File No: LTD/1778

October 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

4,7-Methano-1H-indene-5-acetaldehyde, octahydro-

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

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1778	International Flavours & Fragrances (Australia) Pty Ltd	4,7-Methano-1H-indene-5-acetaldehyde, octahydro-	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Acute toxicity (Category 4)	H302 – Harmful if swallowed
Skin irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

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

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

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

Hazard classification	*Hazard statement*
Acute (Category 1)	H400 – Very toxic to aquatic life
Chronic (Category 1)	H410 - Very toxic to aquatic life with long lasting effects

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

Based on the available information, when used at ≤ 0.04% in deodorants, ≤ 0.3% in fine fragrances, ≤ 0.5% in body lotions and ≤ 0.26% 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 assessed 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 irritation (Category 2): H315 – Causes skin irritation
  - Skin sensitisation (Category 1): H317 – May cause an allergic skin reaction

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

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

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

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

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during reformulation processes:
  - Avoid contact with skin

- 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

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

- A copy of the (M)SDS should be easily accessible to employees.

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

Public Health

- The following measures should be taken to minimise public exposure to the notified chemical:
  - The notified chemical should only be used at ≤ 0.04% in deodorants, ≤ 0.3% in fine fragrances, ≤ 0.5% in body lotions and ≤ 0.26% 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

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the concentration of the notified chemical exceeds or is intended to exceed 0.04% in deodorants, 0.3% in fine fragrances, 0.5% in body lotions and 0.26% in other cosmetic and household products;
- information becomes available on the repeated dose toxicity potential of the notified chemical;

or

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

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

(Material) Safety Data Sheet
The (M)SDS of the notified chemical was 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, flammability, explosive and oxidising properties, acute dermal toxicity, acute inhalation toxicity and repeated dose toxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

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

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
4,7-Methano-1H-indene-5-acetaldehyde, octahydro-
Aquaflora Toco

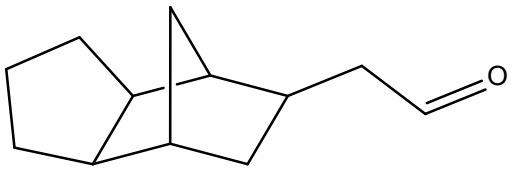
CAS NUMBER
1339119-15-1

CHEMICAL NAME
4,7-Methano-1H-indene-5-acetaldehyde, octahydro-

OTHER NAME(S)
FRET 09-0425
TM 11-213
12-211-01
12-211-03

MOLECULAR FORMULA
$C_{12}H_{18}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
178.27 Da

ANALYTICAL DATA
Reference ^{1}H-NMR, IR, UV, GC, GC-MS spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 90%

IDENTIFIED IMPURITIES

Chemical Name 4,7-Methano-1H-indene-5-carboxaldehyde, octahydro-6-methyl-
CAS No. 1338815-87-4 *Weight %* ~8%

ADDITIVES/ADJUVANTS
None.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless liquid.

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< - 20.0 °C	Measured
Boiling Point	258.0 ± 1 °C at 102.3 kPa	Measured
Relative Density	1020 kg/m^3 at 20 ± 0.5 °C	Measured
Vapour Pressure	6.0 x 10^{-3} kPa at 25 °C	Measured
Water Solubility	5.96 × 10^{-2} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functionalities, however, the notified chemical is not expected to be hydrolysed significantly under normal environmental conditions of pH 4 to 9
Partition Coefficient (n-octanol/water)	log Pow = 3.3 – 3.9	Measured
Surface Tension	log K_{oc} = 2.3 (MCI method) log K_{oc} = 2.3 (Kow method)	Calculated. KOCWIN v2.0, EPI Suite v4.1 (US EPA, 2010).
Dissociation Constant	Not determined	Does not contain ionisable functionalities
Flash Point	118.0 ± 2 °C at 101.3 kPa	Measured
Autoignition Temperature	214.0 ± 5.0 °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. Direct sources of heat and contact with strong acids, alkali or oxidising agents should be avoided.

