animals revealed congestion of the subcutaneous tissue, heart, lungs, spleen, kidneys and duodenum, enlarged stomach. Inspection of the stomach and small intestine contents showed yellow fluid and red fluid in the large intestines. One animal showed congestion of the liver and the other animal showed enlargement of the urinary bladder.

The surviving animals were terminated on day 15. Macroscopy revealed stomach atrophy in 1 animal dosed at 2,000 mg/kg bw. No abnormalities were noted in the other surviving animals.

Remarks - Results: Due to deaths of animals occurred at the dose level of 2,000 mg/kg bw, the LD50 was considered for the notified chemical to be between 300 and

2,000 mg/kg bw by the study authors.

CONCLUSION The notified chemical was harmful via the oral route.

TEST FACILITY Huntingdon Life Sciences (2008b)

B.2. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical

METHOD OECD TG 402 Acute Dermal Toxicity.
EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal).

Species/Strain	Rat/ CD (Crl:CD 'SD')
Vehicle	None, test substance administered as supplied
Type of dressing	Occlusive
Remarks - Method	No significant protocol deviations were noted. The purity of the test substance was recorded to be 99.5%.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5M + 5F	2,000	0/10

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	Very slight erythema was noted in one female on day 2. This effect had resolved by day 3.
Signs of Toxicity - Systemic	There were no unscheduled deaths or systemic responses observed during the study period.
Effects in Organs	Macroscopic examination at study termination on day 15 showed two males with small stomachs, one female with pale liver and kidneys. Another female animal had thinner tissue at the upper part of the stomach. There were no abnormalities noted for the other test animals.
Remarks - Results	The increase in body weights of the test animals over the test period were in the expected range, except for one female which was noted on day 8 with no bodyweight gain.

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

TEST FACILITY Huntingdon Life Sciences (2009c)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 2004/73/EC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3F
Vehicle	Test substance administered as supplied
Observation Period	15 days
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations were noted. The purity of the test substance was recorded as 99.5%. The ages of the test animals were in the range of 40 to 42 weeks instead of required 12 to 40 weeks.

A single 4 hour application of the test material was made to the intact skin

of 3 male rabbits. Test sites were observed for evidence of primary irritation at 1, 24, 48 and 72 hours post patch removal.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	2	2	1.7	2	≥ 15 days	1
Oedema	0	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 to well-defined erythema was evident at the treated site of all animals from 1 hour post application and sustained for the entire study period.

Loss of elasticity was noted in one animal during the 48 hour observations but had subsided by day 15. Exfoliation was noted in all three animals during the second week of observations.

There were no signs of toxicity in any of the test animals during the study.

CONCLUSION

The notified chemical was irritating to rabbit skin.

TEST FACILITY

Huntingdon Life Sciences (2010a)

B.4. Irritation – eye

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation).

Species/Strain: Rabbit/New Zealand White
Number of Animals: 3F
Observation Period: 15 days
Remarks - Method: No significant protocol deviations. The purity of the test substance was recorded as 99.5%.

A single application of 0.1 mL of the test material to the non-irrigated eye of three female rabbits.

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	1	0.7	1.3	2	< 15 days	0
Conjunctiva: chemosis	0	0	0.7	1	< 72 hours	0
Conjunctiva: discharge	0	0	0	2	< 24 hours	0
Corneal opacity	1	0.7	1	1	< 15 days	0
Iridial inflammation	0.3	0	0	1	< 48 hours	0

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

Remarks - Results

Installation of the notified chemical gave rise to a moderate initial pain response in the test animals.

Crimson red conjunctival appearance was apparent in all three animals during the first 48 hours post installation, persisting in two animals at the 72 hour observations and in one animal on day 8. Slight to moderate

discharge was evident in all three animals 1 hour post installation. Very slight chemosis was noted in two animals from 1 to 24 hours post administration. Diffuse areas of opacity were evident in all animals 24 and 48 hours after installation. Iritis was apparent in one animal 24 hours after installation.

Two animals appeared normal by the day 8 observations and all signs had cleared by day 15 in the remaining animal.

There were no signs of toxicity in any of the test animals during the study.

CONCLUSION The notified chemical was irritating to the eye.

TEST FACILITY Huntingdon Life Sciences (2010b)

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

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain Mouse/CBA/Ca

Vehicle Acetone:olive oil (4:1 v/v)

Remarks - Method Pooled treatment group approach was used for the assay

Positive control: HCA (hexyl cinnamic aldehyde)

The test substance was only tested at 10%, 25% and 50%. No concentrations above 50% were tested due to the limitation of the physical properties of the test substance.

