File No: LTD/1876

May 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

5*H*-Cyclopenta[*h*]quinazoline, 6,6a,7,8,9,9a-hexahydro-7,7,8,9,9-pentamethyl-

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.

This Public Report is 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/1876	International Flavours and Fragrances (Australia) Pty Ltd	5*H*-Cyclopenta[*h*]quinazoline, 6,6a,7,8,9,9a-hexahydro-7,7,8,9,9-pentamethyl-	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 of 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*
Acute toxicity, oral (Category 4)	H302 – Harmful if swallowed
Skin irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

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 phrases:

R22: harmful if swallowed
R38: Irritating to skin
R43: May cause sensitisation by skin contact

The environmental hazard classification according to the Globally Harmonised System of 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 1	H400 – Very toxic to aquatic life
Chronic Category 1	H410 – Very toxic to aquatic life with long lasting effects

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 ≤ 0.22% concentration in body lotions, at ≤ 0.7% concentration in fine fragrances or at ≤ 0.05% concentration in household and other cosmetic 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

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Acute toxicity, oral (Category 4): H302 – Harmful if swallowed
  - Skin irritation (Category 2): H315 – Causes skin irritation
  - Skin sensitisation (Category 1): H317 – May cause an allergic skin reaction

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.

Health Surveillance

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

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 during reformulation:
  - Enclosed, automated processes, where possible
  - Adequate 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 during reformulation:
  - Avoid contact with skin and eyes
  - Avoid inhalation

- 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 during reformulation:
  - Coveralls
  - Impervious gloves
  - Respiratory protection, if inhalation exposure may occur

  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 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 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 exceeds or is intended to exceed 0.22% in body lotions, 0.7% in fine fragrances or 0.05% in household and other cosmetic products;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from 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 a product containing the notified chemical provided by the notifier were 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: particle size, dissociation constant and hydrolysis as a function of pH.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA and China

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
AmberTonic

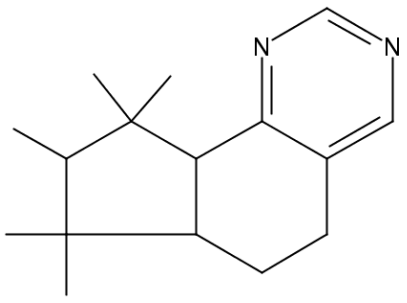
CAS NUMBER
1392325-86-8

CHEMICAL NAME
5*H*-Cyclopenta[*h*]quinazoline, 6,6a,7,8,9,9a-hexahydro-7,7,8,9,9-pentamethyl-

OTHER NAMES
Fret 10-0199
TM 12-206
HPM Quinazoline

MOLECULAR FORMULA
$C_{16}H_{24}N_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
244.38 Da

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

3. COMPOSITION

DEGREE OF PURITY
80-95%

IDENTIFIED IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)

Chemical Name (6aR,9aS)-7-ethyl-7,9,9-trimethyl-6,6a,7,8,9,9a-hexahydro-5*H*-cyclopenta[*h*]quinazoline
CAS No. unassigned *Weight %* 3.9

Chemical Name (6aR,9aR)-7-ethyl-7,9,9-trimethyl-6,6a,7,8,9,9a-hexahydro-5*H*-cyclopenta[*h*]quinazoline
CAS No. unassigned *Weight %* 2.3

Chemical Name (6aR,9aS)-9-ethyl-7,7,9-trimethyl-6,6a,7,8,9,9a-hexahydro-5*H*-cyclopenta[*h*]quinazoline
CAS No. unassigned *Weight %* 1.9

Chemical Name *N*-(1,1,2,3,3-pentamethyl-2,3,5,6,7,7a-hexahydro-1*H*-inden-4-yl)formamide
CAS No. unassigned *Weight %* 1.4

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: White solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	35.4 - 51.6°C	Measured
Boiling Point	339°C at 100.9 kPa	Measured
Density	1,060 kg/m^3 at 24 °C	Measured
Vapour Pressure	2.9 × 10^{-5} kPa at 25 °C	Measured
Water Solubility	9.82 × 10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionalities
Partition Coefficient (n-octanol/water)	5.19 – 5.66	Measured
Adsorption/Desorption	log K_{oc} = 4.364 at 25°C	Estimated data (EPISuite KOCWIN v4.11)
Dissociation Constant	Not determined	The notified chemical does not contain any functional groups that are expected to dissociate in water.
Particle Size	Not determined	Not sold or used in a granular form
Surface tension	53.4 mN/m at 21°C	Measured
Flash Point	168 °C at 102.2 kPa	Measured
Flammability	Not highly flammable	Measured
Autoignition Temperature	366 °C	Measured
Explosive Properties	Not explosive	Measured
Oxidising Properties	Not oxidising	Measured

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 within Australia. The notified chemical will be imported into Australia as a component of fragrance oils 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 ≤ 10% concentration packaged in polypropylene-lined steel drums (usually in the size of 208 L) for transportation by road. Finished consumer products containing ≤ 0.7% notified chemical 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 (at 0.22% concentration in body lotions, at ≤ 0.7% concentration in fine fragrances and at ≤ 0.05% concentration in household and other cosmetic products).

OPERATION DESCRIPTION
The notified chemical will be imported in fragrance oils at ≤ 10% concentration for reformulation into cosmetic and household products.

Reformulation
When reformulated, the notified chemical will be blended into end-use cosmetic and household products at customer sites. Procedures will vary depending on the nature of the consumer 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 fragrance oils containing notified chemical into a container and then add the amount directly into a mixing tank, with periodic sampling for quality control purposes also carried out during the reformulation process. Automated processes may include mixing and filling of end-use containers with finished products.

End-use

Household products
Finished household products containing the notified chemical at ≤ 0.05% 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.

Cosmetic products
Finished cosmetic products containing the notified chemical at ≤ 0.7% 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 could be applied by hand or by using an applicator (including spray 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	Incidental exposure only	Incidental exposure only
Plant operators - mixing compounding	4	250
Plant operators - drum handling	1	250
Plant operators - drum cleaning/washing	2	200
Plant operators - equipment cleaning/washing	2	250
Plant operators - quality control	1	250
Professional users – (e.g. hairdressers, beauty salon workers, cleaners)	Unspecified	Unspecified

EXPOSURE DETAILS

Transport and storage
Transport and storage workers may come in contact with the notified chemical either at ≤ 10% concentration in fragrance oils or at various concentrations in consumer products, only in the event of an unlikely accidental rupture of containers.