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 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 (≤ 0.5% 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 cosmetic and household products (at proposed usage concentrations of ≤ 0.04% in deodorants, ≤ 0.5% in fine fragrances and body lotions and ≤ 0.26% in other cosmetic and household cleaning products).

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 (≤ 0.26% 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 ≤ 0.5% 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 overalls, 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 such as coveralls, goggles and impervious gloves.

End-use

Exposure to the notified chemical in end-use products (at ≤ 0.5% 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 (at ≤ 0.5% concentration) through the use of a wide range of cosmetic and household products. The principal routes of exposure will be dermal, while ocular and inhalation exposures (e.g. through the use of spray products) are also possible.

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 (300-2000) mg/kg bw; harmful
Skin irritation (in vitro)	irritating
Skin corrosion (in vitro)	non-corrosive
Eye irritation (in vitro) – BCOP	not severely irritating
Eye irritation (in vitro) – SkinEthic HCE model	non-irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (1%)	no evidence of sensitisation
Human, skin sensitisation – RIPT (2%)	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration	non genotoxic

Toxicokinetics, metabolism and distribution.
Based on the water solubility (5.96 x 10^{-2} g/L at 20 ºC), partition coefficient (log P_{ow} = 3.3 – 3.9) and the low molecular weight (178.27 Da) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are expected to occur. The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity.
The notified chemical was found to be harmful in an acute oral toxicity study in rats, with the study authors noting the LD50 to be ~500 mg/kg bw. Of the animals treated at 2,000 mg/kg bw, 2/3 were euthanized on the day of dosing due to the occurrence of severe toxicity. The remaining high dose group animal and one animal (1/6) dosed at 300 mg/kg bw, were found dead one day after dosing. Prior to their deaths, clinical signs seen in the animals treated at 2,000 mg/kg bw included ataxia, lethargy, hunched posture, prostration, laboured respiration, decreased respiratory rate, occasional body tremors, hypothermia and/or pallor of the extremities. At necropsy, effects noted in the animals that died during the study included body weight loss, pale and patchy pallor of the liver, pale or dark kidneys, clear liquid present in the stomach, haemorrhage and epithelial sloughing of the gastric mucosa and haemorrhage of the non-glandular epithelium of the stomach.

No acute dermal or inhalation toxicity data were provided for the notified chemical.

Irritation
Two in vitro dermal studies were conducted using reconstructed human epidermis models (EpiSkin). The skin corrosion study indicated that the notified chemical was non-corrosive, whereas the skin irritation study, indicated that the notified chemical was an irritant (relative mean viability of 12.5%).

Two in vitro ocular studies were also conducted. A bovine corneal opacity and permeability (BCOP) test indicated that the notified chemical was not corrosive or severely irritating to the eyes. An in vitro eye irritation study was also conducted using a reconstituted human corneal epithelium model (SkinEthic), which indicated that the notified chemical was non-irritating to the eyes.

Sensitisation.
The notified chemical was found to be a skin sensitiser in mice (Local Lymph Node Assay; stimulation indices of 9.28, 12.75 and 15.41 at 25, 50 and 100% concentrations, respectively). The EC_3 value was calculated to be 7.13%.

The sensitising potential of the notified chemical was tested in two separate human repeat insult patch tests (HRIPT). The notified chemical was not a skin sensitiser when tested at 1% concentration (with 105 subjects completing the study) and at 2% concentration (with 100 subjects completing the study), under the conditions of the studies. No reactions were noted in subjects in either study, during the induction or challenge phases. It is noted, however, that in the study conducted at 2% concentration, responses were seen at challenge in the same subjects at the application sites of the control sample (2% water in vehicle).

Repeated dose toxicity.
No repeated dose toxicity data were provided for the notified chemical.

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.

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 irritation (Category 2)	H315: Causes skin irritation
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):
R22 Harmful if swallowed
R38 Irritating to skin
R43 May cause sensitisation by skin contact

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

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). While the notified chemical is considered to be harmful to human health via the oral route, ingestion is unlikely under the occupational settings described. The notified chemical is considered to be a skin irritant and skin sensitiser. In addition, the repeated dose toxicity effects of the notified chemical have not been determined. Therefore, 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 ≤ 0.5% 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

Sensitisation and skin irritation
While the notified chemical is considered to be a skin irritant, irritation effects are not expected from use of the notified chemical at the proposed concentration. The main risk associated with use of the notified chemical at the proposed concentrations of ≤ 0.04% in deodorants, ≤ 0.5% in fine fragrances and body lotions and ≤ 0.26% in other cosmetic and household products, is its potential to cause sensitisation by skin contact.

