File No: LTD/1950/1951

March 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

LTD/1950: 1-Cyclohexene-1-carboxaldehyde, 4-ethenyl-
LTD/1951: 3-Cyclohexene-1-carboxaldehyde, 1-ethenyl-

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 and Energy.

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1950	Givaudan Singapore Pte Ltd	1-Cyclohexene-1-carboxaldehyde, 4-ethenyl-	Yes	< 1 tonne per annum	Fragrance ingredient
LTD/1951	Givaudan Singapore Pte Ltd	3-Cyclohexene-1-carboxaldehyde, 1-ethenyl-	Yes	< 1 tonne per annum	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 following table.

Hazard classification	*Hazard statement*
Flammable Liquids (Category 3)	H226 – Flammable liquid and vapour
Skin Irritation (Category 2)	H315 – Causes skin irritation
Eye irritation (Category 2A)	H319 – Causes serious eye irritation
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

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 2	H401 – 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 as fragrance ingredients in cosmetic and household products at ≤ 0.0288% in cosmetic products, the notified chemicals are not considered to pose an unreasonable risk to public health.

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

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - H226 – Flammable liquid and vapour
  - H315 – Causes skin irritation

- H317 – May cause an allergic skin reaction
- H319 – Causes serious eye irritation

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

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

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

- No specific engineering controls, work practices or personal protective equipment are required for the safe use of the notified chemical itself. However, these should be selected on the basis of all ingredients in the formulation.

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

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

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

Disposal

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

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemicals 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 chemicals, 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 notified chemical;

- the concentration of the notified chemical exceeds or is intended to exceed 0.0288% in cosmetic products;

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 the chemicals 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.

Safety Data Sheet
The SDS of the notified chemicals provided by the notifier was reviewed by NICNAS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Givaudan Singapore Pte Ltd (ABN: 79 368 011 578)
1 Pioneer Turn
SINGAPORE 627576

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

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
EU REACH (2012), China (2014), Canada NDSL (2014), USA TSCA (2012)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Shisolia (isomer mixture containing the notified chemicals)

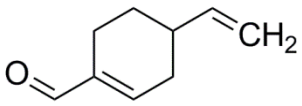
CAS NUMBER
LTD/1950: 1049017-68-6
LTD/1951: 1049017-63-1

CHEMICAL NAME
LTD/1950: 1-Cyclohexene-1-carboxaldehyde, 4-ethenyl-
LTD/1951: 3-Cyclohexene-1-carboxaldehyde, 1-ethenyl-

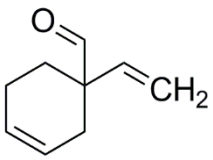
OTHER NAME(S)
GR-50-0091 (isomer mixture containing the notified chemicals)

MOLECULAR FORMULA
$C_9H_{12}O$

STRUCTURAL FORMULA



LTD/1950



LTD/1951

MOLECULAR WEIGHT
136.19 Da

ANALYTICAL DATA
Reference NMR, IR, HPLC, GC, GPC, UV spectra were provided. All analytical data were obtained on the isomer mixture containing the notified chemicals.

3. COMPOSITION

DEGREE OF PURITY
> 95% (isomer mixture)
The notified chemicals are manufactured overseas as a mixture. The ratio of the notified chemicals in the isomer mixture is 35:65 of 1-cyclohexene-1-carboxaldehyde, 4-ethenyl- (LTD/1950) to 3-Cyclohexene-1-carboxaldehyde, 1-ethenyl- (LTD/1951).

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES
The physical and chemical properties are for the isomer mixture containing the notified chemicals.

APPEARANCE AT 20 °C AND 101.3 kPa: liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	-50 °C	Measured
Boiling Point	205 °C at 101.3 kPa	Measured
Density	961 kg/m^3 at 25 °C	Measured
Vapour Pressure	0.04 kPa at 20 °C	Measured
Water Solubility	1.05 g/L at 25 °C	Measured
Hydrolysis as a Function of pH	t1/2 > 1 year at 25 °C at pH = 4, 7, 9	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.4 at 35 °C	Measured
Surface Tension	60.9 mN/m at 19.5 °C	Measured
Adsorption/Desorption	log Koc = 2.08, 2.3 and 2.42	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities
Particle Size	Not determined	Liquid
Flash Point	59 °C at 101.3 kPa	Measured
Flammability (contact with water)	Not determined	Not expected to be flammable based on contact with water based on solubility test observations
Autoignition Temperature	246 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidative properties.

