File No: LTD/1726

October 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

5*H*-Cyclopenta[*h*]quinazoline, 6,7,8,9-tetrahydro-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* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health, and 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/1726	International Flavours & Fragrances (Australia) Pty Ltd	5*H*-Cyclopenta[*h*]quinazoline, 6,7,8,9-tetrahydro-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 for 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 (Category 4)	H302 – Harmful if swallowed
Skin Sensitisation (Category 1B)	H317 – May cause an allergic skin reaction
Specific Target Organ Toxicity – Repeated Exposure (Category 2)	H373 – May cause damage to organs

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
R43: May cause sensitisation by skin contact
R48: Danger of serious damage to health by prolonged exposure

The environmental hazard classification according to the *Globally Harmonised System for 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.

When used at ≤ 0.21% concentration in fine fragrances and ≤ 0.01% in other cosmetic and household products, the notified chemical is not considered to pose an unreasonable risk to public health.

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

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Acute Toxicity (Category 4): H302 – Harmful if swallowed
  - Skin Sensitisation (Category 1B): H317 – May cause an allergic skin reaction
  - Specific Target Organ Toxicity – Repeated Exposure (Category 2): H373 – May cause damage to organs

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

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
  - Provide 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:
  - 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:
  - 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 for 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.

Public Health

The following measures should be taken by formulators to minimise public exposure to the notified chemical:

- The notified chemical should only be used at $\leq$ 0.21% concentration in fine fragrances and $\leq$ 0.01% in other cosmetic and household products;

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 concentration of the notified chemical exceeds or is intended to exceed 0.21% concentration in fine fragrances and 0.01% in other cosmetic and household products;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the notified chemical has changed from fragrance ingredient, or is likely to change significantly;
- the amount of chemical being introduced has increased from one tonne per annum, 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 notified 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 provided by the notifier was 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 Rd
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: dissociation constant, flash point.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
US (2013)
China (2013)
Japan (2013)
EU (2013)

2. IDENTITY OF CHEMICAL

MARKETING NAME
Sinfonide

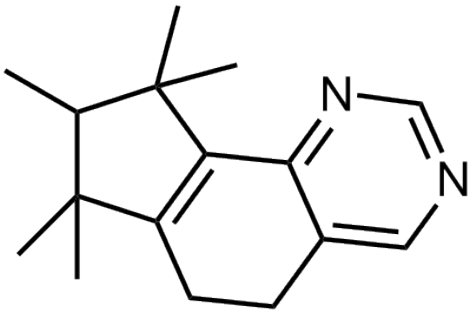
CAS NUMBER
1315251-11-6

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

OTHER NAME(S)
FRET 10-0245
TM 11-205
13-211-03
13-211-05
13-211-07

MOLECULAR FORMULA
$C_{16}H_{22}N_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
242.36 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 94%

IDENTIFIED IMPURITIES/RESIDUAL MONOMERS
2 ethyl isomers of the notified chemical:

Chemical Name	5*H*-Cyclopenta[*h*]quinazoline, 6,7,8,9-tetrahydro-7-ethyl-7,9,9-trimethyl- OR 5*H*-Cyclopenta[*h*]quinazoline, 6,7,8,9-tetrahydro-9-ethyl-7,7,9-trimethyl-		
CAS No.	-	*Weight %*	3.116

ADDITIVES/ADJUVANTS
None.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless crystalline solid.

Property	Value	Data Source/Justification
Melting Point/Freezing Point	70.7 ± 0.5 °C	Measured
Boiling Point	335 ± 1 °C at 101.6 kPa	Measured
Density	1,140 kg/m^3 at 20 ± 1 °C	Measured
Vapour Pressure	1.6×10^{-5} kPa at 25 °C	Measured
Water Solubility	3.95×10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	t½ > 1 year at 25 °C (pH 4–9)	Measured
Partition Coefficient (n-octanol/water)	log Pow = 5.11 at 20 °C	Measured
Surface Tension	60.7–61.4 mN/m at 22 °C	Measured
Adsorption/Desorption	log K_{oc} = 3.55–3.84 at 25 °C	Measured
Dissociation Constant	Not determined	The notified chemical contains potentially cationic functionalities. However, it is not expected to be significantly ionised in the environmental pH range (4–9).
Particle Size	Inhalable fraction (< 100 µm): 5.2%	Measured
Flash Point	Not determined	The notified chemical is a crystalline solid at room temperature.
Flammability	Not highly flammable	Measured
Autoignition Temperature	362 ± 5 °C	Measured
Explosive Properties	Predicted negative	Contains no functional groups that would imply explosive properties
Oxidising Properties	Predicted negative	Contains no functional groups that would imply oxidising properties.

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 for the 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 compounded fragrances.

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 MANUFACTURER/RECIPIENTS
International Flavours & Fragrances (Australia) Pty Ltd.

TRANSPORTATION AND PACKAGING
The notified chemical (at ≤ 5% concentration) will be imported as a component of finished fragrance oils in 208.2 L polypropylene-lined steel drums or as a component of finished products. The imported and formulated products containing the notified chemical will be transported within Australia by road. The end-use products (≤ 0.25% proposed concentration of the notified chemical) will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient and incorporated into a variety of household and cosmetic products at a proposed usage concentration of ≤ 0.25%.

OPERATION DESCRIPTION
The notified chemical will not be manufactured within Australia. No reformulating or repackaging of the notified chemical will occur at the notifier facility. The fragrance oils containing the notified chemical will be stored at this facility until they are sold and shipped to customer facilities.

Reformulation
The procedures for incorporating the notified chemical (at ≤ 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. However, in general, it is expected that for the reformulation process, the notified chemical will be weighed and added to the mixing tank where it will be blended with additional additives to form the finished cosmetic and household products. This will be followed by automated filling of the reformulated products into containers of various sizes. The blending operations are expected to be highly automated and use closed systems and/or adequate ventilation. During the formulation process, samples of the notified chemical and the finished cosmetic products will be taken for quality control testing.

Household products
Household products containing the notified chemical (at ≤ 0.25% proposed usage 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 machines, or open processes and manually by rolling, brushing, spraying and dipping.

Cosmetic products
The finished cosmetic products containing the notified chemical (at ≤ 0.25% proposed usage concentration) will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application could be by hand, sprayed 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	Unknown	Unknown
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)	Not specified	Not specified

EXPOSURE DETAILS

Transport and storage

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

At the notifier facility, the primary work activity undertaken by transport and warehouse workers will include the handling, loading and off-loading of drums containing fragrance oils formulated with the notified chemical at ≤ 5% concentration. Exposure of these workers will be limited to situations involving products sampling for quality control or, in the event of a discharge, clean up from a spill or leaking drum. If such an event occurs, a worker may be exposed through dermal or ocular contact. The notifier states that such exposures will be minimised to the extent possible through the use of personal protective equipment (PPE) including protective coveralls, chemical resistant gloves and safety glasses.

Reformulation

During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 5% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. 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.

End-use

Exposure to the notified chemical in end-use products (at ≤ 0.25% proposed usage concentration) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons) 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 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 through the use of the cosmetic and household products (at ≤ 0.25% proposed usage concentration in individual products). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

Data on typical use patterns of cosmetic and household cleaning product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2012). 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, a dermal absorption of 100% was assumed for the notified chemical. For the inhalation exposure assessment, an adult inhalation rate of 20 m^3/day

(enHealth, 2012) was used and it was assumed that the bioavailability of the notified chemical via the inhalation route is 100%. An adult bodyweight of 64 kg was used for calculation purposes.