Reformulation
During reformulation into consumer products, dermal, ocular and inhalation exposure of workers to the notified chemical at ≤ 10% 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 ≤ 0.7% concentration may occur in professions where the services provided involve the application of cosmetic and household products for 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 ≤ 0.7% concentration through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while inhalation exposure (e.g. through the use of spray products) and accidental oral and ocular exposure 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, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) of 100% was assumed for the notified chemical for calculation purposes. 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%. 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	0.22	1	0.2688

Product type	Amount (mg/day)	C (%)	Retention Factor (RF) (unitless)	Daily systemic exposure (mg/kg bw/day)
Face cream	1540	0.05	1	0.0120
Hand cream	2160	0.05	1	0.0169
Fine fragrances	750	0.7	1	0.0820
Deodorant spray	1430	0.05	1	0.0112
Shampoo	10460	0.05	0.01	0.0008
Conditioner	3920	0.05	0.01	0.0003
Shower gel	18670	0.05	0.01	0.0015
Hand wash soap	20000	0.05	0.01	0.0016
Hair styling products	4000	0.05	0.1	0.0031
Facial cleanser	800	0.05	0.01	0.0001
Total				0.3983

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	0.05	0.95	10	0.0017
Fabric softener	90	0.05	0.95	10	0.0007
Total					0.0024

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	0.05	1980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.05	1980	0.009	0.01	0.03	0.0001
All-purpose cleaner	1	0.05	1980	1	0.01	0.007	0.0011
Total							0.0012

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	0.05	20	1	20	50	1	10	0.0016

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 0.4035 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 = 300 - 2000 mg/kg bw; harmful
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Skin irritation (in vitro)	irritating
Skin corrosion (in vitro)	non-corrosive
Eye irritation (in vitro)	non-irritating
Mouse, skin sensitisation – Local lymph node assay (LLNA)	evidence of sensitisation
Human, skin sensitisation – RIPT*	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 300 ppm (equating to 22.1 mg/kg bw/day for males and 22.6 mg/kg bw/day for females)
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration	non-clastogenic
Rat, reproductive and developmental toxicity	systemic/reproductive NOAEL = 600 ppm (equating to 37 mg/kg bw/day for males and 40.4 mg/kg bw/day for females)

* tested on two formulations containing 10% notified chemical (concentration provided by the notifier)

Toxicokinetics.
Limited data are available on the toxicokinetic properties of the notified chemical. Based on the low molecular weight (< 500 Da), water solubility (9.82×10^{-3} g/L at 20 °C) and partition coefficient (log Pow = 5.19-5.66) of the notified chemical, there is potential for the chemical to cross the gastrointestinal (GI) tract by passive diffusion or to be dermally absorbed. Additionally, there is potential for absorption via the lungs.

Acute toxicity.
The notified chemical was found to be acutely harmful via the oral route in a study conducted in rats. As well as the reported mortality, signs of systemic toxicity included hunched posture, lethargy, pilo-erection, decreased respiratory rate, laboured respiration, splayed or tiptoe gait, body tremor, ataxia, dehydration, diarrhoea and emaciation.

The notified chemical is of low acute dermal toxicity, based on a study conducted in rats at 2000 mg/kg.

No acute inhalation toxicity data were submitted for the notified chemical. An analogue of the notified chemical was found to be of low toxicity in a study conducted in rats (NICNAS, 2015).

Irritation
The notified chemical was found not to be corrosive but is irritating to the skin, based on two *in vitro* studies conducted using the reconstructed human epidermis model.

In an *in vitro* reconstructed human cornea model study the notified chemical was found to be non-irritating to eyes.

Sensitisation
The notified chemical was a skin sensitiser in mice (local lymph node assay: stimulation indices of 1.66, 5.34 and 7.56 at 10%, 25% and 50%, respectively). The EC_3 value was calculated to be 15%. In a human repeat insult patch test (HRIPT), two formulations containing 10% notified chemical did not elicit a positive sensitisation response.

Repeated dose toxicity.
An oral (dietary) repeated dose toxicity study on the notified chemical was conducted in rats, in which the test substance was administered at 300, 800 and 1,200 ppm (equating to 22.1, 59.7 and 87.4 mg/kg bw/day for males and 22.6, 59.1 and 81.4 mg/kg bw/day for females) for 28 consecutive days, with a 14-day recovery period for high dose and control animals

A No Observed Effect Level (NOEL) was not established for the notified chemical, based on treatment related effects in the stomach (stomach changes revealed microscopically).

Reductions in body weight gains, food consumption and food efficiency were noted and were considered by the study authors as a result of treatment-related local irritation rather than systemic toxicity.

Microscopic kidney changes and increased kidney weight were noted in male animals and were considered by the study authors to be directly linked to the accumulation of alpha 2µ-globulin, which is unique to the male rat and therefore to be of no relevance to man.

Liver weight increases, microscopic liver and thyroid changes and associated blood chemistry changes were noted in animals of either sex from all treatment groups, with incidence and severity of changes at 800 ppm and 1200 ppm significantly higher than 300 ppm. Although these changes were considered by the study authors to be likely to represent adaptive changes and not to represent serious damage to health, the effects observed at 800 ppm and 1200 ppm cannot be ruled out as adverse effects given the extent of the liver functional changes.

The No Observed Adverse Effect Level (NOAEL) was therefore established as 300 ppm (equivalent to 22.1 mg/kg bw/day for males and 22.6 mg/kg bw/day for females), the lowest dose tested, in this study.

Mutagenicity/Genotoxicity.
The notified chemical was negative in a bacterial reverse mutation assay and in an *in vitro* chromosomal aberration study in human peripheral lymphocytes.

Toxicity for reproduction.
In a Reproduction/Developmental Toxicity Screening test in rats with dietary administration (OECD TG 421), the No Observed Adverse Effect Level (NOAEL) for systemic toxicity was established as 600 ppm (37 mg/kg bw/day for males/40.4 mg/kg bw/day for females) in this study, based on the treatment-related effects on body weight development for both male and female animals at 1000 ppm (61.7 mg/kg bw/day for males/64.6 mg/kg bw/day for females). The NOAEL for reproductive toxicity was also established as 600 ppm (40.4 mg/kg bw/day), based on an increase in post implantation loss and reduction in litter sizes and total litter weights at the high dose of 1000 ppm (64.6 mg/kg bw/day). The study authors commented that a relationship between the litter size/litter weights and reduced maternal body weight gain cannot be ruled out.

Health hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of 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 (Category 4)	H302 - Harmful if swallowed
Skin Irritation (Category 2)	H315 - Causes skin irritation
Skin Sensitisation (Category 1)	H317 - May cause sensitization by skin contact

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
R43: May cause sensitisation by skin contact

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available toxicological information and use pattern, the critical health effects of the notified chemical are as a skin irritant and skin sensitiser. Adverse effects could also occur after repeated exposure.

Reformulation
During reformulation, workers may be at risk of sensitisation and skin irritation effects when handling the notified chemical at ≤ 10% concentration. It is anticipated by the notifier that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible and appropriate PPE (coveralls, imperious gloves, eye protection and respiratory protection) will be used to limit worker exposure.

Therefore, under the occupational settings described, the risk to the health of 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 and household products containing the notified chemical to clients (*e.g.*, hairdressers, beauty salon workers and cleaners) may be exposed to the notified chemical at concentrations up to 0.7%. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, the risk to such workers is expected to be of a similar or lesser extent than that experienced by consumers using the various products containing the notified chemical.

6.3.2. Public Health

Cosmetic and household products containing the notified chemical at ≤ 0.7% concentration will be available to the public. The main route of exposure is expected to be dermal and inhalation, with some potential for accidental ocular or oral exposure.

