File No: LTD/1857-1860, LTD/1862

October 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

LTD/1857: 8-Decenal, (8*E*)-
LTD/1858: 7-Decenal, (7*E*)-
LTD/1859: 6-Decenal, (6*E*)-
LTD/1860: 8-Decenal, (8*Z*)-
LTD/1862: 6-Decenal, (6*Z*)-

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

This Public Report is 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

TABLE OF CONTENTS

SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1857 LTD/1858 LTD/1859 LTD/1860 LTD/1862	International Flavours & Fragrances (Australia) Pty Ltd	LTD/1857: 8-Decenal, (8*E*)- LTD/1858: 7-Decenal, (7*E*)- LTD/1859: 6-Decenal, (6*E*)- LTD/1860: 8-Decenal, (8*Z*)- LTD/1862: 6-Decenal, (6*Z*)-	Yes	≤ 1 tonne per annum (each chemical)	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Skin irritation (Category 2)	H315: Causes skin irritation
Skin sensitisation (Category 1)	H317: May cause an allergic skin reaction
Flammable liquids (Category 4)	H227: Combustible liquid

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

R38: Irritating to Skin
R43: May cause sensitisation by skin contact

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

Hazard classification	*Hazard statement*
Acute (Category 1)	H400 - Very toxic to aquatic life

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

Based on the available information, when used at ≤ 0.25% in fine fragrances and body lotions, ≤ 0.05% in deodorants and ≤ 0.13% in other cosmetic and household products, the isomer mixture containing the notified chemicals 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 chemicals are not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemicals should be classified as follows:

  - H315: Causes skin irritation
  - H317: May cause an allergic skin reaction
  - H227: Combustible liquid

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

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

Health Surveillance

- As the notified chemicals are skin sensitisers, 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 chemicals during reformulation:
  - Enclosed, automated processes, where possible
  - Ventilation system including local exhaust ventilation, where possible

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure to the notified chemicals during reformulation:
  - 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 chemicals during reformulation:
  - 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 mixture are classified as hazardous to health in accordance with the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

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

Storage

- The handling and storage of the notified chemicals 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 chemicals should be handled by physical containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemicals are 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 (each notified chemical);
- the concentration of the isomer mixture containing the notified chemicals exceeds or is intended to exceed 0.25% in fine fragrances and body lotions, 0.05% in deodorants and 0.13% in other cosmetic and household products;
- information becomes available on the repeat dose toxicity of the notified chemicals;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemicals has changed from fragrance ingredient, or is likely to change significantly;
- the amount of chemicals being introduced has increased, or is likely to increase, significantly;
- the chemicals have begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of each notified chemical or the notified isomer mixture 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 isomer mixture containing the notified chemicals and products containing the isomer mixture provided by the notifier were reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

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

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year)

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: dissociation constant, hydrolysis as a function of pH, absorption/desorption, and flammability

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
US EPA TSCA (2013)
China MEP (2014)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Opalene (isomer mixture containing notified chemicals)

CAS NUMBER
LTD/1857: 174155-47-6
LTD/1858: 21662-10-2
LTD/1859: 147159-48-6
LTD/1860: 174155-46-5
LTD/1862: 105683-99-6

CHEMICAL NAME
LTD/1857: 8-Decenal, (8*E*)-
LTD/1858: 7-Decenal, (7*E*)-
LTD/1859: 6-Decenal, (6*E*)-
LTD/1860: 8-Decenal, (8*Z*)-
LTD/1862: 6-Decenal, (6*Z*)-

OTHER NAME(S)
Fret 08-0334 (isomer mixture containing notified chemicals)
IFF TM 11-212 (isomer mixture containing notified chemicals)
Decenal isomers (generic name listed on the (M)SDS of Opalene)

MOLECULAR FORMULA
LTD/1857-1860, LTD/1862: $C_{10}H_{18}O$

STRUCTURAL FORMULA

Notified chemical in LTD/1857

Notified chemical in LTD/1858

Notified chemical in LTD/1859

Notified chemical in LTD/1860

Notified chemical in LTD/1862

MOLECULAR WEIGHT
LTD/1857-1860, LTD/1862: 154.25 Da

ANALYTICAL DATA
Reference ^{1}H-NMR, IR, GC, GC-MS and UV spectra were provided for the isomer mixture containing the notified chemicals.

3. COMPOSITION

DEGREE OF PURITY
> 90% (isomer mixture)*
*The notified chemicals are manufactured as an inseparable isomer mixture with 7-Decenal, *(7Z)*- (CAS no 21661-97-2, listed in AICS). 7-Decenal, *(7Z)*- is present at 3-10% concentration in the isomer mixture.

The composition of the notified chemicals in the isomer mixture (Opalene) is as follows:

Notified chemical	**Weight %**
8-Decenal, (8*E*)- (LTD/1857)	32-40
7-Decenal, (7*E*)- (LTD/1858)	20-28

Notified chemical	Weight %
6-Decenal, (6*E*)- (LTD/1859)	15-21
8-Decenal, *(*8*Z*)- (LTD/1860)	7-13
6-Decenal, (6*Z*)- (LTD/1862)	1-3

IDENTIFIED IMPURITY (> 1% BY WEIGHT)

Chemical Name Cyclohexanone, 2-butyl-
CAS No. 1126-18-7 *Weight %* ~2.5-6 (in isomer mixture)

4. PHYSICAL AND CHEMICAL PROPERTIES

The following physico-chemical properties are for the isomer mixture containing the notified chemicals.

APPEARANCE AT 20 °C AND 101.3 kPa: clear colourless liquids

Property	Value	Data Source/Justification
Freezing Point	< -20 °C	Measured
Boiling Point	212 °C at 101.6 kPa	Measured
Density	840 kg/m^3 at 20 °C	Measured
Vapour Pressure	2.6 x 10^{-2} kPa at 25 °C	Measured
Water Solubility	0.117 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	The notified chemicals do not contain hydrolysable functionality
Partition Coefficient (n-octanol/water)	log Pow = 3.04 to 3.67	Measured. The notified chemicals are expected to partition to phase boundaries based on their surface activity
Surface Tension	57.6 mN/m at 21.5 °C	Measured
Adsorption/Desorption	Not determined	The notified chemicals are expected to sorb to soil sediment and sludge based on their surface activity.
Dissociation Constant	Not determined	The notified chemicals do not contain ionisable functionality
Flash Point	88 °C at 101.2 kPa	Measured
Flammability	Not determined	The notified chemicals are expected to be combustible based on measured flash point (> 60 ºC and < 93 ºC)
Autoignition Temperature	218 °C	Measured
Explosive Properties	Predicted negative	Based on chemical structure
Oxidising Properties	Predicted negative	Based on chemical structure

DISCUSSION OF PROPERTIES

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

Reactivity

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

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

However, based on the submitted physico-chemical data depicted in the above table, the notified chemicals are not recommended for dangerous goods classification according to the Australian Dangerous Goods Code (ADG).