Cosmetic products (Dermal exposure):

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	0.25	1	0.3055
Face cream	1540	0.25	1	0.0602
Hand cream	2160	0.25	1	0.0844
Fine fragrances	750	0.25	1	0.0293
Deodorant (non-spray)	1500	0.25	1	0.0586
Shampoo	10460	0.25	0.01	0.0041
Conditioner	3920	0.25	0.01	0.0015
Shower gel	18670	0.25	0.01	0.0073
Hand soap	20000	0.25	0.01	0.0078
Hair styling products	4000	0.25	0.1	0.0156
Total				**0.5742**

C = concentration (%); RF = retention factor.
Daily systemic exposure = (Amount × C × RF × dermal absorption)/body weight

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	0.25	0.95	10	0.0085
Fabric softener	90	0.25	0.95	10	0.0033
Total					**0.0119**

Daily systemic exposure = (Amount × C × PR × PT × dermal absorption)/body weight

Household products (Direct dermal exposure):

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.25	1980	0.01	0.01	0.007	0.00001
Dishwashing liquid	3	0.25	1980	0.0093	0.01	0.03	0.00006
All-purpose cleaner	1	0.25	1980	1	0.01	0.007	0.0054
Total							**0.0061**

Daily systemic exposure = (Frequency × C × Contact area × Product Use Concentration × Film Thickness on skin × Time Scale Factor × dermal absorption)/body weight

Cosmetic products (Inhalation exposure):

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure Duration (min)	Fraction Inhaled (%)	Volume (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.25	20	**Zone 1:** 1 **Zone 2:** 20	50	**Zone 1:** 1 **Zone 2:** 10	0.0080

Total Daily systemic exposure = Daily systemic exposure in Zone 1 [(amount × C × inhalation rate × exposure duration (zone 1) × fraction inhaled)/(volume (zone 1) × body weight)] + Daily systemic exposure in Zone 2 [(amount × C × inhalation rate × exposure duration (zone 2) × fraction inhaled)/(volume (Zone 2) × body weight)]

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 0.6002 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 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	LD_{50} ~ 500 mg/kg bw (300–2000 mg/kg bw); harmful
Rat, acute dermal toxicity	LD_{50} > 2,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC_{50} > 5.02 mg/L/4 hours
Skin corrosion (in vitro)	non-corrosive
Skin irritation (in vitro)	non-irritating
Rabbit, skin irritation	slightly irritating
Eye irritation (in vitro)	not corrosive or severely irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (10%)	no evidence of sensitisation
Human, skin sensitisation – RIPT (15%)	no evidence of sensitisation
Human, skin sensitisation – RIPT (20%)	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	LOAEL = 43.1 mg/kg bw/day (males) and 47.4 mg/kg bw/day (females)
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic
Phototoxicity – in vitro – 3T3NRU phototoxicity test	probable phototoxic effects
Phototoxicity – protocol for use with EpiDerm Model	non phototoxic

Toxicokinetics, metabolism and distribution
Limited data are available on the toxicokinetic properties of the notified chemical. Based on the molecular weight (< 500 Da), water solubility and partition coefficient of the notified chemical, the potential to cross the gastrointestinal (GI) tract by passive diffusion or to be dermally absorbed after exposure is possible. Additionally, there is potential for absorption via the lungs. The potential for absorption is supported by the observed effects in animal studies following exposure to the notified chemical.

Acute toxicity
The notified chemical was found to be harmful in an acute oral toxicity study in rats, with the study authors noting the LD_{50} to be ~500 mg/kg bw. Clinical signs observed at the highest (2,000 mg/kg bw) dose level included hunched posture, ataxia, lethargy, body tremors, hypothermia, decreased respiratory rate, convulsions, splayed gait and ptosis, with the animals treated at this dose killed 4 hours after dosing. There were no signs of systemic toxicity at the 300 mg/kg bw dose level.

The notified chemical was found to have low acute dermal toxicity in rats.

In an acute inhalation toxicity study, the notified chemical was found to be of low toxicity (MMAD: 7.04 µm; LC_{50} > 5.02 mg/L; effects did not warrant classification of the chemical for acute toxicity). However, it is noted that a female animal (1/5) died on day 4 post-exposure. Clinical signs noted prior to death in this animal included decreased respiratory rate, hunched posture, pilo-erection, diuresis, ptosis, dehydration and laboured respiration. At necropsy, dark patches were noted in the lungs and the liver exhibited a patchy pallor. The study results do not meet the GHS criteria for Specific Target Organ Toxicity – Single Exposure (Category 2) classification.

Irritation
An acute dermal irritation study in rabbits and in vitro skin corrosion and irritation studies were conducted. The notified chemical was found to be non-corrosive and non-irritating to the skin based on the in vitro studies and

slightly irritating to the skin based on the study in rabbits. The observed effects in the rabbits were only of short duration (< 24 hours).

An in vitro eye irritation study on bovine corneas found the notified chemical not to be corrosive or a severe eye irritant. A rabbit eye irritation study was also conducted for the notified chemical, in which iridial inflammation and moderate conjunctival irritation were observed. However, the effects were insufficient to warrant classification of the chemical as an eye irritant.

Sensitisation
The notified chemical was a skin sensitiser in a local lymph node assay (LLNA) in mice, with reported stimulation indices of 16.1, 16.88 and 9.15 at 10, 25 and 50% concentration, respectively. The EC3 value could not be determined.

The sensitising potential of the notified chemical was tested in three human repeat insult patch tests (HRIPT) at 10%, 15% and 20% concentration, respectively. The notified chemical was not considered to be a skin sensitiser by the study authors in either test.

When tested at 10% concentration, 3 subjects presented with hyperpigmentation during the Induction Phase, while 5 subjects were noted with barely perceptible to mild erythema at induction, lasting 1 to 2 evaluation observations. At Challenge, 3 subjects showed barely perceptible erythema (1 subject at patch removal and 2 subjects at 48 hours after patch removal). A subject exhibiting erythema at 48 hours after patch removal also showed barely perceptible papules at the same observation (it is noted that barely perceptible erythema was also observed in this subject at 2 observations during the Induction phase). No responses were evident in these subjects after 72 hours.

However, treatment induced reactions were less prevalent in the study conducted at 15% concentration, with 1 subject presenting with barely perceptible to mild erythema at the 4th induction only, with a different subject showing barely perceptible erythema 48 hours after Challenge patch removal.

In the study conducted at 20% concentration, effects were noted in 3 subjects during the Challenge phase. One subject presented well defined erythema at patch removal, with barely perceptible severity still evident at the 48 and 72 hour observations. Two subjects showed mild erythema at the 72 hour observation, continuing with mild severity and barely perceptible at the 96 hour observation in each respectively. These reactions were deemed by the study authors to likely be indicative of irritation and delayed irritation (due to lack of oedema and/or itching) and not evidence of sensitisation. Re-challenge was conducted in this study, where no effects were seen in 2/3 of these subjects (with 1 subject declining to participate in re-testing).

Repeated dose toxicity
An oral (dietary) repeated dose toxicity study on the notified chemical was conducted with rats, in which the test substance was administered at 500, 800 and 1,200 ppm (equating to 43.1, 67.6 and 101.0 mg/kg bw/day for males and 47.4, 58 and 85.8 mg/kg bw/day for females) for 28 consecutive days, with a 14 day recovery period for high dose animals.

A range of clinical and laboratory observations were noted, including, for example, reduction in mean body weight gains, reduced food consumption and efficiency, blood chemistry parameter changes and oestrous cycle effects. At necropsy, observed effects included various organ weight variations, reduced sperm concentration and motility values and microscopic histopathological abnormalities in various animals of both sexes at all dose levels, some results showing clear dose-response relationships.

The study authors noted that administration of the test substance resulted in clear functional changes in the livers of animals of both sexes, at all dose levels. Centrilobular hypertrophy and periportal vacuolation of the liver, in conjunction with increased liver weights, was noted in a dose dependent pattern. Observations deemed by the study authors to be indicative of altered organ function included thyroid and pituitary changes and changes in the uteri, oestrous cycle assessment and sperm analysis. The authors attributed the thyroid and pituitary changes to hepatocellular metabolic induction, and in light of these functional changes, the authors noted that the adverse effects seen in the reproductive organs may represent a secondary response to changes in the liver function.

No discernible No Observed Effect Level (NOEL) was determined in the study. Consequently, the Lowest Observed Adverse Effect Level (LOAEL) was established as 500 ppm bw/day (equivalent to a mean achieved dose of 43.1 mg/kg bw/day for males and 47.4 mg/kg bw/day in females) for this study.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation study and was not clastogenic in an *in vitro* mammalian chromosome aberration test.

Phototoxicity
In an *in vitro* phototoxicity study (BALB/c 3T3 cells clone 31) the notified chemical was predicted to have probable phototoxic potential. In a subsequent *in vitro* human skin model test (not an OECD validated test guideline), the notified chemical did not exhibit any phototoxic effects.

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 (Category 4)	H302 – Harmful if swallowed
Skin Sensitisation (Category 1)	H317 – May cause an allergic skin reaction
Specific Target Organ Toxicity – Repeated Exposure (Category 2)	H373 – May cause damage to organs

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
R43: May cause sensitisation by skin contact
R48: Danger of serious damage to health by prolonged exposure

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Reformulation (and quality control processes)
Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemical (at ≤ 5% concentration) during reformulation processes (and during sampling and quality control processes at storage sites). The notified chemical is considered to be a skin sensitiser. The notified chemical is also considered to be harmful to human health via the oral route, however, ingestion is unlikely under the occupational settings described. In addition, toxic effects from repeated exposure to the notified chemical cannot be ruled out. In light of these hazard concerns, caution should be exercised when handling the notified chemical during reformulation and quality control processes.