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties of the isomer mixture containing the notified chemicals, 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 for the Classification and*

Labelling of Chemicals (GHS), as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Flammable Liquids (Category 3)	H226 – Flammable liquid and vapour

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemicals will not be manufactured within Australia. The notified chemicals will be imported into Australia as components of fragrance formulations at ≤ 0.556% concentration.

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

LTD/1950

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

LTD/1951

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

PORT OF ENTRY
Sydney (by sea or air)
Perth (by air)

IDENTITY OF RECIPIENTS
Givaudan Singapore Pte Ltd

TRANSPORTATION AND PACKAGING
The notified chemicals will be imported as a component of fragrance formulations at ≤ 0.556% concentration in glass, lacquer-lined containers of sizes ranging 1–190 kg. Finished consumer products containing ≤ 0.0288% notified chemicals will be transported primarily by road to retail stores in packages suitable for retail sale.

USE
The notified chemicals will be used as a fragrance ingredient in cosmetic and household products (at ≤ 0.0288% concentration in fine fragrances, at ≤ 0.008% concentration in other cosmetics, at ≤ 0.005% concentration in household care products and at ≤ 0.02% concentration in fabric care products).

OPERATION DESCRIPTION
The notified chemicals will be imported as a component of fragrance formulations at ≤ 0.556% concentration for reformulation into cosmetic and household products.

Reformulation
The procedures for reformulating the fragrance formulations containing the notified chemicals will vary depending on the nature of the cosmetic/household products, and may involve both automated and manual transfer steps. In general, it is expected that the reformulation processes will involve blending operations that will normally be automated and occur in an enclosed system, followed by automated filling of the finished products into consumer containers of various sizes.

End-use
The finished products containing the notified chemicals (at ≤ 0.0288% concentration in fine fragrances, at ≤ 0.008% concentration in other cosmetics, at ≤ 0.005% concentration in household care products and at ≤ 0.02% concentration in fabric care products) may be used by consumers and professionals such as hairdressers, workers in beauty salons or cleaners. Depending on the nature of the products, these could be applied in a number of ways, such as by hand, using an applicator or by spray.

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
Mixing	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance	4	2
Quality control	4	2
Packaging	4	2
Professional end users	1–8	200

EXPOSURE DETAILS

Transport and storage workers may come in contact with the notified chemicals, either at ≤ 0.556% concentration in fragrance formulations or at ≤ 0.0288% concentration in consumer products, only in the event of an unlikely accidental rupture of containers.

Reformulation

During reformulation into consumer products, dermal, ocular and inhalation exposure of workers to the notified chemicals at ≤ 0.556% concentration may occur. Exposure is expected to be minimised through the use of exhaust ventilation and/or automated/enclosed systems as well as through the use of personal protective equipment (PPE) such as coveralls, eye protection, impervious gloves and respiratory protection (as appropriate).

End use

Exposure to the notified chemicals in end-use products at ≤ 0.0288% 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 chemicals.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemicals at ≤ 0.0288% concentration through the use of cosmetic and household products. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

Data on typical use patterns of product categories in which 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, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption (DA) of 100% was assumed for the notified chemical for calculation purposes. For the inhalation exposure assessment, a 2-zone approach was used (Steiling *et al.*, 2014; Rothe *et al.*, 2011; Earnest, Jr, 2009). An adult inhalation rate of 20 m^3/day (enHealth, 2012) was used and it was conservatively assumed that the fraction of the notified chemical inhaled is 50%. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes. Exposure to the notified chemicals can be considered together due to the toxicological studies being conducted on a mixture of the chemicals.