Irritation
The notified chemical is a skin irritant. However, skin irritation effects are not expected from use of the notified chemical at the proposed low concentrations in cosmetic and household products.

Sensitisation
An animal sensitisation study (LLNA) and a human sensitisation study were provided for the notified chemical and based on the results of the LLNA study the notified chemical is considered as a sensitiser. When tested at up to 10% concentration in a human repeat insult patch study, the notified chemical was not a skin sensitiser.

Proposed methods for the quantitative risk assessment of dermal sensitisation have been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). As is shown in the table below, the Consumer Exposure Level (CEL) from use of the notified chemical in leave-on and rinse-off cosmetic products may be estimated (SCCS, 2012 and Cadby *et al*, 2002). Consideration of each of the studies and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 39.75 µg/cm^2. In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16), a use and time factor (3.16) and a database factor (1), giving an overall safety factor of ~100.

Product type	Proposed usage concentration (%)	CEL (µg/cm^2)	AEL (µg/cm^2)	Recommended usage concentration (%)
Leave-on cosmetics (assumed: fine fragrances)	0.7	26.25	39.75	≤ 0.7
Rinse-off cosmetics (assumed: hand wash soap)	0.05	0.12	39.75	≤ 0.05
Household product (assumed: cleaning liquid)	0.05	0.09	39.75	≤ 0.05

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical at ≤ 0.7% concentration in leave-on (using fine fragrances as a worst case example), at ≤ 0.05% concentration in rinse-off cosmetic products (using hand wash soap as a worst case example) and at ≤ 0.05% concentration in household products (using cleaning liquid as a worst case example) is not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Repeated dose toxicity
The repeated 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 0.4035 mg/kg bw/day (see Section 6.1.2). Based on the likely adaptive nature of the effects seen in the repeated dose study, it is considered appropriate to use the NOAEL of 40.4 mg/kg bw/day derived from a reproductive toxicity screening study on the notified chemical for quantitative risk assessment. Using this value, the margin of exposure (MOE) was estimated to be 100.12. A MOE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences. Therefore, the MoE is considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 0.22% concentration in body lotions, at ≤ 0.7% concentration in fine fragrances and at ≤ 0.05% concentration in household and other cosmetic 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 not be manufactured in Australia, so there will be no environmental release associated with this activity. The notified chemical will be imported into Australia in the form of fragrance preparations for further reformulation into end-use cosmetic and household products or as a component of end-use products. Environmental release of the notified chemical during transportation and storage will be limited to accidental spills or leaks of drums, which is expected to be minimal.

A typical blending operation will be highly automated in a fully enclosed/contained environment. Potential sources of release include spills, equipment washing, and container residues. A total < 1% of waste may be generated as a result of spills. It is expected that equipment will be cleaned using water that will be reused for subsequent operations. The average amount of residue in empty containers is estimated to be < 1%. Any wash waters resulting from the blending/cleaning operations are likely to be discharged to an on-site wastewater treatment plant and/or a local municipal treatment plant in accordance with local, State and Federal regulations. There may be minor air fugitive emissions with product sampling and consumer product compounding operations but exposures to these emissions are expected to be very low.

RELEASE OF CHEMICAL FROM USE

The notified chemical will enter the aquatic compartment during use of the various products into which it will be incorporated. Cosmetic products are expected to be washed off the hair and skin and will enter the aquatic environment diluted in water. Cleaning products will also be diluted in water and will enter the aquatic environment. It is anticipated that the majority of the notified chemical released will enter into sewer systems.

It is estimated that a maximum of 3% of the consumer products may remain in the consumer containers that will be sent for disposal.

RELEASE OF CHEMICAL FROM DISPOSAL

Empty containers containing the notified chemical at blending facilities will be recycled or disposed of through an approved waste management facility. Empty product containers are expected to be disposed of to landfill.

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 (0% and 3.6% in 28 days with different test methods). For details of the environmental fate studies, please refer to Appendix C.

When released to soil or landfill the notified chemical is expected to associate strongly with organic matter in soil and remain *in situ* based on its very low water solubility, and high affinity for organic phases with a high n-octanol/water partition coefficient (log P_{ow} > 5) and high adsorption/desorption coefficient (log K_{oc} > 4). Based on its surface active property and the measured bioconcentration factor (BCF) for an acceptable analogue (BCF = 677 for low concentration and 884 for high concentration), the notified chemical is not expected to bioaccumulate. In surface waters the notified chemical is expected to disperse and degrade through abiotic and biotic processes to form water and oxides of carbon and nitrogen.

The notified chemical is expected to be moderately volatile due to its vapour pressure of 0.029 Pa. The half-life of the notified chemical in air is calculated to be 12.61 hours based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, in the event of release to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

The notified chemical is expected to partition to phase boundaries as it is surface active. 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} = 4.36), and is expected to eventually degrade to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated assuming a worst case scenario of 100% release of the notified chemical into sewer systems nationwide and no removal from 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	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:	0.61	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 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 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 20.2 µg/kg and 40.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below. The provided studies include acute toxicity of the notified chemical to fish, aquatic invertebrates and algae. Details of these studies can be found in Appendix C.

Endpoint	Result	Assessment Conclusion
Fish Toxicity (96 hours)	LC_{50} = 0.64 mg/L	Very toxic to fish
Daphnia Toxicity (48 hours)	EC_{50} = 1.0 mg/L	Toxic to aquatic invertebrates
Algal Toxicity (72 hours)	ErC_{50} = 3.4 mg/L	Toxic to algae

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is very toxic to fish, toxic to aquatic invertebrates and algae, and is formally classified as ‘Acute Category 1: Very toxic to aquatic life’. Based on the acute toxicity, lack of ready biodegradability and low bioaccumulation potential of the notified chemical, it is classified ‘Chronic Category 1: Very toxic to aquatic life with long lasting effects.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was calculated using the most sensitive toxicity endpoint of the notified chemical among the three test species (LC50=0.64 mg/L for fish). A conservative assessment factor of 100 was used since three trophic levels of ecotoxicological data (fish, invertebrates and algae) have been provided for the PNEC analysis.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish).	0.64	mg/L
Assessment Factor	100	
Mitigation Factor	1	

PNEC:	6.40	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated for a worst case discharge scenario based on the predicted PEC and PNEC.