The use of enclosed, automated processes and PPE (e.g. impervious gloves, coveralls) should minimise the potential for exposure. Occupational surveillance programs should be in place for workers which may be at a significant risk of sensitisation. Therefore, provided that adequate control measures are in place to minimise worker exposure, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Cleaners, hair and beauty care professionals will handle the notified chemical at ≤ 0.25% concentration. 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 these workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical on a regular basis (for details of the public health risk assessment, see Section 6.3.2.).

6.3.2. Public Health

There are various potential risks associated with use of the notified chemical in finished cosmetic and household products.

Repeated dose toxicity
Members of the public may experience repeated exposure to the notified chemical (at the proposed concentration of ≤ 0.25%) through the use of the cosmetic and household products.

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.6002 mg/kg bw/day (see Section 6.1.2) and the LOAEL of 43.1 mg/kg bw/day, which was established in a 28-day repeated dose toxicity study on the notified chemical. A MoE value ≥ 300 is considered acceptable to account for intra- and inter-species differences and the duration of the study, noting also the uncertainty on the significance of effects observed in both sexes at all dose levels. Using the abovementioned LOAEL, a MoE of 24 was estimated, therefore, the MoE is considered to be unacceptable. Reducing the end product concentration of the notified chemical to ≤ 0.21% in fine fragrances and ≤ 0.01% in other cosmetics and household products, gives a recalculated worst case exposure scenario from use of multiple products of 0.0474 mg/kg bw/day. A MoE of 301 is then estimated, which is considered to be acceptable.

Sensitisation
The notified chemical is considered to have the potential to cause skin sensitisation. Methods for the quantitative risk assessment of dermal sensitisation have been proposed and been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). Using fine fragrances (containing notified chemical at ≤ 0.21%) as an example product that may contain the notified chemical, as a worst case scenario, the Consumer Exposure Level (CEL) is estimated to be 7.88 μg/cm^2 (Cadby *et al.*, 2002).

When tested at 20% concentration in a human repeat insult patch study (0.2 mL applied to 3.63 cm^2 patches), the notified chemical was determined by the study authors not to be a skin sensitiser. Although this study has been used for the purposes of quantitative risk assessment of the notified chemical, the availability of additional information on the sensitisation potential of the notified chemical (i.e., HRIPT studies conducted at 10 and 15% concentration and the LLNA study) were taken into account when determining the safety assessment factors that should be applied. Thus, consideration of the details of the studies, and application of appropriate safety factors, allowed the derivation of an Acceptable Exposure Level (AEL) of 12.57 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 (10), giving an overall safety factor of ~1,000.

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical in fine fragrances at ≤ 0.21% concentration (as a worst case example) is not considered to be unreasonable. Based on the lower expected exposure level from use of other cosmetic products and household products (both ≤ 0.01% notified chemical), by inference, the risk of induction of sensitisation associated with the use of these products is also 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.

Phototoxicity
Based on the available evidence, phototoxicity from use of the notified chemical is considered possible. Guidance on the phototoxicity of ingredients for cosmetic use has suggested a safety factor of 10 should be applied for extrapolation of experimental data from skin model assays to man (Kejlova *et al,* 2010). With respect to the concentrations at which the notified chemical was tested in both *in vitro* tests, and use of such a safety factor for the notified chemical, the risk of phototoxic effects associated with the use of the notified chemical in fine fragrances at ≤ 0.21% concentration (as a worst case example) is not considered to be unreasonable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at the revised (lower) concentrations of ≤ 0.21% in fine fragrances and ≤ 0.01% in other cosmetic and household products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of fragrance preparations for local reformulation into a variety of cosmetic and household products. Release during reformulation in Australia is expected to arise from spills, formulation equipment cleaning and residues in import containers (1% of the annual import volume).

RELEASE OF CHEMICAL FROM USE

The notified chemical is expected to be released to sewers in domestic situations across Australia as a result of its use in cosmetic and household products, which will either be washed off the hair and skin of consumers, or disposed of following cleaning activities.

RELEASE OF CHEMICAL FROM DISPOSAL

It is anticipated that ≤ 1% or ≤ 10 kg of the notified chemical is expected to be lost as residues in consumer containers, which will primarily be sent to landfill or recycled.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system before potential release to surface waters on a nationwide basis. The submitted biodegradation studies on the notified chemical indicate that the notified chemical is not expected to be rapidly degraded in sewage treatment plants (STPs). In STPs the notified chemical is expected to be efficiently removed from influent by adsorption to sludge and only a small portion may be released to surface waters. The notified chemical is not likely to bioaccumulate based on its measured bioconcentration factor. A proportion of notified chemical may be applied to land when effluent is used for irrigation, or disposed of to landfill as waste. Notified chemical residues in landfill and soils are expected to have slight mobility based on its measured soil adsorption coefficient (log K_{oc} = 3.55–3.84). In the aquatic and soil compartments, the notified chemical is expected to slowly degrade through biotic and abiotic processes to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

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

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	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 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 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*
Acute		
Fish Toxicity	96 h EC_{50} = 0.55 mg/L	Very toxic to fish
Daphnia Toxicity	48 h EC_{50} = 0.32 mg/L	Very toxic to aquatic invertebrates
Algal Toxicity	72 h E_yC_{50} = 0.59 mg/L	Very toxic to algae
Micro-organism respiration	3 h EC_{50} > 1,000 mg/L	Not expected to inhibit microbial respiration

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is considered to be very toxic to fish, aquatic invertebrates and algae and is formally classified as 'Acute Category 1: Very toxic to aquatic life'. On the basis of the acute toxicity and the lack of ready biodegradability, the notified chemical 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) has been calculated from the acute daphnia toxicity of the notified chemical and an assessment factor of 100 as measured acute endpoints are available for three trophic levels.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC_{50} (Daphnia).	0.32	mg/L
Assessment Factor	100	
PNEC:	3.2	µg/L

7.3. Environmental Risk Assessment

Based on the above PEC and PNEC values, the following Risk Quotient (Q) has been calculated:

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River:	0.61	3.2	0.19
Q - Ocean:	0.06	3.2	0.019

The risk quotient for discharge of the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity. The notified chemical has a low potential for bioaccumulation. Therefore, on the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic and household products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 70.7 ± 0.5 °C

Method OECD TG 102 Melting Point/Melting Range.
Remarks Determined by differential scanning calorimetry
Test Facility Harlan (2012a)

Boiling Point 335 ± 1.0 °C at 101.6 kPa

Method OECD TG 103 Boiling Point.
EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks Determined by differential scanning calorimetry
Test Facility Harlan (2013a)

Density 1,140 kg/m^3 at 20.0 ± 1.0 °C

Method OECD TG 109 Density of Liquids and Solids.
EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks Determined using a gas comparison pycnometer
Test Facility Harlan (2013a)

Vapour Pressure 1.6×10^{-5} kPa at 25 °C

Method OECD TG 105 Water Solubility
Remarks Determined by the Balance Method
Test Facility Harlan (2013b)

Water Solubility 3.95×10^{-3} g/L at 20 °C

Method OECD TG 105 Water Solubility
Remarks Column Elution Method
Test Facility Harlan (2012a)

Hydrolysis as a Function of pH t½ > 1 year at 25 °C (pH 4–9)

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	$t_{½}$
4	25	> 1 year
7	25	> 1 year
9	25	> 1 year

Remarks In the hydrolysis test, the change of the molecular weight of the test substance after 5 days at 50 °C and pH 4.0, 7.0 and 9.0 was determined. It was found that the change of the molecular weight of the test substance was less than 10%. It can be concluded that the test substance can be considered as hydrolytically stable under any of the pH conditions i.e., at pH 4.0, 7.0 and 9.0.
Test Facility Harlan (2013a)

Partition Coefficient (n-octanol/water) log Pow = 5.11 at 20 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks HPLC Method
Test Facility Harlan (2012a).

Surface Tension 60.7–61.4 mN/m at 22 °C

Remarks Determined using a tensiometer and the ring method.

Concentration: 90% of the test substance saturation solubility in water.
Test Facility Harlan (2013a)

Adsorption/Desorption log K_{oc} = 3.55–3.84 at 25 °C

Method OECD TG 106 Adsorption – Desorption Using a Batch Equilibrium Method.