Proposed methods for the quantitative risk assessment of dermal sensitisation have been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). As is shown in the table below, the Consumer Exposure Level (CEL) from use of the notified chemical in a number of different cosmetic and household products may be estimated (SCCS, 2012 and Cadby *et al*, 2002). When tested at 2% 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 to not 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., the LLNA study) was 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 11.24 µg/cm^2. In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16), a use and time factor (3.16) and a database factor (1), giving an overall safety factor of ~100.

Product type	**Proposed maximum usage concentration (%)**	**CEL chemical** (µg/cm^2)	**AEL chemical** (µg/cm^2)	**Proposed usage concentration supported?**	**Recommended usage concentration (%)**
Deodorant spray	0.04	2.86	11.24	Yes	≤ 0.04*
Fine fragrances	0.5	18.75	11.24	No	≤ 0.3
Body lotion	0.5	2.50	11.24	Yes	≤ 0.5*
Other leave-on cosmetics (assumed:face cream)	0.26	7.09	11.24	Yes	≤ 0.26*

*Proposed usage concentration

As the CEL > AEL (fine fragrances category), the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical in fine fragrances at ≤ 0.5% concentration is considered to be unreasonable. Reducing the concentration of the notified chemical in fine fragrances to 0.3% allows recalculation of the consumer exposure to acceptable levels. 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 deodorants at ≤ 0.04% concentration, body lotion at ≤ 0.5% concentration and other leave-on cosmetic products (using face cream as a worst case example) at ≤ 0.26% concentration is not considered to be unreasonable. Based on the lower expected exposure level from use of rinse-off cosmetic products and household products (≤ 0.26% 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.

Repeat dose toxicity
The repeated dose toxicity effects of the notified chemical have not been determined. However, exposure is expected to be limited by the low (revised) concentrations of the notified chemical in end use products.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.04% in deodorants, ≤ 0.3% in fine fragrances, ≤ 0.50% in body lotions and ≤ 0.26% in other cosmetic and household products, is not considered to be unreasonable. In the absence of data on the repeated dose toxicity potential of the notified chemical, use of the notified chemical is supported only under limited exposure conditions, which are reflected in the low concentration of the notified chemical in end-use products.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured in Australia; therefore there will be no release of the notified chemical to the environment from this activity. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

During reformulation processes, limited release of washings containing the notified chemical is expected from cleaning of equipment. The washings are expected to be discharged to an on-site wastewater treatment plant and/or a local municipal treatment plant according to state, territory and local government regulations. A small amount of the notified chemical is estimated to be generated as waste from residues in empty containers and spills during reformulation. Empty containers containing the notified chemical will either be recycled or disposed of through an approved waste management facility.

RELEASE OF CHEMICAL FROM USE

The majority of the notified chemical is expected to be released to sewers across Australia as a result of its use in cosmetic and household products, which will be washed off the hair and skin of consumers as well as from cleaning activities and disposed of to the sewer.

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that some of the product containing the notified chemical will remain in end-use containers. The containers are expected be disposed of through domestic garbage disposal and will enter landfill, or be subjected to recycling processes.

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 biodegradation studies indicate that the notified chemical is not considered to be rapidly degradable in the environment. Based on its moderate adsorption coefficient value (log Koc ~ 2.3), only limited partitioning to sludge is expected. The notified chemical has low potential to bioaccumulate based on its low partition coefficient (3.3 to 3.9). In surface waters, the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The notified chemical is expected to have low volatility from water (log H = 0.7 $Pa/m^3/mol$) and may not preferentially volatilise to air during use or sewage treatment based on calculations for the notified chemical. In the event of release to the atmosphere, the notified chemical is not expected to persist in the air compartment based on calculations (AOPWIN v1.92; US EPA, 2011) for a representative component of the notified chemical.