No significant protocol deviations were noted. Topical application was made to the dorsal surface of the ear. The purity of the test substance was recorded as 99.5%

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	619.29	-
10	338.23	0.55
25	583.79	0.94
50	925.46	1.5
Positive Control		
0 (vehicle control)	361.33	-
10	884.43	2.4
25	2724.58	7.5
50	4139.38	11.5

Remarks - Results No signs of systemic toxicity or local irritation were noted in the test or control animals.

The DPM/lymph node reading from the negative vehicle control in the test group was unusually high compared to the vehicle control in the positive control group, rendering calculated stimulation index (SI) of <1 for test substance at 10% and 25% concentrations. Based on the SI listed above, dose response of the notified chemical was clearly shown although none of the SI was calculated above 3.

	The positive controls gave satisfactory responses confirming the validity of the test system.
CONCLUSION	There was inadequate evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Huntingdon Life Sciences (2008c)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (5% in vehicle)
METHOD	Repeated insult patch test with challenge (Modified Shelanski-Shelanski method)
Study Design	Induction Procedure: Patches in size of 3.63 cm^2 containing 0.2 mL of the test material were applied 3 times a week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 h and graded at 24 h, 48 h and 72 h after the removal of patches on Saturday. Rest Period: 14 days Challenge Procedure: A patch was applied to a naïve site. Patches were removed by the applicants after 24 h. Sites were graded at 24, 48 and 72 h post-patch removal.
Study Group	82 F, 30 M; age range 18-70 years
Vehicle	Diethyl Phthalate, alcohol SD39C
Remarks - Method	Occluded patch type was used. The test substance was tested at the dose level of 0.055 mL/cm^2. The test substance was present at 5% concentration. In the case of control group distilled water was used instead of the notified chemical. A panel of 112 healthy human subjects (devoid of any physical or dermatological conditions) was included in the test. During the induction phase, the test article was placed onto an occlusive patch and applied for total of 9 applications to the back of each subject between the scapulae and waist. The challenge phase patch was applied to a virgin test site. Dermal responses were scored according to a 6-point scale (0, ±, 1 to 4).
RESULTS	
Remarks - Results	101 of 112 subjects completed the study. Seven females and four males discontinued from the study. The reason for discontinuing was not provided. Two subjects were absent for one of the nine applications during the induction phase. One subject was absent for 48 h observation during the challenge phase, however, no dermal reaction was observed at 96 h in this subject. The study authors concluded that the notified chemical did not demonstrate a potential for eliciting dermal irritation or sensitization at a dose of 0.055 cc/cm^2.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	Clinical Research Laboratories, Inc. (2010)

B.7. Repeat dose toxicity – dose range finding study (7 days)

TEST SUBSTANCE	Notified chemical
METHOD	7-day dose range finding study for OECD TG 407 with limited laboratory examinations
Species/Strain	Rat/CD
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 7 days Dose regimen: 7/7 days per week Post-exposure observation period: nil
Vehicle	Corn oil
Remarks - Method	The study was a dose range finding assay for a subsequent 28-day repeated dose oral toxicity study (see Appendix B.8).

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
low dose	3M + 3F	250	0/6
mid dose	3M + 3F	500	0/6
high dose	3M + 3F	1,000	0/6

Mortality and Time to Death
There were no unscheduled deaths during the study.

Clinical Observations
From day one, underactivity and unsteady gait were noted on at least three occasions 1-2 hours after dosing in all animals receiving 1,000 mg/kg bw/day. On the majority of occasions, these signs persisted until the end of the day. In addition, hunched posture was noted in these animals at the last check of day 1 and 1-2 hours after dosing on day 2. Reddening of the skin was noted on one occasion for two males and on two occasions for one female. These clinical signs were not apparent 24 hours after dosing and were not observed on day 7. Lower body weight gain and decreased food intake was observed in males receiving 1,000 mg/kg/ day.

Post – dose chin rubbing and salivation were noted in the majority of animals receiving 500 or 1,000 mg/kg bw/day, from day 3 and in one male receiving 250 mg/kg bw/day on day 7. In all cases this signs had resolved by 1-2 hours after dosing. The study authors concluded that the chin rubbing and salivation were related to the administration route allied to the palatability of the test formulations and were not considered to have toxicological significance.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No details were provided in the report.

Effects in Organs
There was no dose related effects observed on the kidney, liver and spleen weights. Limited macroscopic examinations did not reveal intergroup differences of note.