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemicals are constituents of an inseparable isomer mixture, which will be imported as components of finished fragrance oils. The fragrance oils will contain the isomer mixture at ≤ 10% concentration.

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

LTD/1857

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

LTD/1858

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤ 0.67	≤ 0.67	≤ 0.67	≤ 0.67	≤ 0.67

LTD/1859

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤ 0.53	≤ 0.53	≤ 0.53	≤ 0.53	≤ 0.53

LTD/1860

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤ 0.28	≤ 0.28	≤ 0.28	≤ 0.28	≤ 0.28

LTD/1862

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤ 0.03	≤ 0.03	≤ 0.03	≤ 0.03	≤ 0.03

PORT OF ENTRY
Melbourne

IDENTITY OF MANUFACTURER/RECIPIENTS
International Flavours and fragrances (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemicals will be imported as constituents of finished fragrance oils in 205 L polypropylene-lined steel drums. The imported products containing the notified chemicals will be transported to reformulation sites within Australia by road. The end-use products will be packaged in containers suitable for retail sale.

USE
The notified chemicals will be used as fragrance ingredients. The notified chemicals are manufactured as an inseparable isomer mixture. The inseparable isomer mixture will be imported as a component of finished fragrance oils (at ≤ 10% concentration) and incorporated into a variety of cosmetic and household products (at proposed usage concentrations of ≤ 0.25% in fine fragrances and body lotions, ≤ 0.05% in deodorants and ≤ 0.13% in other cosmetic and household products) in Australia.

OPERATION DESCRIPTION
The notified chemicals will not be manufactured within Australia. No reformulation or repackaging of the notified chemicals will occur at the notifier facility. The imported fragrance oils containing the notified chemicals (at ≤ 10% concentration for the isomer mixture) will be stored at the notifier facility until they are sold and distributed to customer facilities for reformulation into end-use products (cosmetic and household products).

Reformulation
The procedures for incorporating the notified chemicals 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 chemicals 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 reformation process, samples of the notified chemicals and the finished end-use products will be taken for quality control testing.

Cosmetic products
The finished cosmetic products containing the notified chemicals will be used by consumers and professionals (such as beauticians and hair dressers). Depending on the nature of the products, application could be by hand, sprayed or through the use of an applicator.

Household products
Household products containing the notified chemicals may be used by consumers and professional workers (i.e., cleaners). The products may be used in either closed systems with episodes of controlled exposures, for example automatic washing machines, or open processes and manually by rolling, brushing, spraying and dipping.

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 chemicals as components of fragrance oils (at ≤ 10% concentration for the isomer mixture) 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 chemicals (at ≤ 10% concentration for the isomer mixture). Exposure of these workers will be limited to situations involving product 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, impervious gloves and safety glasses.

Reformulation
During reformulation at the consumer product manufacture facilities, dermal, ocular and perhaps inhalation exposure of workers to the notified chemicals (at ≤ 10% concentration for the isomer mixture) 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 PPE such as coveralls, goggles and impervious gloves. The notifier also states that adequate local ventilation and self-contained breathing apparatus are expected to be provided if required.

End-use

Exposure to the notified chemicals in end-use products (at ≤ 0.25% concentration for the isomer mixture) may occur in professions where the services provided involve the application of cosmetic products to clients (i.e., hair and 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 mixture.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemicals (at ≤ 0.25% concentration for the isomer mixture) through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposure (e.g. through the use of spray products) are also possible.

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

- Cosmetic products (Dermal exposure):

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	0.25	1	0.3055
Face cream	1540	0.13	1	0.0313
Hand cream	2160	0.13	1	0.0439
Fine fragrances	750	0.25	1	0.0293
Deodorant spray	1500	0.05	1	0.0117
Shampoo	10460	0.13	0.01	0.0021
Conditioner	3920	0.13	0.01	0.0008
Shower gel	18670	0.13	0.01	0.0038
Hand soap	20000	0.13	0.01	0.0041
Hair styling products	4000	0.13	0.1	0.0081
Facial Cleanser	800	0.13	0.01	0.0002
Total				0.4407

C = concentration of isomer mixture
RF = retention factor.
Daily systemic exposure = (Amount x C x RF x DA)/BW

- Household products (Indirect dermal exposure - from wearing clothes):

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.13	0.95	10	0.0044
Fabric softener	90	0.13	0.95	10	0.0017
Total					0.0062

C = concentration of isomer mixture

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

- 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	0.13	1980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.13	1980	0.009	0.01	0.03	0.0003
All-purpose cleaner	1	0.13	1980	1	0.01	0.007	0.0028
Total							0.0032

C = concentration of isomer mixture
Daily systemic exposure = (Frequency x C x Contact area x Product Use Concentration x Film Thickness on skin x Time Scale Factor x DA)/BW

- Cosmetic products (Inhalation exposure):

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone 2) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.13	20	1	20	50	1	10	0.0042

C = concentration of isomer mixture
Daily systemic exposure = [(Amount x C x Inhalation Rate x Fraction Inhaled x 0.1)/(body weight x 1440)] x [(Exposure Duration (Zone 1)/Volume (Zone 1)) + (Exposure Duration (Zone 2)/Volume (Zone 2))]

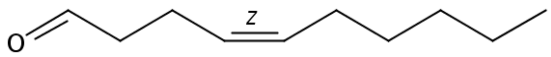
The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemicals. This would result in a combined internal dose of 0.4543 mg/kg bw/day for the isomer mixture. It is acknowledged that inhalation exposure to the notified chemicals from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative (screening level) hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemicals from use of other spray cosmetic and household products with lower exposure factors (e.g., air fresheners).

6.2. Human Health Effects Assessment

Most of the toxicological studies provided were conducted with the isomer mixture containing the notified chemicals. The results from the isomer mixture are considered to represent the toxicity of the individual notified chemicals.

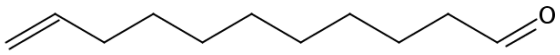
Analogue data was also provided as read-across for some endpoints (acute dermal toxicity, repeated dose toxicity and *in vivo* genotoxicity).

Analogue 1: 4-Decenal, (4Z)- (CAS No. 21662-09-9)
Analogue 1 is a structural isomer of the notified chemicals and is therefore considered acceptable to estimate the acute dermal toxicity of the notified chemicals.



Analogue 1

Analogue 2:10-Undecenal (CAS No. 112-45-8)
Analogue 2 is structurally similar to the notified chemicals differing only in a one carbon greater chain length. Analogue 2 is therefore considered acceptable to estimate the repeated dose toxicity and *in vivo* genotoxicity of the notified chemicals.