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	0.61	6.4	0.095
Q - Ocean:	0.06	6.4	0.009

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment (Q < 1) indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual importation quantity. The notified chemical is not expected to be readily biodegradable or bioaccumulate in the environment. Therefore, the notified chemical is unlikely to result in ecotoxicologically significant concentrations in the aquatic environment on the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 35.4-51.6°C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	Determined by differential scanning calorimetry
Test Facility	Harlan (2013a)

Boiling Point 339 ± 2 °C at 100.9 kPa

Method	OECD TG 103 Boiling Point.
Remarks	Determined by differential scanning calorimetry
Test Facility	Harlan (2014a)

Density 1,060 kg/m^3 at 24 ± 0.5 °C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	Pycnometer method
Test Facility	Harlan (2014a)

Vapour Pressure 2.9×10^{-5} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure.
Remarks	Determined using a vapour pressure balance
Test Facility	Harlan (2014b)

Surface tension 53.4 mN/m at 21± 0.5 °C

Method	OECD TG 115 Surface tension.
Remarks	Concentration: 90% saturation
Test Facility	Harlan (2014a)

Water Solubility 0.00982 g/L at 20 °C

Method	OECD TG 105 Water Solubility. EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Column Elution Method. As the water solubility was determined during the preliminary test to be below 10^{-2} g/L column elution test has been performed.
Test Facility	Harlan (2013a)

Partition Coefficient (n-octanol/water) log Pow = 5.19 – 5.66 at 20 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method. Multiple peaks between log Pow values of 4.10 and 5.84 has been observed. Two peaks with Log Pow = 5.19 and 5.66 have been considered as representation of the main constituents.
Test Facility	Harlan (2013a)

Flash Point 168 ± 2 °C at 102.2 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Closed cup method
Test Facility	Harlan (2014c)

Flammability Not highly flammable

Method	EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks	Determined by measuring burning rate

Test Facility Harlan (2014c)

Autoignition Temperature 366 ± 5 °C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility Harlan (2014c)

Explosive Properties Predicted negative

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks Predicted based on the chemical structure
Test Facility Harlan (2014c)

Oxidizing Properties

Method EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids).
Remarks Predicted based on the chemical structure
Test Facility Harlan (2014c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure.
Species/Strain	Rat/Wistar
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations. Results of the sighting study and main study were reported in combination.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5F	2,000	3/5
2	6F	300	1/6

LD50	300-2000 mg/kg bw
Signs of Toxicity	2000 mg/kg bw group: 2 animals were found dead 1 or 4 days after dosing and 1 animal was killed for humane reason due to appearance of clinical sings of toxicity. Signs of systemic toxicity included hunched posture, lethargy, pilo-erection, decreased respiration rate, laboured respiration, splayed or tiptoe gait, occasional body tremors, ataxia, dehydration, diarrhoea and emaciation. 300 mg/kg bw group: 1 animal was killed for humane reason due to appearance of clinical sings of toxicity. Signs of systemic toxicity included hunched posture, lethargy, pilo-erection and tiptoe gait. Additional signs of decreased respiration rate, laboured respiration, splayed gait, prostration and hypothermia were noted in the humanely killed animal.
Effects in Organs	2000 mg/kg bw group: abnormalities noted at necropsy in the animals that died or were humanely killed included dark liver or patchy pallor of the liver, dark kidneys, solid substance in the stomach, epithelial sloughing of the gastric mucosa and hemorrhagic non-glandular epithelium of the stomach. 300 mg/kg bw group: abnormalities noted at necropsy in the humanely killed animal included clear liquid or solid substance in the stomach and thickened non-glandular epithelium. No abnormalities were noted at necropsy in the animals killed at the end of experiment.
Remarks - Results	The surviving animals in the 2000 mg/kg bw group showed body weight loss in the first week and expected weight gain in the second week. The surviving animals in the 300 mg/kg bw group showed weight gain over the observation period.

CONCLUSION	The notified chemical is of harmful via the oral route.
TEST FACILITY	Harlan (2014d)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/Wistar
Vehicle	Arachis oil BP

Type of dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations. Results of the sighting study and main study were reported in combination.

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	Very slight erythema with or without oedema was noted at the treated sites of male animals up to 3 days post-application and very slight to well-defined erythema with or without oedema was noted for treated female animals up to 4 days post-application. Crust formation was noted at the test site of one female 5-7 days post-application.
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	Four female animals showed body weight loss in the first week and expected weight gain in the second week. The remaining animals showed expected body weight gains over the study period.

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

TEST FACILITY Harlan (2015a)

B.3. Irritation – skin (in vitro)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 439 In vitro Skin Irritation: Reconstructed Human Epidermis Test Method
EPISKIN™ Reconstructed Human Epidermis Model

Vehicle	Distilled water
Remarks - Method	In a preliminary test the test substance was shown to directly reduce MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolim bromide]. Therefore, the study was performed in parallel on viable and water-killed tissues. The test substance (10 mg) was applied to the tissues (pre-moistened with 5 µL distilled water) in triplicate. Following exposure period of 15 minutes (room temperature), the tissues were rinsed, treated with MTT and then incubated at 37 °C for 3 hours. Negative and positive controls were run in parallel with the test substance: - Negative control: phosphate buffered saline - Positive control: 5% sodium dodecyl sulphate in distilled water

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.849	100	10.8
Test substance	0.339	40.0	5.6
Positive control	0.065	7.6	0.9

OD = optical density; SD = standard deviation

Remarks - Results	The results from the additional procedure using water-killed tissues showed a negligible interference due to the test substance's ability to directly reduce MTT. It was considered by the study authors to be unnecessary to use the results from the additional procedure for

quantitative correction.

The relative mean viability of the tissues treated with the test substance was ≤ 50% (predicted as irritant according to the criteria).

The positive and negative controls gave satisfactory results, confirming the validities of the test systems.

CONCLUSION The notified chemical was irritating to the skin under the conditions of the test.

TEST FACILITY Harlan (2014e)

B.4. Corrosion – skin (in vitro)

TEST SUBSTANCE Notified chemical

METHOD OECD No 431 In Vitro Skin Corrosion: Human Skin Model Test.
EPISKIN™ Reconstructed Human Epidermis Model

Vehicle 0.9% sodium chloride in water

Remarks - Method In a preliminary test the test substance was shown to directly reduce MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolim bromide]. Therefore, the study was performed in parallel on viable and water-killed tissues.

The test substance (20 mg) was applied to the tissues (then moistened with 100 µL 0.9% sodium chloride in water) in duplicate. Following exposure periods of 3, 60 and 240 minutes (room temperature), the tissues were rinsed, treated with MTT and then incubated at 37 °C for 3 hours.

Negative and positive controls were run in parallel with the test substance:

- Negative control: 0.9% sodium chloride in water
  Positive control: glacial acetic acid

RESULTS

Test material	*Mean OD_{562} of duplicate tissues*	*Relative mean Viability (%)*
Negative control	0.871	100
Test substance (3min exposure)	0.971	111.5
Test substance (60min exposure)	1.108	127.2
Test substance (240 min exposure)	1.123	128.9
Positive control	0.052	6.0

OD = optical density; SD = standard deviation

Remarks - Results The results from the additional procedure using water-killed tissues showed a negligible interference due to the test substance's ability to directly reduce MTT. It was considered by the study authors to be unnecessary to use the results from the additional procedure for quantitative correction.

The relative mean viability of the tissues treated with the test substance for 240 minutes was ≥ 35% (predicted as non-corrosive according to the criteria).

The positive and negative controls gave satisfactory results, confirming the validities of the test systems.

CONCLUSION The notified chemical was non-corrosive to the skin under the conditions of the test.