Remarks – Results	Several post dose clinical signs were noted at 1,000 mg/kg bw/day, however there was no evidence of progression of the signs during the 7 days of dosing.
CONCLUSION	On the basis of these findings and due to the lack of progression of the observed clinical signs, a dose regime of 0, 15, 150 and 1,000 mg/kg bw/day was selected by the study authors for the subsequent 28-day repeated dose study.
TEST FACILITY	Huntingdon Life Sciences (2009d)

B.8. 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/CD (Crl:CD SD)
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	Corn oil
Remarks - Method	No significant protocol deviations. The purity of the test substance was recorded as 99.5%.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M + 5F	0	0/10
low dose	5M + 5F	15	0/10
mid dose	5M + 5F	150	0/10
high dose	5M + 5F	1,000	0/10
control recovery	5M + 5F	0	0/10
high dose recovery	5M + 5F	1,000	0/10

Mortality and Time to Death

There were no unscheduled deaths during the study.

Clinical Observations

In the group treated at 1,000 mg/kg bw/day, treatment related clinical signs of underactivity, abnormal/unsteady gait, flat/hunched posture and reduced body tone were recorded in both sexes. Post-dose piloerection was note in all females in the group. One female was noted to be prostrate and showed reduced body tone, fast breathing, partially closed eyelids, generally during the latter half of the treatment period. Statistically significant increase in grip strength was observed in females, associated with increased body tone. Increase in forelimb grip strength values in the females continued in the recovery period. Overall group mean bodyweight gains were significantly decreased for both sexes during the treatment period but were regained in the recovery period. Significant increase of water consumption in the animals was also observed.

In the group treated at 150 mg/kg bw/day, increased body tone and slightly elevated forelimb strength was noted in 4 and 2 female animals respectively.

Reduce of bodyweight gain was also recorded for males treated with 150 and 15 mg/kg bw/day and in females treated at 15 mg/kg bw/day. However, this was considered by the study authors not to be related to the treatment.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

At the end of the treatment period, females receiving 1,000 mg/kg bw/day had increased triglyceride values and reduced chloride values. After two weeks of recovery these animals still had triglyceride values slightly higher than control, however, chloride values were considered to be similar to the control. The females in this group had increased group mean alanine aminotransferase (ALT) during the treatment which was not fully recovered after the recovery period. The females receiving 1,000 mg/kg bw/day also had reduced group mean total protein and albumin values and increased albumin/globulin ratio. Total protein and albumin values were not fully recovered, however, the albumin/globulin ratio was recovery after the recovery period. In addition, increase of ketone levels were noted for females receiving 1,000 mg/kg bw/day which was recovered after the recovery period.

Males and females receiving 1,000 mg/kg bw/day had an increased group mean total urinary volume with reduced pH during the treatment. Males receiving 150 mg/kg bw/day were also considered to have reduced pH values at the end of the treatment period. At the end of the recovery period, all parameters were considered to be

recovered.

Effects in Organs

The macroscopic examination revealed enlargement of the liver and thymus in an increased incidence in females and increased kidney weights for both sexes, seen in the animals treated with 1,000 mg/kg bw/day compared to the control group. However these weight values were similar to control in the recovery group after two weeks.

Centrilobular hepatocyte hypertrophy was seen in some female animals given 1,000 mg/kg bw/day, this correlated with the increased adjusted group mean liver weights, macroscopic enlargement and increases in alanine aminotransferase, triglyceride and ketones. There was evidence of recovery for these changes after the recovery period. These findings were considered to be treatment related.

In animals treat at 1,000 mg/kg bw/day, focal areas of either erosion or ulceration of the forestomach, with associated epithelial hyperplasia, hyperkeratosis and sub-mucosal inflammation were recorded and considered to be related to the treatment. There was evidence of recovery after two weeks. The study authors suggested that the erosion or ulceration of the forestomach could be caused by stress or by action of the test chemical via a local irritation effect or via pharmacological effects.

There was evidence of an effect upon the kidneys with increased kidney weights being observed in both females and males receiving 1,000 mg/kg bw/day and an increase in water consumption that might result in reduced urinary pH, increased urinary volume increase and low plasma chloride level observed in animals. However, in the absence of associated histopathological findings and in the presence of evidence of reversibility, these findings were considered to be related to the treatment but not to be adverse.