Analogue 2

The results from toxicological investigations conducted on the isomer mixture containing the notified chemicals and analogues are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute oral toxicity*	LD50 > 5000 mg/kg bw; low toxicity
Rat, acute dermal toxicity*	LD50 > 5000 mg/kg bw; low toxicity
Skin irritation (*in vitro*)- EpiSkin; Irritation	irritating
Skin irritation (*in vitro*)- Episkin; Corrosion	non-corrosive
Eye irritation (*in vitro*)- SkinEthic HCE Model	non-irritating
Eye irritation (*in vitro*)- BCOP	not severely irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (1% of notified chemical isomer mixture)	no evidence of sensitisation
Rat, repeat dose oral (diet) toxicity – 14 days**	NOAEL = 1672 mg/kg bw/day
Rat, repeat dose oral (diet) toxicity – 90 days**	NOAEL = 138.6 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosomal aberration	non genotoxic
Genotoxicity – *in vivo* mouse micronucleus test**	non genotoxic

*Analogue 1
**Analogue 2

Toxicokinetics.
Based on the water solubility (0.117 g/L at 20ºC), partition coefficient (log Pow = 3.04 to 3.67) and the low molecular weight (154.25 Da) of the notified chemicals, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are expected to occur. The notified chemicals may also be absorbed across the respiratory tract.

Acute toxicity.
The isomer mixture containing the notified chemicals was found to be of low acute oral toxicity in rats.
No acute dermal or inhalation toxicity data were provided for the notified chemicals. However, analogue data for acute oral and dermal toxicity studies were provided. These studies (not conducted to OECD guidelines or GLP compliance) indicated that analogue 1 is of low acute oral and dermal toxicity in rats.

Irritation and sensitisation.
The notified chemicals contain structural alerts for corrosion /skin irritation and skin sensitisation (aldehydes) (Barratt *et al.,* 1994; Gerner *et al.,* 2004; Hulzebos *et al.,* 2005).

Two *in vitro* dermal studies were conducted using reconstructed human epidermis models (EpiSkin). The skin corrosion study indicated that the isomer mixture containing the notified chemicals was non-corrosive, whereas the skin irritation study indicated that the isomer mixture could cause skin irritation (relative mean viability of 32.4%).

Two *in vitro* ocular studies were also conducted. An *in vitro* eye irritation study was conducted using a reconstituted human corneal epithelium model (SkinEthic), which indicated that the isomer mixture containing the notified chemicals is non-irritating to the eyes. A bovine corneal opacity and permeability (BCOP) test indicated that the isomer mixture containing the notified chemicals is unlikely to cause serious eye damage.

The isomer mixture containing the notified chemicals was found to be sensitising in a Local Lymph Node Assay. The EC_3 value was calculated to be 66%. The sensitising potential of the isomer mixture was also tested in a separate human repeat insult patch test (HRIPT). The isomer mixture was not a skin sensitizer when tested at 1% concentration (with 105 subjects completing the study). No reactions were noted in subjects during the induction or challenge phases.

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

Analogue data from a repeated dose 90-day oral dietary toxicity study in rats was provided. The doses used for the study were based on a 14-day repeated dose oral dietary toxicity screening study on the analogue that established a NOAEL of 1672 mg/kg bw/day, based on the absence of treatment related adverse effects at the highest dose tested.

In the 90-day study, analogue 2 was incorporated into the basal laboratory diet at concentrations of 200, 2000, 6000 or 20000 ppm (equivalent to mean achieved dosages of 14.3, 138.6, 382.3 or 1135.9 mg/kg bw/day, respectively). The study showed a statistically significant reduction in bodyweight gain for animals treated with 6000 or 20000 ppm. Although a statistically significant reduction in body weight gain was observed at 2000 ppm, it only occurred in Week 5 in males only. A reduction in food consumption and food efficiencies, although not statistically significant, was observed in animals treated at 2000, 6000 or 20000 ppm. There were also significant changes in some serum parameters at 2000, 6000 or 20000 ppm which is suggested by the study authors to may be associated with the reduced food consumption or with the liver effects seen at the histopathological examination. The effect observed in the liver (centrilobular hepatocellular hypertrophy) was of minimal severity and was not accompanied by degenerative or inflammatory changes and is therefore considered an adaptive response. The NOAEL was established as 138.6 mg/kg bw/day, based on bodyweight changes at the higher doses.

Mutagenicity/Genotoxicity.
The notified chemicals have structural alerts for carcinogenicity (Benigni *et al.,* 2008). No carcinogenicity test data on the notified chemicals was provided.

The isomer mixture containing the notified chemicals was negative in a bacteria reverse mutation assay and in an *in vitro* chromosome aberration test. Analogue 2 was negative in an *in vivo* micronucleus test.

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

Hazard classification	*Hazard statement*
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 chemicals are recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):

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
Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemicals (at ≤ 10% concentration for the isomer mixture) during reformulation. The notified chemicals are considered to be skin irritants and skin sensitisers. Therefore, caution should be exercised when handling the notified chemicals during reformulation and quality control processes.

The use of enclosed, automated processes and PPE (i.e., coveralls, goggles and impervious gloves) should minimise the potential for exposure. Therefore, provided that adequate control measures are in place to minimise worker exposure, the risk to workers from use of the notified chemicals is not considered to be unreasonable.

End use
Cleaners, hair and beauty care professionals will handle the notified chemicals at ≤ 0.25% concentration for the isomer mixture. Such professionals may use 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 mixture (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 chemicals are considered to be skin irritants, irritation effects are not expected from use of the notified chemicals at the proposed use concentrations. The main risk associated with use of the notified chemicals at the proposed concentrations in end-use products, is its potential to cause sensitisation by skin contact.

Proposed methods for the quantitative risk assessment of the dermal sensitisation have been the subject of significant discussion (i.e., Api *et al.,* 2008 and RIVM, 2010). Using fine fragrance as an example product that may contain the notified chemicals (at 0.25% concentration for the isomer mixture), as a worst case scenario, the Consumer Exposure Level (CEL) for the isomer mixture is estimated to be 9.38 μg/cm^2/day (Cadby *et al.,* 2002). When tested in an LLNA study, the isomer mixture containing the notified chemicals was a skin sensitiser with an EC_3 value of 66%. Consideration of the study details and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 50.93 μg/cm^2/day. In this instance, the factors employed included an interspecies factor (3), intraspecies factor (10), a matrix factor (3.16), use/ time factor (3.16) and database factor (1), giving an overall safety factor of > 300 (300 used for calculation).

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of fine fragrances (a worst case example of a leave-on cosmetic product) is not considered to be unreasonable. Based on the significantly lower expected exposure level from other leave-on cosmetic products, rinse-off products and household products, 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 chemicals, and a quantitative assessment based on aggregate exposure has not been conducted.

Repeat dose toxicity
The potential systemic exposure to the public from the use of the isomer mixture containing the notified chemicals in cosmetic and household products was estimated to be 0.4543 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 138.6 mg/kg bw/day, which was derived from a 90 day repeated dose oral dietary toxicity study on an analogue chemical, the margin of exposure (MOE) was estimated to be 305. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.