Soil Type	*Distribution Coefficient (Kd)*	*pH*	*K_{oc}*	*Log K_{oc}*
Loam	183	7.3	4.47×10^3	3.64
Silty Loam 1	88.5	6.2	3.58×10^3	3.55
Silty Loam 2	267	5.1	6.86×10^3	3.84
Sandy Loam 1	40.2	5.8	3.98×10^3	3.60
Sandy Loam 2	1.5×10^3	3.1	6.62×10^3	3.82

Remarks The test was conducted on the test substance (notified chemical). Aqueous solutions of the test substance were equilibrated with five soil types and the adsorption and desorption coefficients and constants were determined. The concentration of the test substance remaining in the aqueous phase was determined by High Pressure Liquid Chromatography (HPLC). The amount of the test substance adsorbed on the soils was determined by extraction. The mean of the logarithmic adsorption coefficient (log K_{oc} = 3.69) was reported for the test substance, indicating that the test substance is considered to be immobile in the soils tested.
Test Facility Harlan (2013c)

Particle Size Distribution

Method Procedure designed to be compatible with the European Commission Technical Guidance Document EUR 20268 "Determination of Particle Size Distribution, Fibre Length and Diameter Distribution of Chemical Substances: (2002)

Particle Size (μm)	*Proportion (%)*
< 100	5.2
< 10	Not tested

Remarks Determined by Sieve Method
Test Facility Harlan (2013a)

Flammability Not highly flammable

Method EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks The notified chemical melted and failed to ignite during the 2minutes that the Bunsen flame was applied in the preliminary test. This result obviated the need to perform the main test.
Test Facility Harlan (2013d)

Autoignition Temperature 362 ± 5 °C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks Determined by heating aliquots of the test substance in a flask (flask heater) and observing for any signs of ignition.
Test Facility Harlan (2013d)

Explosive Properties Predicted negative

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks Observation of functional groups that would imply explosive properties.
Test Facility Harlan (2013d)

Oxidizing Properties Predicted negative

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).
Remarks	Observation of functional groups that would imply oxidizing properties.
Test Facility	Harlan (2013d)

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/ Wistar Han™:RccHan™:WIST.
Vehicle	Arachis oil BP.
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3F	300	0/3
2	3F	2,000	3/3
3	3F	300	0/3

LD_{50}	~ 500 mg/kg bw (300–2,000 mg/kg bw).
Signs of Toxicity	The animals treated at the highest dose level (2,000 mg/kg bw) were humanely killed 4 hours after dosing due to the occurrence of clinical signs of toxicity exceeding set severity limits. Clinical signs of systemic toxicity that were observed in the treated animals before termination included hunched posture, lethargy, ataxia, body tremors, hypothermia, decreased respiratory rate, clonic and tonic convulsions, splayed gait and ptosis. There were no signs of systemic toxicity at the 300 mg/kg bw dose level.
Effects in Organs	White liquid present in the stomach was noted in animals treated at 2,000 mg/kg bw. No abnormalities were noted at necroscopy for animals treated at the 300 mg/kg bw dose level.
Remarks - Results	The animals that died during the course of the study all showed decreased body weight at death compared to starting weights. All surviving animals showed body weight gains during the study period. The study authors note that the LD_{50} was ~ 500 mg/kg bw.
CONCLUSION	The notified chemical was found to be harmful via the oral route.
TEST FACILITY	Harlan (2013e)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/ Wistar Han™:RccHan™:WIST.
Vehicle	Arachis oil BP.
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*

1	1 per sex	2,000	0/0
2	4 per sex	2,000	0/0

LD_{50}	> 2,000 mg/kg bw.
Signs of Toxicity - Local	Very slight erythema was noted at the test sites of 3 females. Small superficial scattered scabs and scab lifting to reveal glossy skin were also noted at the test site of 1 female. There were no signs of dermal irritation noted at the test sites of the remaining test animals.
Signs of Toxicity - Systemic	None.
Effects in Organs	No abnormalities were noted at necroscopy.
Remarks - Results	All animals showed body weight gains over the test period.

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

TEST FACILITY Harlan (2013f)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical.

METHOD

Species/Strain	Rat/ Wistar Han™:RccHan™:WIST.
Method of Exposure	Nasal exposure only.
Exposure Period	4 hours.
Physical Form	Solid aerosol (particulate).
Particle Size	7.04 µm
Remarks - Method	GLP Compliance. The test item was ground using a small amount of diethyl ether in a mill (solvent removed prior to use). A sighting test was conducted with 2 animals (1 per sex) exposed to an atmosphere of the test item (with a MMAD of 3.43 µm) at a mean achieved concentration of 2.06 mg/L for ~ 4 hours. The animals exhibited wet fur, hunched posture, pilo-erection, increased respiratory rate and/or sneezing during or shortly after exposure, with hunched posture, pilo-erection and increased respiratory rate exhibited on days 1 to 3 post exposure. At necropsy, the female animal showed dark patches on the lungs and dark kidneys. In the main study, the MMAD of the notified chemical (7.04 µm) was outside of the target range of 1-4 µm. The study authors noted that the fraction < 4 µm was 27.5% and that it was not possible to reduce the particle size further when generating at a target concentration of 5 mg/L. The study authors considered that as major signs of toxicity were not present in the sighting study animals (exposed to 1.11 mg/L of particles < 4 µm), it was preferable to expose the animals in the main study to a higher concentration of test substance (even though this also resulted in an increased MMAD), as this would result in exposure to the highest possible concentration of particles < 4 µm (~ 1.38 µm).

RESULTS

Group	*Number and Sex of Animals*	*Concentration <units>*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	54.42	5.02 ± 0.93	1/10

LC_{50}	> 5.02 mg/L/4 hours
Signs of Toxicity	Wet fur and increased respiratory rate was noted in all animals during the exposure period and up to 1 hour post removal from the chamber. Hunched posture, pilo-erection and increased respiratory rate was noted in all animals on day 1. From day 2 onwards, the male animals only exhibited increased respiratory rate, with all signs cleared by day 7. The female animals exhibited a variety of clinical signs, with 1/5 animals found dead on day 4 post-exposure. This animal exhibited decreased respiratory rate, hunched posture, pilo-erection. diuresis, ptosis, dehydration and laboured respiration on the 2 days prior to death. Signs exhibited in the remaining female animals from days 2–10 post exposure included hunched posture, pilo-erection and/or increased respiratory rate, with dehydration and occasional body tremors noted in 1/4 animals on day 3 and 4 post-exposure.
Effects in Organs	During the necropsy of the female animal that was found dead during the study, dark patches were noted on the lungs and the liver exhibited a patchy pallor. Dark patches on the lungs were also seen in another female animal at necropsy. No other macroscopic abnormalities were noted at necroscopy.
Remarks - Results	All animals exhibited body weight losses on day 1 post exposure. All males exhibited body weight gains for the remainder of the observation period. The female animals showed further weight losses (or weight remained the same) on day 3 post exposure, but the surviving animals then exhibited gains for the remainder of the observation period.
CONCLUSION	The notified chemical is of low toxicity via inhalation.
TEST FACILITY	Harlan (2014)

B.4. Corrosion – skin (in vitro)

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 431 In vitro Skin Corrosion: Human Skin Model Test.
Vehicle	Used as supplied.
Remarks - Method	EPISKIN™ Reconstructed Human Epidermis Model. No significant protocol deviations. GLP Compliance. Negative and positive controls (both used as supplied) were used in parallel with the test substance.

RESULTS

Test material	*Test 1 (3 minute exposure period)*		*Test 2 (1 hour exposure period)*		*Test 3 (4 hour exposure period)*	
	Mean OD_{562} of duplicate tissues	*Relative mean viability (%)*	*Mean OD_{562} of duplicate tissues*	*Relative mean viability (%)*	*Mean OD_{562} of duplicate tissues*	*Relative mean viability (%)*
Negative control	-	-	-	-	0.849	100*
Test substance	0.949	111.8	0.946	111.4	1.029	121.2
Positive control	-	--	-	-	0.050	5.9

OD = optical density
*The mean viability of the negative control tissues is set as 100%.

Remarks - Results	The MTT solution containing the test item remained yellow, indicating that the test item did not reduce MTT. The controls gave responses within the expected range, confirming the validity of the test system.
CONCLUSION	The notified chemical was non-corrosive to the skin under the conditions of the test.
TEST FACILITY	Harlan (2013h)

B.5. Irritation – skin (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 439 In vitro Skin Irritation - Reconstructed Human Epidermis Test Method
Vehicle	None.
Remarks - Method	EPISKIN™ Reconstructed Human Epidermis Model. No significant protocol deviations. GLP Compliance. In the pre-test, the test substance was shown to directly reduce MTT. Therefore, the main test was performed in parallel on viable and water-killed tissues. For the skin irritation test, the test substance (10 µL) was applied to the tissues in triplicate. Following an exposure period of 15 minutes at room temperature, the tissues were rinsed and then incubated in fresh medium at 37 °C for ~42 hours. The tissues were then treated with MTT and incubated at 37 °C for 3 hours. Positive and negative controls were run in parallel with the test substance: - Negative control (NC): Phosphate Buffered Saline Dulbecco's (PBS) with Ca^{++} and Mg^{++} - Positive control (PC): sodium dodecyl sulphate (SDS)

RESULTS

Irritation test

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.863	100.0*	9.8
Test substance	0.108	12.5	4.0
Positive control	0.069	8.0	1.0

OD = optical density; SD = standard deviation
*The mean viability of the negative control tissues is set as 100%.