Cosmetic products (dermal exposure)

Product type	**Amount** (mg/day)	**C** (%)	**Retention Factor (RF)** (unitless)	**Daily systemic exposure** (mg/kg bw/day)
Body lotion	7,820	0.008	1	0.0098

Product type	Amount (mg/day)	C (%)	Retention Factor (RF) (unitless)	Daily systemic exposure (mg/kg bw/day)
Face cream	1,540	0.008	1	0.0019
Hand cream	2,160	0.008	1	0.0027
Fine fragrances	750	0.0288	1	0.0034
Deodorant spray	1,430	0.008	1	0.0019
Shampoo	10,460	0.008	0.01	0.0001
Conditioner	3,920	0.008	0.01	0.0000
Shower gel	18,670	0.008	0.01	0.0002
Hand wash soap	20,000	0.008	0.01	0.0003
Hair styling products	4,000	0.008	0.1	0.0005
Total				0.0208

C = concentration of the notified chemical; RF = retention factor.
Daily systemic exposure = (Amount × C × RF × DA)/BW

Household Products (Indirect dermal exposure – from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.02	0.95	10	0.0007
Fabric softener	90	0.02	0.95	10	0.0003
Total					0.0010

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

Household products (Direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Usage (g/cm^3)	Film Thickness (cm)	Time Scale Factor (unitless)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.005	1980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.005	1980	0.009	0.01	0.03	0.0000
All-purpose cleaner	1	0.005	1980	1	0.01	0.007	0.0001
Total							0.0001

Daily systemic exposure = (Frequency × C × Contact Area × Product Usage × Film Thickness on skin × Time Scale Factor × DA)/BW

Aerosol products (Inhalation exposure)

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone2) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	0.008	20	1	20	50	1	10	0.0003

Daily systemic exposure = [(Amount × C × Inhalation Rate × Fraction Inhaled × 0.1) / BW × 1440)] × [Exposure Duration (Zone 1)/Volume (Zone 1) + Exposure Duration (Zone 2)/Volume (Zone 2)]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 0.0221 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative (screening level) hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposure factors (e.g., air fresheners).

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemicals are summarised in the following table. For full details of the studies, refer to Appendix B. The notified chemicals were tested as a

mixture.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 > 5.2 mg/L/4 hour; low toxicity
Rabbit, skin irritation	irritating
Rabbit, eye irritation	irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOEL 150 mg/kg bw/day NOAEL 450 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus test	non genotoxic

Toxicokinetics
Based on the water solubility (1.05 g/L at 25 °C), partition coefficient (log P_{ow} = 2.4) and the low molecular weight of the notified chemicals, passive diffusion across the gastrointestinal (GI) tract and dermal absorption may occur. The notified chemicals may also be absorbed across the respiratory tract.

Acute toxicity
The notified chemicals were found to be of low acute oral, dermal and inhalation toxicity in rats.

Irritation
The notified chemicals were found to be irritating to skin and eyes in studies conducted in rabbits.

Sensitisation
The notified chemicals were tested for skin sensitisation potential in a mouse local lymph node assay (LLNA). The stimulation indices were 1.42, 1.68, and 6.59 with the notified chemicals (in a mixture) at 1%, 10% and 50% concentration, respectively. An EC3 value of 20.8% was obtained. Based on the results of this study, the notified chemicals are considered skin sensitisers (Category 1B) under the GHS.

Repeated dose toxicity
A repeated dose oral (gavage) toxicity study provided was conducted in rats, in which the notified chemicals were administered at 50, 150 and 450 mg/kg bw/day for 28 consecutive days. The No Observed Effect Level (NOEL) was established as 150 mg/kg bw/day in the study as treatment related changes were observed at the highest dose tested (450 mg/kg bw/day).