Remarks – Results	The changes in liver weights, histopathological stomach effects, and reduced body weight gain in the high dose group were considered to be adverse. Some treatment related disturbances in urinary pH in male animals and forelimb grip strength in female animals were noted in the 150mg/kg/day group, however these changes were considered by the study authors to be minor and not toxicologically significant.
CONCLUSION	The No Observed Adverse Effect Level (NOAEL) for systemic toxicity was established by the study authors as 150 mg/kg bw/day in this study, based on adverse effects observed at the highest dose level of 1,000 mg/kg bw/day.
TEST FACILITY	Huntingdon Life Sciences (2009e)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure and pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA (pKM101)
Metabolic Activation System	S9 fraction from phenobarbital and 5,6-benzoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 5–5,000 µg/plate b) Without metabolic activation: 2–5,000 µg/plate
Vehicle	Dimethyl sulphoxide (DMSO)
Remarks – Method	No significant protocol deviations. The purity of the test substance was recorded as 99.5%. No preliminary test was performed. Main Test 1 was conducted as a plate

incorporation assay. Main Test 2 was undertaken as a pre-incubation assay.

2-Nitrofluorene, sodium azide, 9-aminoacridine and 4-nitroquinoline-1-oxide were used as positive controls in the absence of metabolic activation while benzo[a]pyrene and 2-aminoanthracene were used as positive controls in the presence of metabolic activation. DMSO was used as negative control.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/plate) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 5,000	> 5,000	negative
Test 2	≥ 5,000	> 5,000	negative
Present			
Test 1	> 5,000	> 5,000	negative
Test 2	> 5,000	> 5,000	negative

Remarks - Results

Stability and homogeneity of the test substance in the vehicle was not determined as part of the study. Analysis of achieved concentration was also not performed.

No precipitation of the test substance was noted throughout the study.

No signs of toxicity were observed towards the tester strains in the first mutation test following exposure to the notified chemical. However, toxicity was observed as a slight thinning of the background lawn of non-revertant colonies in the second mutation test following exposure to the notified chemical at 5,000 μg/plate in the absence of S9 mix.

The positive 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

Huntingdon Life Sciences (2008d)

B.10. Genotoxicity – *in vitro* mammalian chromosome aberration test

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: Human
Cell Type/Cell Line: Lymphocytes
Metabolic Activation System: S9 fraction from phenobarbital and 5,6-benzoflavone induced rat liver.
Vehicle: Dimethyl sulphoxide (DMSO)
Remarks - Method: No significant deviations to the protocol were noted. The purity of the test substance was recorded as 99.5%.

Vehicle and positive controls (mitomycin C without metabolic activation and cyclophosphamide with metabolic activation) were used in parallel with the test material

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	12.2, 24.39*, 48.78, 97.56, 195.13*, 390.25*, 780.5, 1561	3 h	18 h
Test 2	12.5, 50, 100, 150*, 200*, 250*, 300, 350, 400, 450	21 h	18 h
Present			
Test 1	12.2, 24.39*, 48.78, 97.56*, 195.13, 390.25*, 780.5, 1561	3 h	18 h
Test 2	12.5, 50, 100, 200, 300, 400, 500, 600*, 700*, 800*	3 h	18 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	≥ 390.25	-	> 1,561	negative
Test 2	-	≥ 250	> 450	negative
Present				
Test 1	≥ 390.25	-	> 1,561	negative
Test 2	-	≥ 800	> 800	negative

Remarks - Results

Stability and homogeneity of the test substance in the vehicle was not determined as part of the study. Analysis of achieved concentration was also not performed.

In both the absence and the presence of S9 mix, the notified chemical caused no statistically significant increases in the proportion of cells with chromosomal aberrations at the dose levels tested, when compared with the vehicle control. Positive controls showed a statistically significant increase in the proportion of aberrant cells, demonstrating the efficiency of the S9 mix and the sensitivity of the test system.

CONCLUSION

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

TEST FACILITY

Huntingdon Life Sciences (2008e)

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 (Worlingworth, UK).
Exposure Period	28 days.
Auxiliary Solvent	None.
Analytical Monitoring	Theoretical Oxygen Demand (ThOD).
Remarks - Method	No significant deviation in protocol.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
4	7	4	71
7	10	7	85
14	19	14	125
21	64	21	97
28	74	28	94

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate reached the threshold level of 60% by 3 days and near complete degradation by 28 days (94%). Therefore, the test indicates the suitability of the inoculums. The notified chemical attained 74% degradation by 28 days, but failed the 10-day window (41%). A degradation plateau was not achieved by 28 days. Therefore, the notified chemical cannot be classified as readily biodegradable according to the OECD (301B) guideline. However, the notified chemical exhibited inherent, primary biodegradability.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Huntingdon Life Sciences (2009f).