Therefore, based on the information available, the risk to the public associated with the use of the isomer mixture containing the notified chemicals at ≤ 0.25% concentration in 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 chemicals will not be manufactured, reformulated or repackaged in Australia; therefore release of the notified chemicals to the environment from this activity is not expected. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemicals are expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

RELEASE OF CHEMICAL FROM USE
The majority of the notified chemicals are expected to be released to sewers across Australia as a result of their use in fragrance, cosmetic and household products, and disposed of to the sewer.

RELEASE OF CHEMICAL FROM DISPOSAL

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

7.1.2. Environmental Fate

For the details of the environmental fate study please refer to Appendix C. The notified chemicals are readily biodegradable based on a biodegradation study of the notified chemicals. Therefore, they are not expected to be persistent in the environment.

Following their use in Australia, the majority of the notified chemicals are expected to be released to sewer on a nationwide basis. The biodegradation study indicated that the notified chemicals are considered to be readily biodegradable in the environment and hence, they are expected to be significantly degraded during the wastewater treatment process. The notified chemicals are expected to partition to phase boundaries as they are surface active. Therefore, the notified chemicals in sewage released to STPs are expected to partition to sludge. Notified chemicals remaining in treated sewage effluents are likely to be released to surface waters or applied to land when used for irrigation. Notified chemicals in sewage sludge are anticipated to be disposed of to landfill or applied to land when sludge is used for soil remediation. Based on their surface active property, the notified chemicals are not expected to bioaccumulate due to their surfactant property. The notified chemicals are expected to degrade in STPs, surface waters, soils and landfill due to their ready biodegradability to form water and oxides of carbon,

The notified chemicals are expected to be volatile and may volatilise to air during use or STP processes. The half-life of the notified chemicals in air is calculated to be 1.3 and 1.5 hours for *trans* and *cis* isomers respectively, based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, in the event of release to the atmosphere, the notified chemicals are not expected to persist in the air compartment.

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 volumes of the notified chemicals are 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 chemicals will be removed during sewage treatment processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	2,680	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	2,680	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	7.34	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:	1.62	µg/L
PEC - Ocean:	0.16	µg/L

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish (96 h)	LC50 = 3.84 mg/L	Toxic to fish
Daphnia Toxicity (48 h)	EC50 = 2.9 mg/L	Toxic to aquatic invertebrates
Algal Toxicity (72 h)	E_rC50 = 0.34 mg/L	Very toxic to algae

Based on the acute ecotoxicity endpoints for the notified chemicals, they are expected to be very toxic to algae. Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009), the notified chemicals are formally classified as Acute Category 1; Very Toxic to aquatic life. Based on the ready biodegradability of the notified chemicals, they have not been formally classified under GHS for chronic category.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentrations (PNEC) for the notified chemicals have been calculated and are presented in the table below. The PNEC is calculated based on the endpoint for the most sensitive species (algae, E_rC50) for the notified chemicals. 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		
E_rC50 (Algae)	0.34	mg/L
Assessment Factor	100	
PNEC:	3.40	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:	1.62	3.4	0.478
Q - Ocean:	0.16	3.4	0.048

The Risk Quotients (Q = PEC/PNEC) have been calculated to be < 1 for both river and ocean compartments.
The notified chemicals are not expected to bioaccumulate and are unlikely to persist in surface waters or soils. Therefore, on the basis of the PEC/PNEC ratio, maximum annual import volume and assessed use pattern, the notified chemicals are not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < -20 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	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 did not show any change in appearance or physical state during cooling. The test substance did not show any indication of freezing.
Test Facility	Harlan (2012a)

Boiling Point 212 ± 1 °C at 101.6 kPa

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	Determined using differential scanning calorimetry
Test Facility	Harlan (2014a)

Density 840 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	Pycnometer method
Test Facility	Harlan (2012a)

Vapour Pressure 2.6 x 10^{-2} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Vapour pressure balance method
Test Facility	Harlan (2015a)

Water Solubility 0.117 g/L at 20 °C

Method	OECD TG 105 Water Solubility. EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Flask Method
Test Facility	Harlan (2012a)

Partition Coefficient (n-octanol/water) log Pow = 3.04 to 3.67

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	HPLC Method
Test Facility	Harlan (2012a)

Surface Tension 57.6 mN/m at 21.5 ± 0.5 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions. EC Council Regulation No 440/2008 A.5 Surface Tension.
Remarks	The mean surface tension of duplicate 90% saturated aqueous solutions of test item was determined using a torsion balance by means of a ring method. The result indicates that the notified chemicals are expected to be surface-active.
Test Facility	Harlan (2014a)

Flash Point 88 ± 2 °C at 101.2 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.

Remarks	Closed cup equilibrium method
Test Facility	Harlan (2014b)

Autoignition Temperature 218 ± 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 material using a Carbolite flask heater and observing any ignition
Test Facility	Harlan (2014b)

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 (2014b)

Oxidizing Properties Predicted negative

Method	EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids)
Remarks	Observation of functional groups that would imply oxidising properties.
Test Facility	Harlan (2014b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture containing notified chemicals at 97.2%)
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Female Wister(RccHan^{TM}:WIST)
Vehicle	None
Remarks - Method	No significant deviations from protocol

RESULTS

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

LD50	> 2000 mg/kg bw
Signs of Toxicity	Hunched posture was noted during the day of dosing in the first group of animals. There were no deaths or test substance-related clinical signs or remarkable body weight changes during the study period.
Effects in Organs	There were no remarkable necropsy findings.
Remarks - Results	None

CONCLUSION	The test substance is of low toxicity *via* the oral route.
TEST FACILITY	Harlan (2014c)

B.2. Acute toxicity – oral

TEST SUBSTANCE	Analogue 1
METHOD	Not stated
Species/Strain	Mice
Vehicle	Not stated
Remarks - Method	No description of method was provided

RESULTS

Main Study

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	10	5000	4/10

LD50	> 5000 mg/kg bw
Signs of Toxicity	Diarrhea, lethargy, piloerection, dyspnea, ptosis and left eye crusted shut were noted. Four animals died during the study period.
Effects in Organs	Necroscopy of the animals showed red/dark discolouration of the stomach, intestine, liver and lungs.
Remarks - Results	The description of the procedure was very short. It was not possible to compare the method used with methods in OECD guidelines. The purity of the test substance was not reported. There was no information on the batch that was tested, the study was not carried out according to GLP, and no data were presented on the development of the body weights. However, the outcome of the study adds some information on the toxicity of the compound.