Remarks - Results	The study authors considered that the results of this test showed no degree of interference due to direct reduction of MTT. It was hence considered unnecessary to use the results of the water-killed tissues 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 (2013e)

B.6. Irritation – skin (in vitro)

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 439 In vitro Skin Irritation: Reconstructed Human *Epidermis* Test Method.
Vehicle	Used as supplied.
Remarks - Method	EPISKIN™ Reconstructed Human Epidermis Model. No significant protocol deviations. GLP Compliance. Negative and positive controls were used in parallel with the test substance.

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability (%)*
Negative control	0.725	Set at 100	5.0
Test substance	0.863	119.1	9.6
Positive control	0.119	16.5	6.0

OD = optical density; SD = standard deviation

Remarks - Results	The MTT solution containing the test item did not turn blue, indicating that the test item did not directly reduce MTT. The controls gave responses within the expected range, confirming the validity of the test system. The study authors considered it unnecessary to perform IL-1α analysis as they deemed these results to be unequivocal.
CONCLUSION	The notified chemical was non-irritating to the skin under the conditions of the test.
TEST FACILITY	Harlan (2013i)

B.7. Irritation – skin

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White.
Number of Animals	3 Males.
Vehicle	Test substance administered as supplied.
Observation Period	14 days.
Type of Dressing	Semi-Occlusive.
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Skin Reaction	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0	0	1	< 24 hours	0
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 erythema was noted for 2 of the test animals immediately after patch removal, with symptoms persisting in 1 of these animals at the 1 hour observations. All treated skin sites appeared normal at the 24 hour observation.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	Harlan (2013j)

B.8. Irritation – eye (in vitro)

TEST SUBSTANCE	Notified chemical (20% w/v dilution).
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants.
Controls	Negative/Vehicle: 0.9% sodium chloride. Positive: 20% w/v Imidazole.
Remarks - Method	No significant protocol deviations. GLP Compliance. Negative and positive control items were tested concurrently.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
Vehicle control	2.7	0.037	3.2
*Test substance**	1.6	0.009	1.7
*Positive control**	52.0	1.44	73.6

SD = Standard deviation; IVIS = in vitro irritancy score
*Corrected for background values

Remarks - Results	The corneas treated with the test item and negative control were clear post-incubation, whereas the corneas treated with the positive control were cloudy. The controls gave satisfactory responses confirming the validity of the test system.
CONCLUSION	The notified chemical was not corrosive or a severe eye irritant under the conditions of the test.
TEST FACILITY	Harlan (2013k)

B.9. Irritation – eye

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

RESULTS

Lesion	*Mean Score* Animal No.*	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*

	1	2	3			
Conjunctiva: redness	0.3	0.7	0.7	2	< 72 hours	0
Conjunctiva: chemosis	0.3	0.7	0	2	< 72 hours	0
Conjunctiva: discharge	0	0.3	0.3	1	< 48 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0.3	0	1	< 48 hours	0

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

Remarks - Results

Ocular reactions produced included iridial inflammation and moderate conjunctival irritation in all treated eyes 1 hour after treatment. No corneal effects were noted during the study. 1 treated eye appeared normal at the 48 hour observation and 2 treated eyes appeared normal at the 72 hour observation.

CONCLUSION

The notified chemical is slightly irritating to the eye.

TEST FACILITY

Harlan (2013l)

B.10. 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 (CBA/CaOlaHsd).

Vehicle

Acetone/olive oil (4:1 v/v; AOO).

Remarks - Method

No significant protocol deviations.
GLP Compliance.

A preliminary toxicity study (1 mouse) was performed with the test substance at 50% w/w and was used to select the concentrations for the main test. Mean ear thickness measurements changed by < 25% over 6 days in this test, with no signs of systemic toxicity or local irritation. Light brown coloured residual test item was noted post-dosing on the ears of the animal treated with the test item on days 1 to 3.

Vehicle and positive controls (α-Hexylcinnamaldehyde, as a 25% v/v dilution in AOO) were used in parallel with the test material.

RESULTS

Concentration (% w/w)	*Mean Disintegrations (DPM/animal))*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	1,356.89 (± 386.52)	N/A
10	21,842.08 (± 9,827.15)	16.1
25	22,910.70 (± 3,619.76)	16.88
50	12,419.70 (± 6,409.89)	9.15
Positive Control	14,430.07 (± 5,754.04)	10.63

Remarks - Results

No signs of systemic toxicity were noted in the test or control animals during the study. Light brown coloured residual test item was noted on days 1 to 3 post-dosing on the ears of animals treated at 50% w/w.

The results show that the test substance elicited stimulation indices > 3 for all concentration levels tested. Statistically significant differences were noted between the control group and all dose groups.

The EC3 value could not be determined. The positive control gave a satisfactory response confirming the validity of the test system.

CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.
TEST FACILITY	Harlan (2011a)

B.11. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (10% w/w in vehicle).
METHOD	Repeated insult patch test with challenge.
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 hours and graded after an additional 24 hours (or 48 hours for patches applied on Friday). Rest Period: approximately 2 weeks. Challenge Procedure: A patch was applied to a naïve site. Patches were removed by technicians after 24 hours. Sites were graded 24 and 48 hours post-patch removal. Subjects exhibiting reactions during the Challenge Phase of the study underwent re-evaluation 72 hours after patch removal.
Study Group	81 F, 31 M; age range 18–70 years
Vehicle	EtOH:DEP(1:3)
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm^2 patch, and allowed to evaporate for 30–90 minutes prior to patch application. A panel of 112 healthy human subjects (devoid of any physical or dermatological conditions) was amassed. A control substance (unspecified; 5% in EtOH:DEP, 1:3) was also applied to subjects in a similar manner to the test substance.
RESULTS	
Remarks - Results	107/112 subjects completed the study, with 5/112 subjects reported to have discontinued for reasons unrelated to the test material (4–9 induction observations recorded). With respect to the test substance, 3 subjects presented with hyperpigmentation during the Induction Phase. Five subjects were noted with barely perceptible to mild erythema at induction, lasting 1 to 2 evaluation observations. At Challenge, 3 subjects showed barely perceptible erythema (1 subject at patch removal and 2 subjects 48 hours after removal). A subject exhibiting erythema at 48 hours after patch removal also showed barely perceptible papules at the same observation (it is noted that barely perceptible erythema was also observed in this subject at 2 observations during the Induction phase). No responses were evident in these subjects after 72 hours. With respect to the control substance, 4 subjects were noted to have responses during the induction phase. These included mild erythema and edema (observation 1; changed site; no responses thereafter); hyperpigmentation and dryness (observation 4; changed site; no responses thereafter) and barely perceptible erythema (2 subjects; observations 8 or 9; one of these subjects also showed a similar response to the test substance at the same observation). One of the latter subjects also exhibited barely perceptible erythema at challenge patch removal. None of the subjects that exhibited responses to the test substance at challenge showed responses to the control substance at challenge.
CONCLUSION	The test substance was considered by the study authors to be non-

	sensitising under the conditions of the test.
TEST FACILITY	Clinical Research Laboratories Inc. (2013b)

B.12. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (15% w/w in vehicle).
METHOD	Repeated insult patch test with challenge.
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 hours and graded after an additional 24 hours (or 48 hours for patches applied on Friday). Rest Period: approximately 2 weeks. Challenge Procedure: A patch was applied to a naïve site. Patches were removed by technicians after 24 hours. Sites were graded 24 and 48 hours post-patch removal. Subjects exhibiting reactions during the Challenge Phase of the study underwent re-evaluation 72 hours after patch removal.
Study Group	81 F, 31 M; age range 19–70 years
Vehicle	EtOH:DEP(1:3)
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm^2 patch, and allowed to evaporate for 30–90 minutes prior to patch application. A panel of 112 healthy human subjects (devoid of any physical or dermatological conditions) was amassed. A control substance (unspecified; 5% in EtOH:DEP, 1:3) was also applied to subjects in a similar manner to the test substance.
RESULTS	
Remarks - Results	106/112 subjects completed the study, with 6/112 subjects reported to have discontinued for reasons unrelated to the test material (0–7 induction observations recorded). With respect to the test substance, 1 subject was noted with barely perceptible erythema at the 4th induction observation only. At Challenge, a different subject showed barely perceptible erythema 24 hours after patch removal. No responses to the control substance were evident.
CONCLUSION	The test substance was considered by the study authors to be non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2014a)

B.13. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (20% w/w in vehicle).
METHOD	Repeated insult patch test with challenge.
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 hours and graded after an additional 24 hours (or 48 hours for patches applied on Friday). Rest Period: approximately 2 weeks. Challenge Procedure: A patch was applied to a naïve site. Patches were

removed by technicians after 24 hours. Sites were graded 24 and 48 hours post-patch removal. Subjects exhibiting reactions during the Challenge Phase of the study underwent re-evaluation 72 hours after patch removal.