TEST FACILITY Harlan (2014f)

B.5. Irritation – eye (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	According to reference (Van Goethem et al., 2006) SkinEthic Reconstituted Human Corneal Epithelium Model
Vehicle	None
Remarks - Method	In a preliminary test the test substance was shown to directly reduce MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolim bromide]. Therefore, the study was performed on freeze-killed tissues in addition to the normal test procedure. The test substance (30 mg) was applied to the tissues (dosed at regular timed intervals) in triplicate. Following exposure period of 10 minutes (room temperature), the tissues were rinsed, treated with MTT and then incubated at 37 °C for 3 hours. Negative and positive controls were run in parallel with the test substance: - Negative control: Solution A supplied by SkinEthic - Positive control: 2% sodium dodecyl sulphate in sterile water

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*
Negative control	1.021	100
Test substance	1.028	100.7
Positive control	0.164	16.1

OD = optical density; SD = standard deviation

Remarks - Results	The results from the additional procedure using freeze-killed tissues showed a negligible interference due to the test substance's ability to directly reduce MTT. It was considered by the study authors to be unnecessary to use the results from the additional procedure for quantitative correction. The relative mean viability of the tissues treated with the test substance was > 60% (predicted as non-irritating according to the criteria). The positive and negative controls gave satisfactory results, confirming the validities of the test systems. The negative control performed within the acceptability range. The positive control performed as expected.
CONCLUSION	The notified chemical was non-irritating to eyes under the conditions of the test.
TEST FACILITY	Harlan (2015b)

B.6. 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	Conducted in parallel with the test substance

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	3152.71 ± 1650.91	-
10%	5F	5233.81 ± 1952.43	1.66
25%	5F	16820.96 ± 2430.17	5.34
50%	5F	23833.2 ± 2369.35	7.56
Positive Control			
25%	5F	15867.33 ± 4857.65	5.03

EC3 15%

Remarks - Results In the preliminary study, there were no signs of systemic toxicity or excessive irritation (the latter was indicated by ≥ 25% increase in mean ear thickness) noted. Very slight erythema was noted on both ears at days 3 and 4.

In the main study, there were no deaths or signs of systemic toxicity observed in the test or control animals. Very slight erythema was noted on the ears of animals treated with the test substance at 25% concentration (the positive control group) at days 2 and 3.

All treated animals showed bodyweight changes comparable to those of the vehicle control group.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY Harlan (2013b)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE Formulations containing the notified chemical at 10%

METHOD Repeated insult patch test (RIPT) – Shelanski Method

Study Design Induction Procedure: Patches containing 0.2 mL 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: ~14 days
Challenge Procedure: A patch was applied to an untreated site. Patches were removed by the applicants after 24 hours. Sites were graded 24, 48, 72 and 96 hours (if exhibiting reactions) post-application.

Study Group 84F, 28M; age range 18-70 years

Vehicle None

Remarks - Method Occluded. The test substance was spread on a 3.63 cm^2 patch.

RESULTS

Remarks - Results 106/112 subjects completed the study. No withdrawals were related to the application of the test substance.

CONCLUSION The notified chemical was non-sensitising under the conditions of the test.

TEST FACILITY CRL (2015)

B.8. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rats/Wistar
Route of Administration	Oral – diet
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Basal laboratory diet
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose ppm*	*Dose mg/kg bw/day)*	*Mortality*
control	5 per sex	0	0	0/10
low dose	5 per sex	300	22.1(M)/22.6(F)	0/10
mid dose	5 per sex	800	59.7(M)/59.1(F)	0/10
high dose	5 per sex	1200	87.4(M)/81.4(F)	0/10
control recovery	5 per sex	0	0	0/10
high dose recovery	5 per sex	0	0	0/10

Mortality and Time to Death
There were no unscheduled deaths.

Clinical Observations
No clinical signs of systemic toxicity were noted. There were no treatment-related changes in the behavioural parameters and sensory reactivity and no toxicologically significant changes in functional performance.

Reductions in body weight gains and food efficiency noted for female animals in the mid-dose and high-dose groups and reductions in food consumption noted for female animals in the high-dose group were considered by the study authors as a result of treatment-related local irritation (revealed by microscopic findings) rather than systemic toxicity.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No toxicologically significant effects were seen in the haematological parameters tested.

Male animals in the high-dose group showed increases in total protein, albumin, calcium concentration and a reduction in glucose. Male animals in the mid-dose and high-dose groups showed an increase in gamma glutamyltranspeptidase. Female animals in the high-dose group showed increases in chloride and calcium concentration and a reduction in aspartate aminotransferase. All treated female animals showed increases in total protein, gamma glutamyltranspeptidase and reductions in glucose and albumin/globulin ratio. All animals in the mid-dose and high-dose groups showed an increase in cholesterol. Female animals in the low-dose group showed a statistically significant reduction in bilirubin while male animals in the low-dose group showed a statistically significant increase in alanine aminotransferase. Male animals showed a statistically significant reduction in aspartate aminotransferase following recovery. These changes in blood chemistry parameters were considered by the study authors to be likely to represent adaptive liver and thyroid changes and not to represent serious damage to health.

No treatment-related effects were noted in the urinalytical parameters.

Effects in Organs

Organ weights
Increased relative liver weights were noted for animals in all treatment groups (increase by 37.1% and 63.4% for high dose males and females respectively, by 30.5% and 41.7% for mid dose males and females respectively and by 4.5% and 15.5% for low dose males and females respectively). Male animals in the high-dose group showed a statistically significant increase in both absolute and relative kidney weight.

No toxicologically significant effects were noted for male animals in the low-dose group and in the animals following recovery.

A statistically significant increase in both absolute and relative thymus weight noted for female animals in the mid-dose group and a statistically significant reduction in absolute and relative adrenal weight and a statistically significant increase in absolute and relative heart weight noted in the recovery female animals were considered by the study authors to be due to the intergroup differences and of no toxicological importance.

Necropsy
No adverse effects were noted at necropsy.

Histopathology
Liver: Centrilobular hypertrophy was noted for animals in all treatment groups (4/5 and 5/5 in high dose males and females respectively, 3/5 and 5/5 in mid dose males and females respectively and 3/5 and 1/5 in low dose males and females respectively). Periportal vacuolation (fat-type) was noted for animals in the mid dose (2/5 and 5/5 in males and females respectively) and high dose (5/5 and 4/5 in males and females respectively) groups. Periportal cellular change (eosinophilic, homogenous cytoplasm) was noted for 5/5 males in the mid dose or high dose groups. These changes showed evidence of reversibility following recovery. Increased absolute liver weights were noted for animals in all treatment groups (increase by 41% and 45% for high dose males and females respectively, by 41.4% and 35.9% for mid dose males and females respectively and by 3% and 2.2% for low dose males and females respectively).

Kidneys: Increased incidence and severity of hyaline droplets was noted for all male animals from all treatment groups. Multifocal basophilic tubules were noted in male animals of all treatment groups. These changes persisted in recovery male animals following recovery.

Thyroids: Follicular epithelial hypertrophy was noted in animals of either sex from all treatment groups (4/5 and 5/5 in high dose males and females respectively, 4/5 and 5/5 in mid dose males and females respectively and 1/5 and 2/5 in low dose males and females respectively) and persisted in one recovery male only following recovery.