CONCLUSION	The test substance is of low toxicity *via* the oral route.
TEST FACILITY	M B Research (1978)

B.3. Acute toxicity – dermal

TEST SUBSTANCE	Analogue 1
METHOD	Not stated
Species/Strain	Guinea pigs
Vehicle	Not stated
Type of dressing	Not stated
Remarks - Method	No description of method was provided.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5	5000	0/5

LD50	> 5000 mg/kg bw
Signs of Toxicity	Adipsia, anorexia and emaciation were noted.
Effects in Organs	There were no deaths or test substance-related clinical signs during the study period.
Remarks - Results	Moderate redness of skin and slight oedema were observed in 4 and 3 animals, respectively. The description of the procedure was very short. It was not possible to compare the method used with methods in OECD guidelines. The purity of the test substance was not reported. The exposure period was not stated. There was no information on the batch that was tested, the study was not carried out according to GLP, and no data were presented on the development of the body weights. However, the outcome of the study adds some information on the toxicity of the compound.
CONCLUSION	The test substance is of low toxicity *via* the dermal route.
TEST FACILITY	M B Research (1978)

B.4. Irritation – skin (*in vitro* skin irritation)

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture containing notified chemicals at 97.2%)
METHOD	OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method (2013) EC Council Regulation No 761/2009 B.46. *In vitro* Skin irritation - Human Epidermis Model Test (2009) EpiSkin™ Reconstituted Human Epidermis Model
Vehicle	None
Remarks - Method	The test substance (10 µL) was applied to the tissues in triplicate. Following 15 minute exposure periods, the tissues were rinsed and then incubated at 37 °C for approximately 42 hours, prior to treatment with MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] for 3 hours at 37 ºC. Positive (sodium dodecyl sulphate; 5%) and negative (phosphate buffered saline) controls were run in parallel with the test substance. MTT viability assay was performed in parallel on viable and water-killed tissues to detect and correct for the test substance interference, if needed.

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*± SD of OD_{562}*	*Relative mean Viability (%)*	*± SD of relative mean viability (%)*
Negative control	1.004	0.101	100*	10.0
Positive control	0.087	0.013	8.7	1.3
Test substance	0.325	0.058	32.4	5.8

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

Remarks - Results

The relative mean viability of the test substance treated tissues was 32.4±5.8% after a 15-minute exposure period and a 42 hour post-exposure incubation period.

The test substance did directly reduce MTT; however, the results of the water-killed tissues showed no direct interference. It was therefore considered unnecessary to use the results of the water-killed tissues for qualitative correction of results or for reporting purposes.

The positive and negative controls met the criteria set by the test laboratory, confirming the validity of the test system.

The relative mean tissue viability was ≤ 50%, therefore the test substance was considered as irritating.

CONCLUSION

The test substance was irritating to the skin under the conditions of the test.

TEST FACILITY

Harlan (2014d)

B.5. Irritation – skin (*in vitro* skin corrosion)

TEST SUBSTANCE

IFF TM 11-212 (isomer mixture containing notified chemicals at 97.2%)

METHOD

OECD TG 431 *In vitro* Skin Corrosion - Human Skin Model Test (2004)
EC Council Regulation No 440/2008 B.40 BIS. *In vitro* Skin Corrosion - Human Skin Model Test
EpiSkin™ Reconstituted Human Epidermis Model

Vehicle

None

Remarks - Method

The test substance (50 µL) was applied to the tissues in duplicate for exposure periods of 3, 60 and 240 minutes, prior to treatment with MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] for 3 hours at 37 ºC.

Positive (glacial acetic acid; 99.7%) and negative (sodium chloride solution; 0.9% w/v) controls were run for an exposure period of 240 minutes. MTT viability assay was performed in parallel on viable and water-killed tissues to detect and correct for the test substance interference, if needed.

The study authors used the criterion in the Episkin INVITTOX No 118 protocol (relative mean tissue viability ≥ 35% with 240 minutes treatment time) to determine if materials are non-corrosive.

RESULTS

Test material	*Exposure period (minutes)*	*Mean OD_{562} of duplicate tissues*	*True viability**	*Relative mean Viability (%)*
Negative control	240	1.120	-	100**
Positive control	240	0.044	-	3.9
Test substance	240	0.993	0.827	73.8
	60	1.167	0.992	88.6

3	1.181	1.181	105.4

*true viability= mean OD tvt- (OD tkt- OD ukt)
**The mean viability of the negative control was set at 100%
OD = optical density; tvt = treated viable tissues; tkt = treated killed tissues; ukt = untreated killed tissues

Remarks - Results: The test substance was shown to directly reduce MTT. Using the results of the water-killed tissues, the corrected relative mean viabilities of the test substance treated tissues were:

240 minutes exposure: 73.8%
60 minutes exposure: 88.6%
3 minutes exposure: 105.4%

The positive and negative controls met the criteria set by the test laboratory, confirming the validity of the test system.

CONCLUSION: The test substance was non-corrosive to the skin under the conditions of the test.

TEST FACILITY: Harlan (2014e)

B.6. Irritation – eye (*in vitro*)

TEST SUBSTANCE: IFF TM 11-212 (isomer mixture containing notified chemicals at 97.2%)

METHOD: Determination of Ocular Irritation Potential Using the SkinEthic Reconstituted Human Corneal Epithelium (HCE) Model (10-Minute Exposure)

Vehicle: None

Remarks - Method: The test substance (30 µL) was applied to the tissues in triplicate. Following 10 minute exposure periods, the tissues were rinsed and then incubated at 37 °C for approximately 42 hours, prior to treatment with MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] for 3 hours at 37 ºC.

Positive (sodium dodecyl sulphate; 2% w/v) and negative (Solution A) controls were run were run in parallel with the test substance for 10 minutes. Solution A is composed of Na_2HPO_4 (0.142 g/L), glucose (1.802 g/L), HEPES (7.149 g/L), KCl (0.224 g/L), NaCl (97.597 g/L).

MTT viability assay was performed in parallel on viable and water-killed tissues to detect and correct for the direct test substance interference with MTT, if needed.

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean viability (%)*
Negative control	0.815	100*
Positive control	0.145	17.8
Test substance	0.682	83.7

*The mean viability of the negative control was set at 100%
OD = optical density

Remarks - Results: The relative mean viability of the test substance treated tissues was 83.7% after a 10 minute exposure period. The test substance did not directly reduce MTT.

The positive and negative controls met the criteria set by the test laboratory, confirming the validity of the test system.

CONCLUSION	The test substance was considered to be non-irritating to the eye under the conditions of the test.
TEST FACILITY	Harlan (2014f)

B.7. Irritation – eye (*in vitro*)

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture containing notified chemicals at 97.2%)
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Assay (2013)
Vehicle	None
Remarks - Method	The test substance (0.75 mL) was applied to the corneas for 10 minutes followed by an incubation period of 120 minutes. Negative (sodium chloride solution; 0.9% w/v) and positive (ethanol) controls were tested concurrently.