Re-Challenge Procedure: 3 subjects were asked to participate (due to effects seen during the original Challenge Phase) approximately 5 weeks after the Challenge Phase. 2 subjects agreed to participate. Followed the same procedure as the previous Challenge Phase (using the upper arm as application site rather than the upper back).

Study Group	96 F, 16 M; age range 19–70 years
Vehicle	EtOH:DEP(1:3)
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm^2 patch, and allowed to evaporate for 30–90 minutes prior to patch application.

A panel of 112 healthy human subjects (devoid of any physical or dermatological conditions) was amassed.

A control substance (unspecified; 5% in EtOH:DEP, 1:3) was also applied to subjects in a similar manner to the test substance (excluding Re-Challenge phase).

RESULTS

Remarks - Results

103/112 subjects completed the study, with 9/112 subjects reported to have discontinued for reasons deemed by the study authors as unrelated to the test material (0–9 induction observations recorded).

With respect to the test substance, 2 subjects were noted with barely perceptible to mild erythema at induction at 2 observations each.

Three subjects showed effects to treatment with the test substance during the Challenge Phase. One subject presented well defined erythema at patch removal, with barely perceptible erythema still evident at 24 and 48 hours after patch removal (no reaction was evident 72 hours after patch removal; this subject also exhibited mild erythema in response to the control substance at patch removal; subject declined participation in a Re-Challenge Phase). Two subjects showed mild erythema at 48 hours after patch removal, with 1 subject showing the same response 72 hours after patch removal (barely perceptible erythema was also noted in this subject at Induction) and the other subject showing mild erythema at this observation. These reactions were deemed by the study authors to likely be indicative of irritation and delayed irritation (due to lack of oedema and/or itching).

At re-challenge, no effects were seen in the 2 subjects at any observation time point.

CONCLUSION

The test substance was considered by the study authors to be non-sensitising under the conditions of the test.

TEST FACILITY

CRL (2014b)

B.14. Repeat dose toxicity

TEST SUBSTANCE

Notified chemical.

METHOD

OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.

Species/Strain	Rat/ Wistar Han™:RccHan™:WIST.
Route of Administration	Oral – dietary.
Exposure Information	Total exposure days: 28 days. Post-exposure observation period: 14 days.

Remarks - Method	Dose regimen: 7 days per week. No significant protocol deviations. GLP Compliance. The mean achieved doses were 43.1, 67.6 and 101 mg/kg bw/day for males and 47.4, 58 and 85.8 mg/kg bw/day for females. While testing of control and high dose recovery groups were conducted, no raw data for the findings were included in the final study report.

RESULTS

Group	*Number and Sex of Animals*	*Dose ppm bw/day*	*Mortality*
control	5 per sex	0	0/10
low dose	5 per sex	500	1/10
mid dose	5 per sex	800	0/10
high dose	5 per sex	1200	0/10
control recovery	5 per sex	0	0/10
high dose recovery	5 per sex	1200	0/10

Mortality and Time to Death

A male animal in the low dose group died during blood sampling on day 28. No clinical signs were noted in this animal prior to death and no macroscopic abnormalities were detected at necropsy. The study authors attributed this death to a heightened stress response associated with the blood sampling procedure, and not related to the treatment.

No other unscheduled deaths occurred during the study period.

Clinical Observations

No clinical signs were observed or toxicologically significant changes noted in behaviour, functional performance, or sensory activity assessment, for animals of either sex, dosed at any level, throughout the study period.

Decreases in mean body weight gains were noted in both sexes at different dose levels (see table below) at the weekly observations. It is noted that mean body weight gains during the treatment-free period were similar to the control animals for the high dose recovery group males, and exceeded controls for the equivalent female group.

Treatment (ppm)	**Males**	**Females**
1200	decreased mean body weight gain at weeks 1, 2* & 4*	mean body weight decrease at week 1 decreased mean body weight gain at weeks 2*, 3 & 4
800	decreased mean body weight gain at weeks 1 and 4*	decreased mean body weight gain at weeks 1 and 4
500	decreased mean body weight gain at week 1	decreased mean body weight gain at week 1*

*not statistically significant

While no adverse effects on water consumption were observed, mean weekly food consumption and food efficiency were reduced relative to control animals at various points in the study, particularly in high dose animals.

Based on oestrous cycle assessments, the study authors noted that 2 females from the high dose group and 1 female from the mid dose group were acyclic throughout the assessment period.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Males from all dose groups showed statistically significant increases in prothrombin time at the end of the treatment period. Females of the high and mid dose groups showed statistically significant decreases in reticulocyte %. A statistically significant decrease in WBC count was seen in high dose recovery group males and the corresponding females showed statistically significant reductions in haemoglobin, and a decrease in

haematocrit levels The observations in females and recovery animals were considered by the study authors to not be toxicologically significant haematological effects.

There were various statistically significant effects on blood chemistry parameters seen in all dose groups at the end of the treatment period (see table below). No statistically significant effects were seen in the high dose recovery groups relative to the control groups.

Treatment (ppm)	Males	Females
1200	increased gamma glutamyl transpeptidase, phosphorus decreased bilirubin, urea, calcium concentration, alkaline phosphatase	increased gamma glutamyl transpeptidase, cholesterol, phosphorus decreased albumin/globulin ratio
800	increased gamma glutamyl transpeptidase decreased bilirubin, urea, calcium concentration, alkaline phosphatase	increased gamma glutamyl transpeptidase, cholesterol, phosphorus decreased albumin/globulin ratio
500	increased gamma glutamyl transpeptidase decreased bilirubin	increased gamma glutamyl transpeptidase, bile acid, cholesterol, phosphorus decreased albumin/globulin ratio.

There were no toxicologically significant effects detected on the urinalytical parameters measured.

Effects in Organs

A mid dose female animal had small adrenals, uterus and cervix at necropsy. No other macroscopic abnormalities were noted in any other test animals.

Males in the high dose group showed reduced sperm concentration and motility values, however, these observations did not translate to effects detected in morphological assessment or in changes in homogenisation-resistant spermatid counts.

Various statistically significant effects were seen on organ weights of animals of both sexes and all dose groups:

Treatment (ppm)	Males	Females
1200	increased liver (absolute & relative) decreased pituitary (absolute & relative) decreased prostate & seminal vesicles (absolute & relative)	increased liver (absolute & relative) decreased pituitary (absolute & relative) decreased uterus & cervix (absolute & relative)
800	increased liver (absolute & relative) decreased pituitary (absolute & relative) decreased prostate & seminal vesicles (absolute & relative)	increased liver (absolute & relative) decreased pituitary & thyroid (absolute & relative) decreased uterus & cervix (absolute & relative)
500	increased liver (absolute & relative) decreased pituitary (absolute & relative) decreased prostate & seminal vesicles (absolute & relative)	increased liver (absolute & relative) decreased pituitary & thyroid (absolute & relative)

While the mean value for thyroid weight change in high dose females was not statistically significant (as seen in the low and mid dose groups), the majority of the individual values were outside the normal expected range, hence a dose response relationship could not be excluded.

High dose recovery group females continued to show a statistically significant increase in absolute and relative liver weights at the end of the recovery period. The effects seen in high dose recovery group males, while showing statistically significant changes in thyroid (reduced absolute and relative values) and left epididymis weights (decreased and increased for absolute and relative values, respectively), were considered by the study authors to lack toxicologically significant intergroup differences.