Stomach: Erosion or ulceration was present in the glandular region of female animals in the high dose group. Inflammatory change, and/or non-glandular hyperplasia were noted for female animals in the mid-dose and high-dose groups. Complete regression was noted following recovery.

Remarks – Results
Reductions in body weight gains, food consumption and food efficiency were considered by the study authors as a result of treatment-related local irritation (stomach changes revealed microscopically) rather than systemic toxicity.

The liver weight changes, microscopic liver and thyroid changes and associated blood chemistry changes noted in animals of either sex from all treatment groups were considered by the study authors to be likely to represent adaptive changes and not to represent serious damage to health. However the incidence and severity of these changes were significantly higher in the high and mid dose groups than in the low dose group, and the effects at these doses cannot be ruled out as adverse effects.

Microscopic findings of the kidney and the increased kidney weight in male animals were considered by the study authors to be directly linked to the accumulation of alpha 2µ-globulin, which is unique to the male rat and therefore to be of no relevance to man.

CONCLUSION
A No Observed Effect Level (NOEL) was not established, as treatment-related effects were noted at all dose levels tested. The No Observed Adverse Effect Level (NOAEL) was established as the lowest dose tested, which was 22.1 mg/kg bw/day for male animals and 22.6 mg/kg bw/day for female animals, based on liver-associated changes in the higher dose groups.

TEST FACILITY Harlan (2015c)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure (Test 1)/Pre incubation procedure (Test 2)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 1.5-1500 µg/plate (TA1537, TA98, TA100), 1.5-1500 µg/plate (TA1535), 15-5000 µg/plate (WP2uvrA) b) Without metabolic activation: 1.5-1500 µg/plate (TA1537, TA98, TA100), 0.15-150 µg/plate (TA1535), 15-5000 µg/plate (WP2uvrA)
Vehicle	Dimethyl sulphoxide
Remarks - Method	Positive controls: With metabolic activation: 2-aminoanthracene (TA1535, TA1537, TA100, WP2uvrA); benzo(a)pyrene (TA98) Without metabolic activation: N-ethyl-N'-nitro-N-nitrosoguanidine [TA1535, TA100, WP2uvrA]; 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 (WP2uvrA)/> 500 (TA100)	> 500	> 5000	Negative
Test 2		> 15	> 1500	Negative
Present				
Test 1	> 5000 (WP2uvrA)/> 500 (TA100)	> 500	> 5000	Negative
Test 2		> 150	> 1500	Negative

Remarks - Results	No significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation. The positive and negative controls gave a satisfactory response confirming the validity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Harlan (2013c)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Human
Cell Type	Peripheral lymphocytes
Metabolic Activation System	S9 mix from phenobarbitone/β-naphthoflavone induced rat livers
Vehicle	Dimethyl sulphoxide
Remarks - Method	Whole blood cultures were used. A dose range-finding study was carried out at 9.54 – 2442 µg/mL. 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	2.5, 5*, 10*, 20*, 40*, 60, 80, 120	4h	24h
Test 2	5*, 10*, 20*, 30, 40, 80	24h	24h
Present			
Test 1	5, 10, 20*, 40*, 60*, 80	4h	24h
Test 2	10*, 20*, 40*, 60, 70, 80	4h	24h

*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	> 9.54	> 10	> 120	Negative
Test 2	> 19.08	> 20	> 80	Negative
Present				
Test 1	> 9.54	< 10	> 80	Negative
Test 2		> 10	> 80	Negative

Remarks - Results

In Test 1, haemolysis was observed at the end of exposure at ≥ 10 µg/mL and ≥ 20 µg/mL in the presence and absence of the metabolic activation, respectively. In Test 2, haemolysis was observed at the end of exposure at ≥ 20 µg/mL and ≥ 40 µg/mL in the presence and absence of the metabolic activation, respectively. It was stated by the study authors that haemolysis was an indication of a toxic response to erythrocytes and not indicative of any genotoxic response to the lymphocytes.

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 human peripheral lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY

Harlan (2015d)

B.11. Developmental toxicity

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 421 Reproductive/Developmental Toxicity Screening Test.

Species/Strain	Rat/Wistar
Route of Administration	Oral – diet
Exposure Information	Exposure days: males 43 days, females approximately 54 days
Vehicle	Dietary admixures
Remarks - Method	No significant protocol deviations.

RESULTS

Treatment Group	*Number of Animals*	*Dose ppm (mg/kg bw/day)*		*Mortality*
		Males	*Females*	
Control	12M/12F	0	0	0/24
Low dose	12M/12F	300 (17.9)	300 (20.9)	0/24
Mid dose	12M/12F	600 (37.0)	600 (40.4)	0/24
High dose	12M/12F	1000 (61.7)	1000 (64.6)	0/24

Mortality and Time to Death
There were no unscheduled deaths.

Effects on Parental Animals
No clinical signs were noted. Reductions in body weight gains were noted for male animals in the high-dose group during Week 2 and a subsequent reduction in overall body weight gain. Reductions in body weight gains, food consumption and food conversion efficiency were noted during the first week for all treated female animals and continued during gestation and lactation periods for those in the mid-dose and high-dose groups. Absolute body weights from Day 0 of gestation to Day 4 of lactation were considerably reduced in high-dose females. These effects were considered by the study authors to be possibly associated with gastric irritancy rather than systemic toxicity, as gastric irritancy was noted in the 28-day oral repeated dose study (Harlan 2015c).

No treatment-related changes occurred in the male organ weights.

No macroscopic or microscopic changes were seen in the tissues examined, that were considered treatment-related. Small testes and epididymides were seen in one control and one high dose male, associated with tubular atrophy of the testes. One additional high dose male had mild tubular atrophy, not associated with macroscopic change. Mild or minimal vacuolation of the pituitary gland in high dose males was considered linked to adaptive responses in tissues such as liver and thyroid.

No treatment-related adverse effects on mating performance and fertility were noted. An increase in post implantation loss and a reduction in litter size at birth and on Days 1 and 4 postpartum were noted in the high-dose group.

Effects on Foetus
Lower litter weights resulted from reductions in litter sizes were noted at birth and on Days 1 and 4 postpartum in the high-dose group.

Remarks - Results
The study authors noted that a relationship between the reductions in litter sizes, litter weights and maternal body weight gains during gestation and lactation and the reductions in food consumption could not be excluded. The effects at the mid dose were considered by the study authors to be equivocal and of limited toxicological significance.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) for systemic toxicity was established as 600 ppm (37 mg/kg bw/day for males/40.4 mg/kg bw/day for females) in this study, based on the treatment-related effects on body weight development for both male and female animals at 1000 ppm (61.7 mg/kg bw/day for males/64.6 mg/kg bw/day for females). However, the study authors stated that the NOAEL was established based on limited evaluation.

The NOAEL for reproductive toxicity was established as 600 ppm (40.4 mg/kg bw/day) in this study, based on the increase in post implantation loss and reduction in litter sizes and total litter weights at the high dose of 1000 ppm (64.6 mg/kg bw/day).