RESULTS

Test material	*Mean opacities of triplicate tissues*	*Mean permeabilities of triplicate tissues*	*IVIS*
Negative control	2.3	0.031	2.8
*Positive control**	22.3	1.715	48.1
*Test substance**	7.7	0.272	11.7

IVIS = in vitro irritancy score
*Corrected for background values

Remarks - Results	The test substance demonstrated an IVIS of 11.7. The corneas treated with the test substance were clear post treatment and slightly cloudy post incubation. According to the prediction model, the test substance is unlikely to cause serious eye damage, however, the requirement of classification for eye irritation cannot be ruled out. The controls gave satisfactory results confirming the validity of the test system.
CONCLUSION	The test substance was not corrosive or a severe eye irritant under the conditions of the test.
TEST FACILITY	Harlan (2014g)

B.8. Skin sensitisation – mouse Local Lymph Node Assay (LLNA)

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture containing notified chemicals at 96%)
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010) EC Council Regulation No 440/2008 B.42 Skin Sensitisation (Local Lymph Node Assay)
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone/olive oil 4:1
Remarks - Method	An exception to the GLP compliance was noted. No analysis was carried out to determine the homogeneity, concentration or stability of the test item formulation. The study authors assumed that the test item formulation was stable during application. Positive control: α-hexyl cinnamaldehyde (85%) at 25% v/v in acetone:

olive oil (4:1)
Negative control: vehicle only

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)**	*Stimulation Index***
Test Substance			
0 (vehicle control)	5/F	979.18	1.00
25	5/F	1883.16	1.92
50	5/F	1774.7	1.81
100	5/F	5305.24	5.42
Positive Control			
25	5/F	7142.2	7.29

* total number of lymph nodes per animal is 2
**Stimulation Index = Test/Vehicle Control Ratio

EC3	66%
Remarks - Results	No signs of systemic toxicity or death were noted during the study.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance.

TEST FACILITY Harlan (2012b)

B.9. Skin sensitisation – human volunteers

TEST SUBSTANCE 12-210-01 (containing the notified isomer mixture at ~1% w/w)

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 h and graded after an additional 24 h (or 48 h for the patches removed on a Saturday). Rest Period: ~14 days Challenge Procedure: patches were applied to previously untreated sites. Patches were removed after 24 h and evaluated for dermal reactions. The test sites were re-evaluated at 48 h and 72 h.
Study Group	85F, 28M; age range 18-70 years
Vehicle	Ethanol: Diethyl Phthalate (1:3)
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm × 3.63 cm patch.

RESULTS

Remarks - Results	105/113 subjects completed the study. 8 subjects discontinued study participation for reasons unrelated to the test material. No adverse responses were noted at induction or challenge phases

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

TEST FACILITY CRL (2012)

B.10. Repeat dose toxicity (14-day screening study)

TEST SUBSTANCE Analogue 2 (98.2%)

METHOD 14-day Repeated Dose Oral (Dietary) Toxicity Screening/Palatability Study in the Rat

Species/Strain	Sprague-Dawley Crl: CD BR
Route of Administration	Oral –diet

Exposure Information	Total exposure days: 14 days Dose regimen: 7 days per week
Vehicle	The test substance was incorporated into the basal laboratory diet at concentrations of 2000, 6000 and 20000 ppm (equivalent to mean achieved dosages of 196, 541 and 1672 mg/kg bw/day, respectively).
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Mortality*
		Nominal (ppm)	*Actual (mg/kg bw/day)**	
Control	3/sex	0	0	0
low dose	3/sex	2000	196	0
mid dose	3/sex	6000	541	0
high dose	3/sex	20000	1672	0

*mean achieved dosage of the analogue 2

Mortality and Time to Death

No mortality was observed during the treatment phase.

Clinical Observations

There were no toxicologically significant effects observed during the study.

Effects in Organs

A slight increase in liver weight both absolute and relative to terminal body weight was observed in animals of all treated groups. The study authors did not consider this toxicologically significant in the absence of dose related response. No macroscopic abnormalities were detected at necroscopy.

Remarks - Results	Effects were detected on body weight change, dietary intake and food consumption in animals treated with 20000 ppm, which were observed to have generally or completely regressed from Day 4 onwards. The effects in organ weight were not considered to be of toxicological importance due to the lack of dose related response.
CONCLUSION	The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1672 mg/kg bw/day in this study, based on absence of adverse effects at the highest dose tested.
TEST FACILITY	Harlan (2011)

B.11. Repeat dose toxicity (90-Day Oral Toxicity Study)

TEST SUBSTANCE	Analogue 2 (98.2%)
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents (1998). EC Directive 88/302/EEC B.26 Sub-Chronic Oral Toxicity Test: 90-Day Repeated Oral Dose Study using Rodent Species.
Species/Strain	Sprague-Dawley Crl: CD BR
Route of Administration	Oral –diet
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week
Vehicle	The test substance was incorporated into the basal laboratory diet at concentrations of 200, 2000, 6000 and 20000 ppm (equivalent to mean achieved dosages of 14.3, 138.6, 382.3 and 1135.9 mg/kg bw/day, respectively).

Remarks - Method No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Mortality*
		Nominal (ppm)	*Actual (mg/kg bw/day)**	
Control	10/sex	0	0	0
low dose	10/sex	200	14.3	0
mid dose (I)	10/sex	2000	138.6	0
mid dose (II)	10/sex	6000	382.3	0
high dose	10/sex	20000	1135.9	0

*mean achieved dosage of the analogue 2

Mortality and Time to Death
No mortality was observed during the treatment phase.

Clinical Observations
There were no toxicologically significant effects observed during the study.

There was a statistically significant reduction in bodyweight gain in high dose males throughout the study period and also in males treated with 6000 ppm and in females treated with 20000 ppm during the first few weeks of treatment. In week 5 only, males treated with 2000 ppm also showed a statistically significant reduction. Although not statistically significant a dose related reduction in actual bodyweight was evident in males treated with 20000, 6000 or 2000 ppm, and in females treated with 20000 or 6000 ppm. This was correlated with a reduction in food consumption.

Functional observations
There were no treatment related changes in behavioural parameters measured and sensory reactivity. There were no toxicologically significant changes in functional parameters measured.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Blood chemistry
Several serum measures showed statistically significant changes:
Alkaline phosphatase (increased, both sexes, 2000, 6000, 20000 ppm), albumin count and albumin/globulin ratio (increased, male only, 2000, 6000, 20000 ppm), total protein and albumin (reduced, female only, 6000, 20000 ppm), cholesterol concentration (reduced, females only, 20000 ppm), urea values (increased, both sexes, 20000 ppm).

The study authors suggest that the change in these parameters may be associated with the reduced food consumption or with the liver effects seen at the histopathological examination.

Haematology
No toxicologically significant effects were detected.

Urinalysis
No treatment related effects were detected.

Effects in Organs
No toxicologically significant effects were detected in the organ weights measured. Morphological evaluation of epididymal and testicular sperm showed no treatment related differences in count, morphology, or stages of spermatogenesis. No macroscopic abnormalities were detected at necroscopy.

Epithelial acanthosis of the limiting ridge of the stomach was observed in animals (both sexes) treated with 2000 or 20000 ppm and also in females (6000 ppm). This finding was indicative of a local irritant potential of the test substance and was considered to be associated with the route of administration. Therefore, the study authors considered this unrelated to systemic toxicity. Centrilobular hepatocellular hypertrophy at minimal

severity was observed in males only (2000, 6000, 20000 ppm). This finding was not accompanied by degenerative or inflammatory changes, therefore the study authors considered it to be an adaptive effect.