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 moderate soil adsorption coefficient. 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)

The calculation for the Predicted Environmental Concentration (PEC) is summarised in the table below. Based on the reported use in cosmetics and household cleaning products, it is assumed that 100% of the total import volume of the notified chemical will be released to the sewer. The release is assumed to be nationwide over 365 days per year. It is conservatively assumed that 0% of the notified chemical will be removed during sewage treatment processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year

Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.61	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.61 µg/L may potentially result in a soil concentration of approximately 4.0 µg/kg from each year of irrigation. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 20.2 µg/kg and 40.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

Ecotoxicological data were submitted for the notified chemical. Details of the studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity (96 h)	LC50 = 4.81 mg/L	Toxic to fish
Daphnia Toxicity (48 h)	EC50 = 0.69 mg/L	Very toxic to aquatic invertebrates
Algal Toxicity (72 h)	E_rC50 = 3.1 mg/L	Toxic to algae

The notified chemical is considered to be toxic to fish and algae, and very toxic to aquatic invertebrates. On the basis of the acute toxicity data, the notified chemical is very toxic to aquatic organisms. Therefore, Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009), the notified chemical is formally classified as Acute Category 1; Very toxic to aquatic life. Based on its acute toxicity and lack of ready biodegradability, the notified chemical has been formally classified under GHS as 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) for the notified chemical has been calculated and is presented in the table below. The PNEC is calculated based on the endpoint for the most sensitive species (daphnia, EC50) for the notified chemical. Acute ecotoxicity endpoints for aquatic species from three trophic levels are available. Therefore, an assessment factor of 100 has been used.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Invertebrates).	0.69	mg/L
Assessment Factor	100	
PNEC:	6.9	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	6.9	0.088
Q - Ocean:	0.06	6.9	0.009

The risk quotient for discharge containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its reported use pattern and annual importation quantity. The notified chemical has low potential for bioaccumulation. Therefore, on the basis of the PEC/PNEC ratio, maximum annual import 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/Freezing Point < -20 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	Determined in duplicate experiments by placing a test tube containing an aliquot of the test substance in a dry ice/acetone bath until the temperature of the substance reached ~-20 ºC. The test substance showed a slight increase in viscosity, with no change in appearance during cooling. The test substance did not show any indication of freezing
Test Facility	Harlan (2012a)

Boiling Point 258 ± 1.0 °C at 102.3 kPa

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	Determined via differential scanning calorimetry (DSC), heating aliquots of the test item up to 450 °C.
Test Facility	Harlan (2013a)

Relative Density 1020 kg/m^3 at 20.0 ± 0.5 °C

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

Vapour Pressure 6.0 x 10^{-3} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Determined using a vapour pressure balance.
Test Facility	Harlan (2013b)

Water Solubility 5.96 × 10^{-2} g/L at 20 °C

Method	OECD TG 105 Water Solubility.
Remarks	Flask Method
Test Facility	Harlan (2012a)

Partition Coefficient (n-octanol/water) log Pow = 3.3 – 3.9

Method	OECD TG 117: Partition Coefficient (n-octanol/water), High Performance Liquid Chromatography (HPLC) Method
Remarks	HPLC Method
Test Facility	Harlan (2012a)

Surface Tension 64.0 mN/m at 21.0 ± 0.5 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions. EC Council Regulation No 440/2008 A.5 Surface Tension.
Remarks	Concentration: 90% saturated aqueous solution Determined using a tensiometer and the ring method.
Test Facility	Harlan (2013a)

Flash Point 118.0 ± 2.0 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Determined using a closed cup equilibrium method.
Test Facility	Harlan (2013c)

Autoignition Temperature 214.0 ± 5.0 °C

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

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 (2013c)

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 (2013c)

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 (RccHan™:WIST)
Vehicle	Arachis oil BP (300 mg/kg bw) or none (2,000 mg/kg bw).
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