Microscopic abnormalities were detected in the liver, pituitary, thyroid, stomach, uterus, vagina and sternal bone marrow of various animals. Centrilobular hypertrophy of the liver was detected in animals of both sexes in all treatment groups, in a dose dependent pattern. The study authors indicated that this liver effect was resolved after the recovery period. Periportal vacuolation was also present in animals from all groups, persisting after recovery in 2 treated females. Degranulation/hypertrophy of pituicytes was present in males from all treatment groups and 1 female of the highest dose group during the treatment period, but had resolved after recovery. Follicular epithelial hypertrophy was observed in the thyroid glands of animals of both sexes from all treatment groups, but resolved after recovery. Stomach effects were noted in some high dose females (3/5 of the animals examined), with non-glandular mucosal hyperplasia of mild (2/3) to moderate (1/3) severity accompanied by mild (1/3) to moderate (1/3) inflammation. However, the study authors indicated that these stomach effects had resolved after the recovery period. Some kidney effects were seen including mineralisation (2/5 high dose females) and evidence of basophilic tubules (1 male from the low and high dose groups), however these effects were also seen in the female control animals and were hence discounted by the study authors as not of toxicological significance.

On inspection of the female animals, uterine atrophy was found in some of the high and mid dose animals, often associated with anoestrus morphology in the vagina. However, this was not detected after recovery. An increase in fat vacuolation in the sternal bone marrow was also noted in some mid and high dose females, with some evidence of the effect continuing into the recovery period. However, the study authors considered that the number of animals, with effect persistence, fell within the limits of normal variability.

Remarks – Results

The study authors noted that administration of the test substance resulted in clear functional changes in the liver of animals of both sexes, at all dose levels. Observations deemed by the authors to be indicative of altered organ function included the thyroid and pituitary changes and changes in the uteri, oestrous cycle assessment and sperm analysis. The authors attributed the thyroid and pituitary changes to hepatocellular metabolic induction, and in light of these functional changes, the authors noted that the adverse effects seen in the reproductive organs may represent a secondary response to the changes in the liver function.

Consequently, the study authors could not establish a No Observed Effect Level (NOEL) for the study.

CONCLUSION

The Lowest Observed Adverse Effect Level (LOAEL) was established by the study authors as 500 ppm (equivalent to a mean achieved dose of 43.1 mg/kg bw/day for males and 47.4 mg/kg bw/day in females) in this study, based on the observation of adverse effects at all treatment levels.

TEST FACILITY	Harlan (2014)

B.15. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure/Pre incubation procedure.
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 5–5,000 µg/plate b) Without metabolic activation: 5–5,000 µg/plate
Vehicle	Dimethyl formamide.
Remarks - Method	No significant protocol deviations. GLP Compliance. A preliminary test was conducted using TA100 and WP2uvrA in the presence and absence of metabolic activation between 0.15–5,000 µg/plate. Test 1 (plate incorporation) and Test 2 (pre incubation) were conducted on separate days using fresh cultures of the bacterial strains and test substance formulations, with the dose ranges for Test 2 selected based on

the results of Test 1 (maximum concentration of 150 µg/plate for strains TA1535 and TA1537 in the absence of metabolic activation).

Vehicle and positive controls were used in parallel with the test material. Positive controls: i) without S9: *N*-ethyl-*N*'-nitro-*N*-nitrosoguanidine (used as the positive control for the tester strains: WP2uvrA$^-$, TA100, TA1535), 9-aminoacridine (TA1537) and 4-nitroquinoline-1-oxide (TA98); ii) with S9: 2-aminoanthracene (TA100, TA1535, TA1537, WP2uvrA$^-$) and benzo(a)pyrene (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	> 5,000	≥ 500	≥ 5,000	negative
Test 2		≥ 50	≥ 5,000	negative
Present				
Test 1	> 5,000	≥ 500	≥ 5,000	negative
Test 2		≥ 500	≥ 5,000	negative

Remarks - Results

In Test 1, the test substance caused a reduction in the frequency of revertant colonies for the bacterial strains TA1535, TA98 and TA1537 (in both the presence and absence of S9-mx) and WP2*uvra* (absence of S9-mix only). However, these responses were not accompanied by any visible reduction in the growth of bacterial background lawns.

In Test 2, the test substance caused a visible reduction in the frequency of revertant colonies and/or in the growth of the bacterial background lawn, with and without metabolic activation.

No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose material, either with or without metabolic activation.

The controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

CONCLUSION

The notified chemical was considered to be not mutagenic to bacteria under the conditions of the test.

TEST FACILITY

Harlan (2012c)

B.16. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical.

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Human.

Cell Type/Cell Line: Lymphocytes.

Metabolic Activation System: S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver.

Vehicle: Acetone.

Remarks - Method: No significant protocol deviations.
GLP Compliance.

Preliminary assays were performed both with and without the metabolic activation system (at 2%) for concentrations 4.73–1,211 µg/mL with 4 hour exposure time and 20 hour fixation time (and a 24 hour continuous exposure in the absence of metabolic activation). The maximum dose was based on use of acetone as solvent. Precipitation was noted in the parallel

blood-free cultures at ≥ 302.75 µg/mL. Haemolysis was noted at ≥ 18.92 µg/mL in all exposure groups.

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

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 4, 8*, 16*, 24*, 32, 48, 64	4	24
Test 2	0*, 4, 8*, 16*, 24, 32*, 48	24	24
Present			
Test 1	0*, 8*, 16*, 32*, 48, 64, 80	4	24
Test 2	0*, 4, 8, 16*, 32*, 40*, 48, 56, 64	4	24

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 37.84	≥ 32	> 64	negative
Test 2	≥ 18.92	≥ 24	> 48	negative
Present				
Test 1	≥ 75.69	≥ 48	> 80	negative
Test 2	-	≥ 40	> 64	negative

Remarks - Results

The maximum concentrations selected for metaphase analysis (Test 1) corresponded to the maximum concentrations with metaphases suitable for scoring.

The test item did not induce any statistically significant increases in the frequency of cells with aberrations, or polyploidy cell frequency, with or without metabolic activation. No precipitate of the test item was observed at the end of exposure in either group. However, haemolysis was seen in both tests (at ≥ 8 µg/mL in both exposure groups in test 1 and ≥ 32 µg/mL in the absence of S9-mix and ≥ 8 µg/mL in the presence of S9-mix in test 2).

The controls gave satisfactory responses confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

Harlan (2013m)

B.17. Phototoxicity (in vitro)

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 432 In vitro – 3T3 NRU Phototoxicity Test
Vehicle: 1% v/v DMSO in EBSS.
Remarks - Method: No significant protocol deviations.
GLP Compliance.

Irradiation was performed with a solar simulator (produced wavelength of simulator with filter was > 320 nm).

Negative and positive (chlorpromazine) controls, with and without irradiation with artificial sunlight, were used in parallel with the test substance.

A range finding experiment was conducted with the notified chemical at concentrations ≤ 31.25 µg/mL. The main experiment was conducted at ≤ 20 µg/mL.

RESULTS

Test material	*ED_{50} Value (+ UV) [µg/mL]*	*ED_{50} Value (- UV) [µg/mL]*	*PIF*	*MPE*
Positive control	0.77	17.51	22.65	0.373
Test substance	4.82	10.07	2.09	0.117

Remarks - Results: A dose dependent cytotoxic response was observed after treatment of cells with the notified chemical in both the presence and absence of irradiation with artificial sunlight. This cytotoxicity was noted in the range finding experiment and confirmed by the main experiment.

The study authors deemed these results equivocal.

The controls gave responses within the expected range, confirming the validity of the test system.

CONCLUSION: The notified chemical was predicted to have probable phototoxic effects on BALB/c 3T3 cells, under the test conditions.

TEST FACILITY: Harlan (2012)

B.18. Phototoxicity – skin (in vitro)

TEST SUBSTANCE: Notified chemical.

METHOD: Phototoxicity protocol for use with EpiDerm™ Model (EPI-200) (MatTek Corporation, 1997).
Positive control: 0.05% w/v Chlorpromazine in deionised water.
Negative control/vehicle: Sesame oil.
Remarks - Method: GLP Compliance.

This study was performed as a follow up to the *in vitro* Balb/c 3T3 phototoxicity study (Harlan, 2012) in order to confirm the equivocal result.

Suspensions (20 µL) of the test substance (0.316–10%) in sesame oil were applied onto filter pads and then onto the skin equivalents (in duplicate; tissues incubated 24 hours). Following removal of the filter pads, one group treated with the test substance was irradiated with artificial sunlight

(60 mins; 1.7 mW/cm^2 UVA resulting in an irradiation dose of 6 J/cm^2 UVA). The other group was maintained in the dark for 1 hour. Following rinsing, the tissues were incubated for 24 hours and then subject to MTT assay.

Negative and positive controls (with and without irradiation with artificial sunlight) were used in parallel with the test substance.