Remarks – Results

There was a statistically significant reduction in bodyweight gain for animals treated with 6000 or 20000 ppm. Although a statistically significant reduction in body weight gain was observed at 2000 ppm, it only occurred in Week 5 in males only. A reduction in food consumption and food efficiencies, although not statistically significant, was observed in animals treated at 2000, 6000 or 20000 ppm.

There were also significant changes in some serum parameters at 2000, 6000 or 20000 ppm which is suggested by the study authors to may be associated with the reduced food consumption or with the liver effects seen at the histopathological examination. The effect observed in the liver (centrilobular hepatocellular hypertrophy) was of minimal severity and was not accompanied by degenerative or inflammatory changes and is therefore considered an adaptive response.

The study authors established a No Observed Effect Level (NOEL) of 14.3 mg/kg bw/day, based on the absence of treatment related effects at this dose. The No Observed (Adverse) Effect Level (NOAEL) is considered by NICNAS to be 138.6 mg/kg bw/day, based on bodyweight changes at the higher doses.

CONCLUSION	The NOAEL was established as 138.6 mg/kg bw/day in this study, based on bodyweight changes at the higher doses.
TEST FACILITY	Harlan (2012c)

B.12. Genotoxicity – bacteria

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture at 96%)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria (2008). Plate incorporation procedure (Test 1: Range-finding test))/Pre incubation procedure (Test 2: Main test)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2*uvrA*
Metabolic Activation System	S9 microsomal fraction from β-naphthoflavone/phenobarbital-induced rat liver
Concentration Range in Main Test	<u>All *Salmonella* strains</u> With and without metabolic activation: 0.5-500 µg/plate <u>*E.coli* strain</u> With and without metabolic activation: 1.5-1500 µg/plate
Vehicle	Dimethyl sulphoxide (DMSO)
Remarks - Method	A correction for the purity of the test substance was made when the test item formulations were prepared. No other deviation from standard protocol. A preliminary toxicity test (0-5000 µg/plate) was performed to determine the toxicity of the test material in the presence and absence of metabolic activation (TA100 or WP2*uvrA*). Tests 1 and 2 were conducted on seperate days using fresh cultures and test substance solutions. The concentration range was amended in test 2, based on the results of test 1. <u>Test 1</u>: TA100 (without S9): 0.15, 0.5, 1.5, 5, 15, 50, 150 µg/plate TA100 (with S9), other *Salmonella* strains (with/without S9): 0.5, 1.5, 5, 15, 50, 150, 500 µg/plate WP2*uvrA* (with/without S9): 1.5, 5,15, 50, 150, 500, 1500 µg/plate

Test 2: see above (Concentration Range in Main Test)

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/plate) Resulting in:* *Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 50 (TA100)	≥ 150	> 150 (TA100) > 500 (other *Salmonella)* > 1500 (*E.coli)*	Negative
Test 2	≥ 500 (WP2*uvrA*)	≥ 150	> 500 (*Salmonella)* > 1500 (*E.coli)*	Negative
Present				
Test 1	≥ 150 (TA100)	≥ 150	> 500 > 1500 (*E.coli)*	Negative
Test 2	≥ 500 (WP2*uvrA*)	≥ 150 ≥ 500 (WP2*uvrA*)	> 500 (*Salmonella)* > 1500 (*E.coli)*	Negative

Remarks - Results

No toxicologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test item, either with or without metabolic activation or exposure method. A small, statistically significant increase in TA100 revertant colony frequency was observed in the presence of S9 at 15 μg/plate in test 1. The study authors did not consider this effect to be of biological relevance in the absence of any evidence of a dose-response relationship or reproducibility. Furthermore, the individual revertant counts at 15 μg/plate were within the in-house historical untreated/vehicle control range for the tester strain and the fold increase was only 1.18 times the concurrent vehicle control.

The positive and negative controls gave satisfactory results confirming the sensitivity of the test system.

CONCLUSION

The test substance was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY

Harlan (2012d)

B.13. Genotoxicity – *in vitro*

TEST SUBSTANCE

IFF TM 11-212 (isomer mixture at 96%)

METHOD

OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test (1997).
EC Directive 2000/32/EC B.10 Mutagenicity - *In vitro* Mammalian Chromosome Aberration Test.

Species/Strain: Human/ F (Test 1), M (Test 2)

Cell Type/Cell Line: Peripheral lymphocytes

Metabolic Activation System: S9 microsomal fraction from β-naphthoflavone/phenobarbital-induced rat liver

Vehicle: Dimethyl sulphoxide (DMSO)

Remarks - Method

A correction for the purity of the test substance was made when the test item formulations were prepared. No other significant deviation from the protocol.

Mytomycin C (MMC) and cyclophosphamide (CP) were used as positive controls in the absence and presence of metabolic activation, respectively.
The doses selected for the study were based on the outcomes of a

preliminary study (cytotoxicity and/or the presence of precipitate). The 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 – 5000 µg/mL.

The S9 fraction was used at 2% and 1% final concentration in test 1 and in test 2, respectively.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 1, 2, 4, 8*, 16*, 24*, 32*, 48, MMC 0.4*	4 h	20 h
Test 2	0*, 2, 4, 8, 16*, 24*, 32*, 48*, 64, MMC 0.2*	24 h	-
Present			
Test 1	0*, 2, 4, 8, 16, 24*, 32*, 48*, 64*, CP 5*	4 h	20 h
Test 2	0*, 2, 4, 8, 16, 24*, 32*, 48*, 64*, CP 5*	4 h	20 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	≥ 19.53	≥ 32	> 48	Negative
Test 2	≥ 39.06	≥ 48	> 64	Negative
Present				
Test 1	≥ 39.06	≥ 64	> 64	Negative
Test 2		≥ 64	> 64	Negative

Remarks - Results

In the preliminary toxicity study, haemolysis was noted at ≥ 19.53 µg/mL and ≥ 39.06 µg/mL in test 1and test 2, respectively. In addition, greasy and/or oily precipitate was seen in the cultures at ≥ 156.25 µg/mL in the absence of S9. Cloudy precipitate was seen in the cultures at ≥ 312.5 µg/mL in the presence of S9.

In the main test, there was dose related inhibition of the mitotic index in test 1, with 76% at 32 µg/mL and 62% at 64 µg/mL, in the absence and presence of S9, respectively. Although these dose levels achieved greater than optimum toxicity they were selected as the maximum dose levels for metaphase analysis in test 1 as they provided an intermediate dose in a relatively steep toxicity curve. In test 2, the dose related 57% and 60% mitotic index inhibition were observed at 48 µg/mL and 64 µg/mL, in the absence and presence of S9, respectively.

The test item did not induce any statistically significant increase in the frequency of cells with aberrations either in the presence or absence of metabolic activation, in either test. No statistically significant increases in polyploidy cells were observed.