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

LD50	~ 500 mg/kg bw (300 – 2,000 mg/kg bw)
Signs of Toxicity	Signs seen in the 2,000 mg/kg bw group animals (presenting from one hour after dosing) included ataxia, lethargy, hunched posture, prostration, laboured respiration, decreased respiratory rate, occasional body tremors, hypothermia and/or pallor of the extremities. No signs of toxicity (prior to death) were noted in the animal treated at 300 mg/kg bw that died during the study. Hunched posture was noted in one surviving animal treated at 300 mg/kg bw, 4 hours post dosing. This sign had resolved by the day 1 observation
Effects in Organs	Abnormalities were noted at necropsy in the animals that died (spontaneously or were humanely euthanised) including pale and patchy pallor of the liver, pale or dark kidneys, clear liquid present in the stomach, haemorrhage and epithelial sloughing of the gastric mucosa and haemorrhage of the non-glandular epithelium of the stomach. No macroscopic abnormalities were seen in the animals that survived the duration of the study.
Remarks - Results	Two animals treated at 2,000 mg/kg bw were euthanized on the day of dosing due to the occurrence of clinical signs of toxicity. The remaining high dose group animal, as well as one animal dosed at 300 mg/kg bw, were found dead one day after dosing. 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 LD50 was ~500 mg/kg bw.
CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	Harlan (2014a)

B.2. Corrosion – skin (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 431 In vitro Skin Corrosion – Reconstructed Human Epidermis (RHE) Test Method
Vehicle	None.

Remarks - Method

EPISKIN™ In Vitro Reconstructed Human Epidermis (RHE) Model.
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 (true viability values are presented for the test substance in the results table below).

For the main test, the test substance (50 µL) was applied to the tissues in duplicate. Following exposure periods of 3 minutes (37 °C; test 1), 1 hour (37 °C; test 2) and 4 hours (37 °C; test 3), the tissues were rinsed, treated with 2.0 mL of MTT solution (0.3 mg/mL) and then incubated at 37 °C for 3 hours.

Positive and negative controls were run in parallel with the test substance:
- Negative control (NC): 0.9% sodium chloride solution
- Positive control (PC): Glacial acetic acid

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	-	-	-	-	0.818	100*
Test substance	1.110	135.7	0.854	104.4	0.933	114.1
Positive control	-	--	-	-	0.027	3.3

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

Remarks - Results

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

CONCLUSION

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

TEST FACILITY

Harlan (2013d)

B.3. 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.4. Irritation – eye (in vitro)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants

Vehicle: None.

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

The optical density was determined at 492 nm.

0.9% w/v sodium chloride solution was used as a negative control and ethanol was used as a positive control in the study.

RESULTS

Test material	*Mean opacities of triplicate tissues (SD)*	*Mean permeabilities of triplicate tissues (SD)*	*IVIS (SD)*
Vehicle control	1.0	0.028	1.4
*Test substance**	3.7	0.102	5.2
*Positive control**	21.0	0.903	34.6

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

Remarks - Results: The corneas of the test item and negative control were clear post treatment

and post incubation, whereas the corneas treated with the positive control were cloudy during those periods.

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

CONCLUSION The notified chemical was not corrosive or a severe eye irritant under the conditions of the test.

TEST FACILITY Harlan (2013f)

B.5. Irritation – eye (in vitro)

TEST SUBSTANCE Notified chemical

METHOD Determination of Ocular Irritation Potential Using the SkinEthic Reconstituted Human Corneal Epithelium Model

Vehicle None.

Remarks - Method GLP Compliance.

The test substance (30 µL) was applied to the tissues in triplicate. Following 10 minute exposure periods, the tissues were rinsed and then treated with MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; 0.5 mg/mL; incubation period of 3 hours at 37 °C]. Following extraction, the optical densities were determined (562 nm).

A positive (sodium dodecyl sulphate (SDS) in sterile water at 2% w/v) and negative control (Solution A supplied by SkinEthic) were run in parallel with the test substance.

The test substance was considered by the study authors to be an irritant if the relative mean tissue viability was ≤ 60%.

The study authors indicated that a preliminary test had been conducted, which indicated that the test substance directly reduces MTT, therefore a MTT viability assay was performed in parallel on viable and freeze-killed tissues.