TEST FACILITY Envigo (2016)

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
- 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*
1	0.0	1	33.0
7	0.3	7	61.3
10	2.0	10	71.1
14	2.0	14	78.3
21	3.1	21	83.5
28	3.6	28	87.1

Remarks - Results: All validity criteria for the test were satisfied. The percentage biodegradation of the notified chemical (expressed as a % ThOD) averaged 3.6% after 28 days. The test item did not show biodegradation exceeding the pass level of 60%. Biodegradation of the reference substance (sodium benzoate) attained 61.3% by Day 7, 78.3 % by Day 14 and 87.1 % by Day 28. In the Toxicity Control (TC) test mixture, 36.3% degradation occurred within 14 days and the value exceeded 25% based on total ThOD, which indicated that the test item can be assumed to be not inhibitory under the conditions of this test.

CONCLUSION: The notified chemical is not readily biodegradable.

TEST FACILITY: SRICIL (2013)

C.1.2. Ready biodegradability

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
- Inoculum: Activated sludge
- 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*
1	0	1	40
8	0	7	76
10	0	10	90
14	0	14	84
21	0	21	84

28	0	28	95

Remarks - Results	All validity criteria for the test were satisfied. The test item attained 0% biodegradation after 28 days and therefore cannot be considered to be readily biodegradable under the strict terms and conditions. Statistical analysis of the Day 29 IC values for the control and test item vessels showed there were no statistically significant differences between the control and the test item. The test item was therefore considered not to have a toxic effect on the sewage sludge microorganisms used in the study and this was confirmed by the toxicity control results.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Harlan (2014g)

C.1.3. Bioaccumulation

TEST SUBSTANCE	Analogue chemical (5H-cyclopenta[h]quinazoline, 6,7,8,9-tetrahydro-7,7,8,9,9-pentamethyl-, CAS No. 1315251-11-6)
METHOD	OECD TG 305 Bioconcentration: Flow-through Fish Test. U.S. EPA Ecological Effects Test Guidelines OPPTS 850.1730.
Species	Bluegill (*Lepomis macrochirus*)
Exposure Period	Exposure: 35 days Depuration: 14 days
Auxiliary Solvent	Not reported
Concentration Range	Nominal: 0, 0.004 and 0.040 mg/L
Analytical Monitoring	Gas chromatography (GC) analysis
Remarks - Method	Bluegill sunfish, *Lepomis macrochirus*, were exposed to the test substance under flow-through conditions at two mean measured concentrations, 0.0040 and 0.040 mg/L.
RESULTS	
Bioconcentration Factor	677 for the low concentration and 884 for the high concentration
Remarks - Results	Whole body 14C-residue concentrations reached steady-state equilibrium by 21 days of uptake; the steady state Bioconcentration Factor (i.e. BCFss) was estimated at 677 for the low concentration and 884 for the high concentration. Based on the ratio of the uptake and depuration rate constants (k1 and k2 respectively) the BCF was estimated at 615 for the low concentration and 824 for the high concentration. The calculated times to 95% depuration of the 14C-residue in whole fish tissue were 2.4 and 3.6 days in the low and high treatment groups, respectively.
CONCLUSION	The test substance is not bioaccumulative.
TEST FACILITY	ABC (2014)

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. SEPA, P.R. China, The Guidelines for the Testing of Chemical No. 203
Species	Zebra fish (*Dania rerio*)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	Gas chromatography (GC)
Remarks – Method	The test was conducted in accordance with the test guideline without

significant deviations. Good Laboratory Practice (GLP) was followed.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality*				
Nominal	*Measured*		*2h*	*24 h*	*48 h*	*72 h*	*96 h*
0.40	0.392	10	0	0	0	0	0
0.48	0.459	10	0	0	0	0	0
0.57	0.538	10	0	0	0	0	0
0.67	0.635	10	0	0	2	3	4
0.80	0.725	10	0	3	8	10	10

LC50	0.64 mg/L (95% confidence limits were 0.61 - 0.67 mg/L)
Remarks – Results	All validity criteria for the test were satisfied. During the 96 hours exposure period, no toxic symptoms or mortality was observed in the solvent control group and the lowest concentration test group (arithmetic mean measured concentration of 0.392 mg/L). Toxic symptoms, such as erratic swimming and pigmentation were observed in test groups at measured concentrations from 0.459 mg/L to 0.725 mg/L, and mortality was observed at measured concentrations from 0.635 mg/L and 0.725 mg/L.

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

TEST FACILITY SRICIL (2014)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test - Static.
EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia -

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None reported
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	High performance liquid chromatography with mass spectrometry (HPLC-MS)
Remarks - Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed. A preliminary media preparation trial indicated that the most appropriate method of preparation for the test item was using the saturated solution method due to low solubility.

RESULTS

Concentration mg/L	*Number of D. magna*	*Number Immobilised*	
Nominal		*24 h [acute]*	*48 h [acute]*
1.0	20	0	0
3.2	20	0	0
10	20	0	0
32	20	8	20
100	20	20	20

EC50	1.0 mg/L at 48 hours
NOEC	0.56 mg/L at 48 hours
LOEC	1.8 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. All the measurements were obtained at 95% confidence limits of 0.56 – 1.8 mg/L.

CONCLUSION The notified chemical is toxic to aquatic invertebrates.

TEST FACILITY Harlan (2014h)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test.
C.3 of Commission Regulation (EC) No 761/2009 Algal Inhibition Test.

Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 1.0, 3.2, 10.0, 32.0 and 100.0 mg/L
Auxiliary Solvent	None reported
Water Hardness	None reported
Analytical Monitoring	High performance liquid chromatography with mass spectrometry (HPLC-MS)
Remarks - Method	The test was conducted in accordance with the test guideline without significant deviations. Good Laboratory Practice (GLP) was followed. A preliminary media preparation trial indicated that the most appropriate method of preparation for the test item was using the saturated solution method due to low solubility.

RESULTS

Biomass		*Growth*	
E_yC50	*NOE_yC*	*E_rC50*	*NOE_rC*
mg/L at 72h	*mg/L at 72h*	*mg/L at 72 h*	*mg/L at 72h*
1. 1	0.2	3.4	0.2
95% confidence limits (0.88- 1.4 mg/L)		95% confidence limits (2.9- 3.9 mg/L)	

Remarks - Results All validity criteria for the test were satisfied. Analysis of the 3.2, 10, 32 and 100% v/v saturated solution test preparations at 0 hours showed measured test concentrations to range from 0.24 to 7.4 mg/L. A decline in measured test concentration was observed at 24,48 and 72 hours to between 0.099 and 5.5 mg/L and hence it was considered appropriate to calculate the results based on the time-weighted mean measured test concentration.

CONCLUSION The notified chemical is toxic to algae

TEST FACILITY Harlan (2014i)

BIBLIOGRAPHY

ABC (2014) ^{14}C-FRET 10-0245: Bioconcentration and Metabolism Study with Bluegill, *Lepomis macrochirus* (Study No. 69247, August, 2014). Columbia, Missouri, USA, ABC Laboratories Inc (Unpublished report submitted by the notifier).