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

CONCLUSION

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

TEST FACILITY

Harlan (2012e)

B.14. Genotoxicity – *in vivo*

TEST SUBSTANCE	Analogue 2 (97.7%)
METHOD	OECD TG 474 (1997). Mammalian Erythrocyte Micronucleus Test. EC Directive 2000/32/EC B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test (2000).
Species/Strain	Mouse/NMRI
Route of Administration	Oral
Vehicle	Corn oil
Remarks - Method	The ratio between polychromatic and normochromatic erythrocytes was determined in the same sample and reported as number of polychromatic erythrocytes (PCEs) per 2000 erythrocytes to describe a cytotoxic effect due to the treatment with the test item. The analysis of the test item formulations showed, that the analysed samples correspond to the nominal values. The obtained results ranged between 85.8% - 101.2% of the nominal values.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	5/sex	0	24
II (low dose)	5/sex	500	24
III (mid dose)	5/sex	1000	24
IV-A (high dose)	5/sex	2000	24
IV-B (high dose)	5/sex	2000	48
V (positive control*)	5/sex	40	24

*CP=cyclophosphamide

RESULTS

Group	*PCEs with micronuclei (%)*	*Range*	*PCE/2000 erythrocytes*
I (vehicle control)	0.105	0-5	1129
II (low dose)	0.135	1-5	962
III (mid dose)	0.160	1-6	1001
IV-A (high dose)	0.110	0-4	1032
IV-B (high dose)	0.100	0-5	1120
V (positive control)	2.700	40-79	1098

Doses Producing Toxicity	None
Genotoxic Effects	None
Remarks - Results	There was no statistically significant or biologically relevant enhancement in the frequency of the detected micronuclei at any preparation interval and dose level. The mean values of micronuclei observed after treatment with the test item were below or near to the value of the vehicle control group. The positive and vehicle controls gave satisfactory responses confirming the validity of the test system. No clinical signs of toxicity or cytotoxicity were noted at any dose level; therefore it is not certain if the test substance reached the bone marrow.
CONCLUSION	The test substance was not clastogenic under the conditions of this *in vivo* mammalian erythrocyte micronucleus test.
TEST FACILITY	RCC (2007)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture containing notified chemicals at 97.2%)
METHOD	Guidelines for the Hazard Evaluation of New Chemical Substances, State Environmental Protection Agency of P.R.C (HJ/T 154-2004) OECD TG 301 F Manometric Respiratory Test.
Inoculum	Activated Sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	BOD (biochemical oxygen demand) was determined, and their percentage over ThOD (theoretical oxygen demand) was used for the expression of biodegradability.
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation (BOD)*	*Day*	*% Degradation (BOD)*
7	55.4	8	60.8
14	67.9	14	74.7
28	76.7	28	82.9

Remarks – Results	All validity criteria for the test were satisfied. The reference compound, sodium benzoate, reached the 60% pass level by day 5 indicating the suitability of the inoculum. The toxicity control exceeded 25% biodegradation (required by guideline) showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The percent degradation of the notified chemicals reached > 60% at the end of the 10-day window. The degree of degradation of the notified chemicals was 76.7%, after 28 days. Therefore, the test substances can be classified as readily biodegradable according to the OECD (301 F) guideline.
CONCLUSION	The test substance is readily biodegradable.
TEST FACILITY	Supervision and Test Center (2012)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture containing notified chemicals at 95.5%)
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static Test
Species	Zebra fish (*Danio rerio*)
Exposure Period	96 hours
Auxiliary Solvent	Not reported
Water Hardness	Not reported
Analytical Monitoring	Gas Chromatography (GC) Analysis
Remarks – Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Concentration		*Number of Fish*	*Cumulative Mortality (%)*
Nominal (mg/L)	*Geometric mean(mg/L)*		*96 h*
Control	Control	10	0
4.0	1.32	10	0
5.7	1.6	10	0
8.0	2.97	10	20
11.3	7.01	10	100
16.0	6.58	10	100

LC50	3.84 (3.21 – 4.59) mg/L at 96 hours
NOEC	Not reported
Remarks – Results	All validity criteria for the test were satisfied. The treatment solutions were renewed every 24 hours. The actual concentrations of the test substance in freshly prepared treatment solutions were measured at the beginning of 0 hour and 72 hour exposure periods and that for 24hour-old solutions were measured at the end of 24 hour and 96 hour exposure periods. The end points were calculated based on the geometric mean of measured concentrations. The 96-hour LC50 with 95% confidence limit were calculated by trimmed Spearman-Karber method.
CONCLUSION	The test substance is toxic to fish.
TEST FACILITY	Safety Evaluation Center (2012)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture containing notified chemicals at 97.2%)
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test and Reproduction Test – Semi-static. EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia - static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Not applied
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography (GC) Analysis
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative percent immobilised*	
Nominal	*Time weighted mean measured*		*24 h*	*48 h*
Control	Control	20	0	0
1.0	0.6	20	0	0
1.8	1.2	20	0	0
3.2	2.3	20	5	10
5.6	4.2	20	80	100
10	7.9	20	100	100

EC50	2.9 mg/L at 48 hours (95% CL 2.7 – 3.2 mg/L) (time weighted mean measured concentration)
NOEC	1.2 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The treatment solutions were renewed every 24 hours. The actual concentrations of the test substance in freshly prepared treatment solutions were measured at the beginning of 0 hour and 24 hour exposure periods and that for 24hour-old solutions were measured at the end of 24 hour and 48 hour exposure periods. A decline in measured test concentrations was observed in the old media at 24 and 48 hours in the range of 37% to 72% of nominal. Therefore, the toxicity data were reported based on time weighted mean measured concentration. The 48-hour EC50 with 95% confidence limit were calculated by trimmed Spearman-Karber method.
CONCLUSION	The test substance is toxic to aquatic invertebrates
TEST FACILITY	Harlan (2014h)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	IFF TM 11-212 (isomer mixture containing notified chemicals at 97.2%)
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	Green alga (*Pseudokirchneriella subcapitata*)
Exposure Period	72 hours
Concentration Range	Nominal: 1.0, 1.8, 3.2, 5.6, and 10 mg/L Actual: 0.095, 0.21, 0.31, 0.42, 0.96 mg/L (time-weighted mean measured test concentrations)
Auxiliary Solvent	Not applied
Water Hardness	Not provided
Analytical Monitoring	Gas Chromatography (GC) Analysis
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Biomass		*Growth*	
E_bC50 *mg/L at 72 h*	*NOEC* *mg/L*	*E_rC50* *mg/L at 72 h*	*NOEC* *mg/L*
0.25 (95% CL 0.24 – 0.27)	0.21	0.34 (95% CL 0.32 – 0.35)	0.27

Remarks - Results	All validity criteria for the test were satisfied. The test concentrations declined significantly during the 72-hour test period reaching below the limit of quantification (LOQ). Therefore, the tested endpoints were based on the geometric mean measured test concentrations. All statistical analyses were performed using the SAS computer software package.
CONCLUSION	The test substance is very toxic to algae.
TEST FACILITY	Harlan (2015b)

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