RESULTS

Test material	*Mean OD_{562} of duplicate tissues*	*Relative mean viability (%)*
Negative control	1.105	100*
Test substance	0.768	69.5
Positive control	0.217	19.6

OD = optical density

*The mean viability of the negative control tissues is set as 100%.

Remarks - Results The mean OD_{562} of test substance-treated tissues was corrected from 0.959 to 0.768 taking into account the direct MTT reduction.

The relative mean viability of the test substance treated tissues after a 10-minute exposure period was 69.5%.

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

CONCLUSION The notified chemical was considered to be non-irritating to the eye under the conditions of the test.

TEST FACILITY Harlan (2014b)

B.6. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/ CBA/CaOlaHsd
Vehicle	Acetone/olive oil (AOO; 4:1)
Remarks - Method	No significant protocol deviations. GLP Compliance. A preliminary toxicity study was performed with the undiluted test substance and was used to select the concentrations for the main test. Mean ear thickness measurements changed by < 10% over 6 days in this test. Vehicle and positive controls (α-Hexylcinnamaldehyde, as a 25% v/v dilution in AOO) were used in parallel with the test material.

RESULTS

Concentration (% v/v)	*Proliferative response (DPM/animal)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	1,958.35 (± 123.95)	-
25	18,170.34 (± 2,583.93)	9.28
50	24,972.76 (± 3,502.62)	12.75
100	30,187.18 (± 8,869.82)	15.41
Positive Control		
25	14,284.40 (± 4,781.44)	7.29

Remarks - Results	No signs of systemic toxicity were noted in the test or control animals. Mild erythema was noted on the ears of animals in the test group treated with the undiluted test substance on days 2 and 3 of the study. An EC-3 of 7.13% was calculated for the notified chemical. The positive and vehicle controls gave satisfactory responses 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 (2012b)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (1% w/w)
METHOD	Repeated insult patch test with challenge. A vehicle control (water; 1% in vehicle) was used in parallel with the test material.
Study Design	Induction Procedure: Patches containing 0.2 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: approximately 2 weeks Challenge Procedure: A patch was applied to a naïve site. Patches were

	removed by technicians after 24 h. Sites were graded 24 and 48 h post-patch removal.
Study Group	82 F, 31 M; age range 18 - 69 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 113 healthy human subjects (devoid of any physical or dermatological conditions) was amassed.
RESULTS	
Remarks - Results	105/113 subjects completed the study. The eight subjects who discontinued were deemed by study authors to do so for reasons unrelated to the test material. Discontinuation occurred in the induction phase (1-7 induction observations recorded). No reactions were evident in any test subject during either the induction or challenge phases.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2012)

B.8. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (2% w/w)
METHOD	Repeated insult patch test with challenge. A vehicle control (water; 2% in vehicle) was used in parallel with the test material.
Study Design	Induction Procedure: Patches containing 0.2 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: approximately 2 weeks Challenge Procedure: A patch was applied to a naïve site. Patches were removed by technicians after 24 h. Sites were graded 24 and 48 h post-patch removal.
Study Group	87 F, 25 M; age range 18 - 70 years
Vehicle	Et0H: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.
RESULTS	
Remarks - Results	100/112 subjects completed the study. The twelve subjects who discontinued were deemed by study authors to do so for reasons unrelated to the test material (0-9 induction observations recorded). No reactions were evident in any subject administered the test substance during either the induction or challenge phases. There were responses seen at the treatment sites of the vehicle control. Barely perceptible erythema was seen in three subjects during the challenge period. One of these subjects experienced mild erythema with itchiness on one of the challenge days.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.

TEST FACILITY CRL (2014)

B.9. 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: 0.5 - 500 µg/plate
b) Without metabolic activation: 0.5 - 500 µg/plate

Vehicle Dimethyl sulphoxide.

Remarks - Method No significant protocol deviations.
GLP Compliance.

A preliminary toxicity test (0 - 5000 µg/plate) was performed to determine the toxicity of the test material (TA100 and WP2uvrA$^-$ only).