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	*Brachydanio rerio* (zebra fish).
Exposure Period	96 hours.
Auxiliary Solvent	None.
Water Hardness	126 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*
0	0	7	0	0	0	0	0	0
1	1.11	7	0	0	0	0	0	0

1.8	2.05	7	0	0	0	0	0	0
3.2	3.21	7	0	0	0	0	0	0
5.6	5.82	7	0	0	0	0	1	2
10	10.45	7	0	0	0	1	4	7

LC50 6.73 mg/L at 96 hours.
NOEC 3.21 mg/L at 96 hours.
Remarks – Results All validity criteria for the test were satisfied. The 96 h LC50 and NOEC for fish were determined to be 6.73 mg/L and 3.21 mg/L, respectively, based on measured concentrations.

CONCLUSION Under the study conditions, the notified chemical is considered to be toxic to fish on an acute basis.

TEST FACILITY Safety Evaluation Center (2010).

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 202 *Daphnia sp*. Acute Immobilisation Test – Static.
Species *Daphnia magna.*
Exposure Period 48 hours.
Auxiliary Solvent None.
Water Hardness 220 mg $CaCO_3$/L.
Analytical Monitoring GC-MS.
Remarks - Method No significant deviation in protocol.

RESULTS

Concentration mg/L			*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*			*24 h*	*48 h*
	0 h	*48 h*			
Control	Control	Control	20	0	0
3.41	2.65	2.69	20	0	0
7.51	6.83	6.75	20	0	0
16.5	12.8	15.9	20	0	0
36.4	28.1	35.6	20	95	100
80	64.9	77.4	20	95	100

EC50 21.3 mg/L (95% CL 14.3-31.6 mg/L) at 48 hours.
NOEC 14.3 mg/L at 48 hours.

Remarks - Results All validity criteria for the test were satisfied. The actual concentrations of the notified chemical were measured at 0 and 48 hours within the 48 h test period. The test solutions were not renewed during the 48 h test period. The 48 h EC50 and NOEC for daphnids were determined to be 21.3 mg/L and 14.3 mg/L, respectively, based on measured concentrations.

CONCLUSION Under the study conditions, the test chemical is considered to be harmful to daphnids on an acute basis.

TEST FACILITY Huntingdon Life Sciences (2010c).

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 201 Freshwater Alga, Growth Inhibition Test.
Species *Pseudokirchneriella subcapitata* (green alga).

Exposure Period	72 hours.
Concentration Range	Nominal: 0.441-50 mg/L. Actual: 0.196-37.4 mg/L.
Auxiliary Solvent	None.
Water Hardness	Not reported.
Analytical Monitoring	GC-MS.
Remarks - Method	The definitive test was conducted at 20.8-24.0 °C, outside the 21-24 °C range stated in the protocol. The coefficient of variation for the average specific growth rates in the control cultures between 48 and 72 hours was 37%, exceeding the 35% criteria stated in the protocol. Neither deviation from protocol was deemed to have had a significant impact on the validity or integrity of the study. All other validity criteria were met and satisfied.

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*
14.3 (95% CL 11.7-16.7)	1.19	27.7 (95% CL 25.0-28.4)	1.19

Remarks - Results	All validity criteria for the test were satisfied. The actual concentrations of the notified chemical were measured at 0 and 72 hours within the 72 h test period. The 72 h E_bC50 and E_rC50 were determined to be 14.3 and 27.7 mg/L, respectively, based on measured concentrations. The 72 h NOE_rC was determined to be 1.19 mg/L.
CONCLUSION	Under the study conditions, the notified chemical is considered to be harmful to algae on an acute basis.
TEST FACILITY	Huntingdon Life Sciences (2010d).

C.2.4. 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: 10-1000 mg/L. Actual: Not determined.
Remarks – Method	Actual volumes of the notified chemical added to the test mixtures were slightly higher than the specified volumes stated in the protocol. The differences in volumes were not deemed to have had a significant impact on the validity or integrity of the study. All other validity criteria were met and satisfied. Chemical 3,5-dichlorophenol was used as the reference control. The respiration rate was determined by measurement of BOD during the test after 3 hours of exposure.
RESULTS	
EC50	210 mg/L (95% CL 176-248 mg/L) at 3 hours.
Remarks – Results	All validity criteria for the test were satisfied. Concentration-related inhibition of respiration rates were observed at concentrations between 100-1000 mg/L, with 94-96% inhibition at 1000 mg/L. The 3 h EC50 was determined to be 210 mg/L, based on measured 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	Huntingdon Life Sciences (2009g).

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