ACI (2010) Consumer Product Ingredient Safety, Exposure and risk screening methods for consumer product ingredients, 2nd Edition, American Cleaning Institute, Washington DC.

Api AM, Basketter DA, Cadby PA, Cano MF, Ellis G, Gerberick GF, Griem P, McNamee PM, Ryan CA and Safford R (2008) Dermal Sensitisation Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Regulatory Toxicology and Pharmacology, 52:3-23.

Cadby, PA., Troy, WR., Vey, MGH. (2002) Consumer Exposure to Fragrance Ingredients: Providing Estimates for Safety Evaluation. Regulatory Toxicology and Pharmacology, 36:246-52.

CRL (2015) Repeated Insult Patch Test (RIPT) - Shelanski Method (Study No. CRL48915, July, 2015). Piscataway, New Jersey, USA, Clinical Research Laboratories Inc (Unpublished report submitted by the notifier).

Earnest, C.W., Jr. (2009) A Two-Zone Model to Predict Inhalation Exposure to Toxic Chemicals in Cleaning Products, MScEng thesis, The University of Texas at Austin.

enHealth (2012) Australian Exposure Factor Guide, companion document to: Environmental Health Risk Assessment: Guidelines for assessing human health risks from environmental hazards, EnHealth, Commonwealth of Australia.

Envigo (2016) IFF TM 12-206 (FRET 10-0199): Oral (Dietary) Reproduction/Developmental Toxicity Screening Test in the Rat (OECD 421) (Study No. 41403524, January, 2016). Shardlow, Derbyshire, UK, Envigo Research Limited (Unpublished report submitted by the notifier).

Harlan (2013a) IFF TM 12-206: Determination of General Physico-Chemical Properties (Study No. 41202098, February, 2013). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2013b) IFF TM 12-206: Local Lymph Node Assay in the Mouse (Study No. 41202099, February, 2013). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2013c) IFF TM 12-206: Reverse Mutation Assay "Ames test" Using *Salmonella Typhimurium* and *Escherichia Coli* (Study No. 41202100, February, 2013). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014a) IFF TM 12-206 (FRET 10-0199): Determination of General Physico-Chemical Properties (Study No. 41400008, April, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014b) IFF TM 12-206 (FRET 10-0199): Determination of Vapor Pressure (Study No. 41400009, May, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014c) IFF TM 12-206 (FRET 10-0199): Determination of Hazardous Physico-Chemical Properties (Study No. 41400010, June, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014d) IFF TM 12-206 (FRET 10-0199): Acute Oral Toxicity in the Rat – Fixed Dose Method (Study No. 41400011, June, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014e) IFF TM 12-206 (FRET 10-0199): Determination of Skin Irritation Potential Using the EPISKIN Reconstructed Human Epidermis Model (Study No. 41400013, May, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014f) IFF TM 12-206 (FRET 10-0199): In vitro Skin Corrosion in the EPISKIN Reconstructed Human Epidermis Model (Study No. 41400012, May, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014g) IFF TM 12-206 (FRET 10-0199): Assessment of Ready Biodegradability; CO_2 Evolution Test (Study No. 41400018, December, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014h) IFF TM 12-206 (FRET 10-0199): Daphnia sp., 48-Hour acute Immobilization Test (Study No. 41400015, July, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2014i) IFF TM 12-206 (FRET 10-0199): Algal Growth Inhibition Test (Study No. 41400016, July, 2014). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2015a) IFF TM 12-206 (FRET 10-0199): Acute Dermal Toxicity (Limit Test) in the Rat (Study No. 41500960, August, 2015). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2015b) IFF TM 12-206 (FRET 10-0199): Assessment of Ocular Irritation Potential Using the SkinEthic Reconstructed Human Corneal Epidermis Model (10-Minute Exposure) (Study No. 41400014, January 2015). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2015c) IFF TM 12-206 (FRET 10-0199): Twenty-Eight Day Repeated Dose Oral (Dietary) Toxicity Study in the Rat with Recovery Groups (Study No. 41401832, July, 2015). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Harlan (2015d) IFF TM 12-206 (FRET 10-0199): Chromosome Aberration Test in Human Lymphocytes *in vitro* (Study No. 41402070, May, 2015). Shardlow, Derbyshire, UK, Harlan Laboratories Ltd (Unpublished report submitted by the notifier).

Loretz, L., Api, A.M., Barraj, L., Burdick, J. Davis, D.A., Dressler, W., Gilberti, E., Jarrett, G., Mann, S., Pan, Y.H.L., Re, T., Renskers, K., Scrafford, C., Vater, S. (2006) Exposure data for personal care products : Hairspray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant, Food and Chemcial Toxicology 44:2008-2018.

NICNAS (2015) 5*H*-Cyclopenta[*h*]quinazoline, 6,7,8,9-tetrahydro-7,7,8,9,9-pentamethyl- (LTD1726): Public Report. National Industrial Chemicals Notification and Assessment Scheme, Sydney.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances, 3rd edition [NOHSC:1008(2004)]. National Occupational Health and Safety Commission, Canberra, AusInfo.

RIVM (2010) Observations on the Methodology for Quantitative Risk Assessment of Dermal Allergens, Report 320015003/2010, National Institute for Public Health and the Environment.

Rothe, H., Fautz, R., Gerber, E., Neumann, L., Rettinger, K., Schuh, W., Gronewold, C. (2011) Special aspects of cosmetic spray evaluations: Principles on inhalation risk assessment, Toxicology Letters 205 (2011) 97-104.

SRICIL (2013) Ready Biodegradability Test of TM 12-206 (Study No. G1340A0010, December, 2013). Shengyang, Liaoning, China, Safety Evaluation Centre of Shenyang Research Institute of Chemical Industry Ltd (Unpublished report submitted by the notifier).

SRICIL (2014) TM 12-206 Fish Acute Toxicity Test (Study No. G1323J0010, January, 2014). Shengyang, Liaoning, China, Safety Evaluation Centre of Shenyang Research Institute of Chemical Industry Ltd (Unpublished report submitted by the notifier).

SCCS (2012) Notes of Guidance for testing of Cosmetic Ingredients and Their Safety Evaluation (7th revision) European Commission - Scientific Committee on Consumer Safety.

Steiling, W., Bascompta, M., Carthew, P., Catalano, G., Corea, N., D'Haese, A., Jackson, P., Kromidas, L., Meurice, P., Rothe, H., Singal, M. (2014) Principle considerations for the risk assessment of sprayed consumer products, Toxicology Letters 227:41-49.

United Nations (2009) Globally Harmonised System of Classification and Labelling of Chemicals (GHS), 3rd revised edition. United Nations Economic Commission for Europe (UN/ECE), <http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html >.

Van Goethem F., Adriaens E., Alepee N., Straube F., De Wever B., Cappadoro M., Catoire S., Hansen E., Wolf A. and Vanparys P. (2006) Prevalidation of A New in vitro Reconstituted Human Cornea Model to Assess the Eye Irritating Potential of Chemicals. Toxicology in vitro 20, pp. 1-17.