Tests 1 (range-finding test using direct plate incorporated method) and 2 (pre-incubated) were conducted on separate days using fresh cultures and test substance solutions. The concentration range was amended from 1.5 - 1,500 µg/plate in Test 1 to 0.5 – 500 µg/plate in Test 2.

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	≥ 150	≥ 150	> 1,500	negative
Test 2		≥ 50	> 500	negative
Present				
Test 1	≥ 150	≥ 150	> 1,500	negative
Test 2		≥ 50	> 5 00	negative

Remarks - Results Significant increases in the frequency of revertant colonies were not recorded, with or without metabolic activation.

The test substance induced a toxic response with visible reduction in the growth of the bacterial background lawn, with and without metabolic activation.

No test item precipitate was observed on any of the test plates.

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

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

TEST FACILITY Harlan (2012c)

B.10. 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 Dimethyl sulphoxide.
Remarks - Method No significant protocol deviations.
GLP Compliance.

A preliminary toxicity study was performed (4 hour exposure, with and without activation followed by a 20 hour recovery period, and a continuous 24 hour exposure without activation) at concentrations 19.53 – 5,000 µg/mL. Haemolysis was noted at ≥ 39.06 µg/mL in cultures corresponding to all three exposure groups. In addition, greasy and/or oily precipitate was seen in the cultures at ≥ 156.25 µg/mL.

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

The S9 fraction was used in Test 1 at 2% final concentration and in Test 2 at 1% final concentration.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 5, 10, 20*, 30*, 40*, 60*, 80, 120	4 h	24 h
Test 2	0*, 5, 10*, 20*, 40*, 60, 80, 100	24 h	24h
Present			
Test 1	0*, 5, 10, 20*, 40*, 60, 80*, 120, 160	4 h	24 h
Test 2	0*, 5, 10, 20*, 40*, 60*, 80*, 100	4 h	24 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 39.06	≥ 60	> 120	negative
Test 2	≥ 39.06	> 40	> 100	negative
Present				
Test 1	≥ 78.13	> 80	> 160	negative
Test 2		> 80	> 100	negative

Remarks - Results In Test 1, haemolysis was observed at ≥ 30 µg/mL in the absence of S9 and ≥ 40 µg/mL in the presence of S9. In Test 2, haemolysis was observed at ≥ 60 µg/mL in the absence of S9 and ≥ 40 µg/mL in the presence of S9.

The study authors noted that due to the steepness of the toxicity curve, optimum toxicity was difficult to achieve, but considered that the test item had been adequately tested.

No toxicologically significant increases in the number of cells with

	aberrations or polyploidy cells were noted at any dose level, with or without metabolic activation, in either of the two experiments. The positive and vehicle controls gave satisfactory responses confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Harlan (2012d)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F: Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sewage sludge.
Exposure Period	28 days.
Auxiliary Solvent	Not reported.
Analytical Monitoring	Biological Oxygen Demand (BOD) determined by BOD consumption apparatus. Evolved carbon dioxide was absorbed using potassium hydroxide solution.
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
3	4.7	3	14.4
8	1.1	8	60.8
14	1.1	14	74.7
28	0.5	28	82.9

Remarks - Results

All validity criteria for the test were satisfied. The reference compound, sodium benzoate, achieved > 60% degradation by Day 8, and therefore the test is considered valid for this criterion.

The toxicity control achieved 36.9% degradation by Day 14 and, as this surpasses the pass level of 25%, the test material is considered non-inhibitory to the inoculum used in the study.

The test substance achieved 0.5% degradation after 28 days and, as the pass level of > 60% was not reached, it is not considered to be readily biodegradable.

CONCLUSION The notified chemical is not readily biodegradable.

TEST FACILITY Supervision and Test Center (2012)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B: Ready Biodegradability: CO_2 Evolution Test.
Inoculum	Activated sludge.
Exposure Period	28 days.
Auxiliary Solvent	Not reported.
Analytical Monitoring	Inorganic carbon (IC) and total carbon (TC) analyses: Tekmar-Dohrmann Apollo 9000 (or) Shimadzu TOC-V_{CPH} (or) Shimadzu TOC-L_{CSH} Total Organic Carbon (TOC) analysers
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	0	6	69
14	0	14	86
28	0	28	84

Remarks - Results

All validity criteria for the test were satisfied. The reference compound, sodium benzoate, achieved > 60% degradation by Day 6, and therefore the test is considered valid for this criterion.