RESULTS

Test material	*Concentration (%)*	*Mean OD_{570} of duplicate tissues*	*Relative mean Absorbance (%)*
		Without Irradiation	
Negative control	100	1.286	100
Test substance			
Test 1	0.316	1.436	111.7
Test 2	1.0	1.093	85.0
Test 3	3.16	1.072	83.3
Test 4	10	0.912	70.9
Positive control	0.05	0.567	44.1
		With Irradiation	
Negative control	100	1.206	100
Test substance			
Test 1	0.316	1.192	98.9
Test 2	1.0	1.168	96.8
Test 3	3.16	0.918	76.1
Test 4	10	0.771	63.9
Positive control	0.05	0.066	5.5

SD= Standard Deviation

Remarks - Results

Cytotoxic effects were not observed after exposure of the skin equivalents to the test item suspension, neither in the presence or the absence of irradiation with artificial sunlight.

The controls gave responses within the expected range.

CONCLUSION

The notified chemical did not exhibit any phototoxic effects on the skin equivalents under the conditions of the test.

TEST FACILITY

Harlan (2013)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sewage sludge from a predominantly domestic sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Total Organic Carbon (TOC) Method
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Notified chemical		*Sodium benzoate (reference substance)*	
Day	*% Degradation*	*Day*	*% Degradation*
3	10	3	44
14	31	14	102
28	17	28	89
29*	20	29	97

* Day 29 values corrected to include any carryover of CO_2.

Remarks - Results	The validity criteria for the test were met. The toxicity control attained 57% degradation by day 14 of the study thereby confirming that the notified chemical was not toxic to the sewage treatment micro-organisms used in the study. After 28 days the toxicity control had attained 58% degradation. The notified chemical attained 20% degradation after 28 days and, therefore, cannot be considered as readily biodegradable under the conditions of OECD Guideline 301B.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Harlan (2013n)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD 301F Manometric Respirometry Test
Inoculum	Activated sewage sludge from a predominantly domestic sewage treatment plant
Exposure Period	28 Days
Auxiliary Solvent	None
Analytical Monitoring	Biological Oxygen Demand (BOD)
Remarks – Method	No significant protocol deviations. GLP Compliance.

RESULTS

Notified Chemical		*Sodium Benzoate (Reference Substance)*	
Day	*% Degradation*	*Day*	*% Degradation*
3	0.5	3	62.0
14	1.6	14	84.4
28	1.0	28	86.6

Remarks – Results: The validity criteria for the test were met.

The toxicity control attained 39.3% degradation by day 14 of the study thereby confirming that the notified chemical was not toxic to the sewage treatment micro-organisms used in the study. After 28 days the toxicity control had attained 40.3% degradation.

CONCLUSION: The notified chemical is not readily biodegradable.

TEST FACILITY: Safety Evaluation Centre (2012a)

C.1.3. Bioaccumulation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 305 Bioconcentration: Flow-through Fish Test.

Species: *Lepomis macrochirus*

Exposure Period: Exposure: 21 days Depuration: 14 days

Auxiliary Solvent: Dimethyl Formamide (DMF)

Concentration Range: Nominal: 0.0040 and 0.040 mg/L
Actual: 0.00350 and 0.0362 mg/L

Analytical Monitoring: GC/FID

Remarks - Method: No significant protocol deviations.
GLP Compliance.

A preliminary range finding test was conducted to determine the concentrations to be used in the definitive test. The definitive test was conducted at concentrations of 0.0040 and 0.040 mg notified chemical/L.

RESULTS

Bioconcentration Factor: 615 at low concentration (0.0035 mg/L), and 824 at higher concentration (0.0362 mg/L)

Remarks - Results: The calculated time to 95% depuration of the ^{14}C-residue in whole fish tissue was 2.4 days in the low treatment concentration and 3.6 days in the high treatment. The validity criteria for the test were met.

CONCLUSION: The notified chemical is not considered to be bioaccumulative.

TEST FACILITY: ABC Laboratories (2013a)

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: *Danio rerio*

Exposure Period: 96 hour

Auxiliary Solvent: DMF

Water Hardness: Not reported

Analytical Monitoring: GC/FID conducted in accordance with the guidelines above.

Remarks – Method: No significant protocol deviations.
GLP Compliance.

A preliminary range finding test was conducted to determine the concentrations to be used in the definitive test. The definitive test was performed with renewal of the test solution every 24 hours.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*			
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
Control	ND	10	0	0	0	0
Solvent Control	ND	10	0	0	0	0
0.4	0.41	10	0	0	0	0
0.52	0.45	10	0	1	2	2
0.66	0.63	10	0	3	4	7
0.85	0.76	10	7	10	-	-
1.1	0.95	10	8	10	-	-

LC_{50}	0.55 mg/L at 96 hours.
Remarks – Results	The validity criteria for the test were met.
CONCLUSION	The notified chemical is very toxic to fish.
TEST FACILITY	Safety Evaluation Centre (2013a)

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	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	No significant protocol deviations. GLP Compliance. A preliminary range finding test was conducted to determine the concentrations to be used in the definitive test. An amount of test substance (1,100 mg) was dispersed in 11 litres of reconstituted water. This mixture was stirred for 72 hours. The mixture was filtered to remove undissolved material to give a 100% v/v saturated solution. A series of dilution was made from this saturated solution to give test concentrations of 0.1, 1.0 and 10% v/v solution.

RESULTS

Concentration		*Number of D. magna*	*Number Immobilised*	
Nominal (% v/v saturated solution)	*Measured mg/L*		*24 h*	*48 h*
Control	-	5	0	0
1.0	-	5	0	0
3.2	-	5	0	0
10	0.18	5	0	0
32	-	5	0	5
100	1.8	5	5	5

EC_{50}	0.32 mg/L at 48 hours
NOEC	0.18 mg/L at 48 hours
Remarks - Results	The validity criteria for the test were met. Analysis of the 10, 32 and 100% v/v saturated solution test substance preparations at 0 hours showed measured test concentrations to range from 0.18 to 1.8 mg/L. There was no significant change in measured

concentrations at 48 hours and so the results were based on 0 hour measured test concentrations only.

CONCLUSION The notified chemical is very toxic to aquatic invertebrates.

TEST FACILITY Harlan (2013o)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.

Species *Pseudokirchneriella subcapitata*

Exposure Period 72 hours

Concentration Range Nominal: 1.0, 3.2, 10, 32 and 100% v/v saturated solutions.
Actual: 0.0062, 0.011, 0.057, 0.2 and 0.72 mg/L

Auxiliary Solvent None

Water Hardness 0.15 mM Ca^{2+} and Mg^{2+}

Analytical Monitoring HPLC

Remarks – Method No significant protocol deviations.
GLP Compliance.

A preliminary range finding test was conducted to determine the concentrations to be used in the definitive test.

An amount of notified chemical (1,100 mg) was dispersed in 11 litres of reconstituted water. This mixture was stirred for 72 hours. The mixture was filtered to remove undissolved material to give a 100% v/v saturated solution. A series of dilution was made from this saturated solution to give test concentrations of 0.1, 1.0 3.2, 10 and 32% v/v solution.

RESULTS

Biomass		*Growth*	
EyC_{50}> mg/L at 72 h	*NOEC mg/L*	*ErC_{50} mg/L at 72 h*	*NOEC mg/L*
0.59	0.057	> 0.72	0.057

Remarks - Results The validity criteria for the test were met.
A decline in total measured test substance concentration was observed at 72 hours in the range than the limit of quantification (LOQ 0.0048) to 0.45 mg/L. This observation was initially thought to be due to adsorption of test substance on algal cells. However, later it was concluded that the test substance is unstable under test conditions. Therefore, it was considered appropriate to calculate the results based on geometric mean measured test concentrations only.

The EC_{50} is treated as an acute value for classification purposes. This EC_{50} should normally be based on growth rate inhibition. If the only EC_{50} based on reduction in biomass is available, or it is not indicated which EC50 is reported, this value may be used in the same way. The ErC_{50} was not defined and is therefore not acceptable for classification. Therefore, the EyC_{50} of 0.59 mg/L has been used as the end point for GHS classification.

CONCLUSION The notified chemical is very toxic to algae.

TEST FACILITY Harlan (2013p)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum Activated sewage sludge from domestic sewage treatment plant

Exposure Period 3 hours

Concentration Range Nominal: 10, 100 and 1,000 mg/L

	Actual: Not measured
Remarks – Method	No significant protocol deviations. GLP Compliance.
RESULTS	
IC50	> 1,000 mg/L
NOEC	1,000 mg/L
Remarks – Results	All validity criteria were satisfied.
CONCLUSION	The notified chemical is not expected to be inhibitory to micro-organisms at concentrations < 1,000 mg/L.
TEST FACILITY	Harlan (2013q)

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