The toxicity control achieved 41% degradation by Day 14 and, as this surpasses the pass level of 25%, the test material is considered non-inhibitory to the inoculum used in the study.

The test substance achieved 0% degradation after 28 days and, as the pass level of > 60% was not reached, it is not considered to be readily biodegradable. Biodegradation above 20% may be regarded as evidence of inherent primary degradation.

CONCLUSION The notified chemical is not readily biodegradable.

TEST FACILITY Harlan (2013g)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD
- Species: Zebra fish (*danio rerio*)
- Exposure Period: 96 hours.
- Auxiliary Solvent: Not reported.
- Water Hardness: Not reported.
- Analytical Monitoring: GC Analysis.
- Remarks – Method: No significant protocol deviations. GLP Compliance.

RESULTS

Concentration (mg/L)		*Number of Fish*	*Cumulative mortality (%)*				
Nominal	*Geometricm mean measured*		*2 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	10	0	0	0	0	0
4.1	3.0	10	0	0	0	0	0
5.1	5.1	10	0	2	3	4	4
6.1	5.7	10	0	6	8	8	9
7.1	6.7	10	0	6	7	10	10
8.2	7.9	10	1	10	10	10	10

LC50 4.81 (4.36 – 5.32) mg/L at 96 hours

NOEC Not reported.

Remarks – Results

All validity criteria for the test were satisfied. The treatment concentrations were renewed every 24 hours. The actual concentrations of the treatments were measured at 0 and 24 hours test periods.

The 96-hour LC50 was calculated based on the geometric mean measured concentrations of 0 and 24 hours, by trimmed Spearman-Karber (TSK) method.

CONCLUSION	The notified chemical is toxic to fish.
TEST FACILITY	Supervision and Test Center (2013)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static Test
Species	*Daphnia magna*
Exposure Period	48 hours.
Auxiliary Solvent	Not reported.
Water Hardness	136 mg $CaCo_3$/L
Analytical Monitoring	GC Analysis.
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*Cumulative % Immobilised*	
Nominal	*Geometric mean measured*		*24 h*	*48 h*
Control	Control	20	0	0
1.0	0.32	20	0	0
1.8	0.75	20	5	55
3.2	1.5	20	65	100
5.6	2.7	20	100	100
10	5.0	20	100	100

EC50	0.69 (0.59 – 0.82) mg/L at 48 hours
NOEC	0.32 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The treatment concentrations were measured at the beginning and end of the test. The 48-hour EC50 was calculated based on the geometric mean measured concentrations of 0 and 24 hours, by trimmed Spearman-Karber (TSK) method. The endpoints were calculated using the ToxCalc software package.
CONCLUSION	The notified chemical is very toxic to aquatic invertebrates.
TEST FACILITY	Harlan (2013h)

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 mg/L Time-weighted mean measured: 0.21, 0.9, 3.0, 6.3 and 16 mg/L
Auxiliary Solvent	Not reported.
Water Hardness	Not reported.
Analytical Monitoring	Analysis of the test substance was not performed.
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Biomass (72 h)		*Growth (72 h)*	
E_yC50 (mg/L)	*NOE_yC (mg/L)*	*E_rC50 (mg/L)*	*NOE_rC (mg/L)*
1.4 (1.2 – 1.7)	0.9	3.1(3.0 – 3.2)	0.9

Remarks - Results

All validity criteria for the test were satisfied. The end points were determined based on the time-weighted mean measured test concentrations. The treatment concentrations were measured at the beginning of the test and every 24 hours during the 72-h test period.

The E_rC50 and E_yC50 were calculated by computerised interpolation using the XIfit software package. Where appropriate 95% confidence limits for the EC50 values were calculated, using the simplified method of evaluating does-effect experiments of Litchfield and Wilcoxon.

CONCLUSION

The notified chemical is toxic to algae.

TEST FACILITY

Harlan (2013i)

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