Mutagenicity/Genotoxicity
The notified chemicals were not considered to be mutagenic in a bacterial reverse mutation assay when tested in *Salmonella typhimurium* strains with and without metabolic activation. The notified chemicals were clastogenic to V79 cells of the Chinese hamster in an *in vitro* mammalian chromosome aberration test. In the test there was strong cytotoxicity at the highest concentration. Treatment at higher concentrations (62.5 and 93.4 µg/mL) resulted in chromosomal aberrations rates still exceeding the laboratories historical data range, but were not statistically significant. This may be attributed to a high aberration rate in the solvent control. There was no evidence of an increase in polyploidy metaphases.

The notified chemicals were not clastogenic in an *in vivo* mammalian erythrocyte micronucleus test. Therefore, based on the available evidence, the notified chemicals are not expected to be mutagenic or genotoxic.

Health hazard classification
Based on the available information, the notified chemicals are 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***
Skin Irritation (Category 2)	H315 – Causes skin irritation

Eye irritation (Category 2A)	H319 – Causes serious eye irritation
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the available information the critical health effects of the notified chemicals are skin and eye irritation and skin sensitisation.

Reformulation

During reformulation workers are not expected to be at risk of irritation and sensitisation when handling the notified chemical at ≤ 0.556% concentration. It is anticipated by the notifier that engineering controls such as exhaust ventilation and/or automated/enclosed systems will be implemented where possible, and appropriate PPE (coveralls, imperious gloves, eye protection and respiratory protection) will be used as appropriate to minimise workers exposure.

Therefore, under the occupational settings described, the risk to the health of 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 in a variety of cosmetic and household products (at concentrations ≤ 0.0288%). 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 chemicals (for details of the public health risk assessment, see Section 6.3.2).

6.3.2. Public Health

Members of the public may be repeatedly exposed to the notified chemicals during the use of a variety of cosmetic and household products at various concentrations.

Irritation

The notified chemicals are skin and eye irritants. The main risk of irritation will be from the use of cosmetic products containing the notified chemicals. However, given the low proposed use concentration of the notified chemicals in cosmetic products (i.e. ≤ 0.0288%), skin and eye irritation effects are not expected.

Sensitisation

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). Using fine fragrance as an example product that may contain the notified chemical at a maximum concentration of 0.0288%, as a worst case scenario, the Consumer Exposure Level (CEL) for the notified chemical is estimated to be 1.08 μg/cm^2/day (Cadby *et al.,* 2002). When tested in an LLNA study, the notified chemical was a skin sensitiser with an EC3 value of 20.8%. Consideration of each of the studies and application of appropriate safety factors, allowed the derivation of an Acceptable Exposure Level (AEL) of 15.96 μg/cm^2. In this instance, the factors employed included an interspecies factor (3), intraspecies factor (10), a matrix factor (3.16), a use/time factor (3.16) and database factor (1), giving an overall safety factor of ~300.

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 chemical, and a quantitative assessment based on aggregate exposure has not been conducted.

Repeated-dose toxicity

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemicals using the worst case exposure scenario from use of multiple products of 0.0221 mg/kg bw/day (see Section 6.1.2). Using a NOEL of 150 mg/kg bw/day derived from a 28-day repeated dose oral toxicity study on

the notified chemical, the margin of exposure (MOE) was estimated to be 6,774. A MOE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences.

Therefore, based on the information available, the risk to the public associated with use of the notified chemicals in a variety of cosmetic and household products at concentrations ≤ 0.0288% 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 be imported as a component of fragrance formulations, for reformulation into finished cosmetic formulations and household products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. In the event of spills, the product containing the notified chemicals is expected to be collected with adsorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated, and is expected to occur within a fully enclosed environment. Therefore, significant release of the notified chemicals from this process to the environment is not expected. Wastes containing the notified chemicals generated during reformulation include equipment wash water, residues in empty import containers and spilt materials. It is estimated by the notifier that up to 2% of the import volume of the notified chemicals (or up to 20 kg) may be released from reformulation processes. This will be collected and released to sewers in a worst case scenario, or disposed of to landfill in accordance with local government regulations. Empty import containers are expected to be recycled or disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

The notified chemicals are expected to be released to the aquatic compartment through sewers during its use in various cosmetic formulations and household products.

RELEASE OF CHEMICAL FROM DISPOSAL

It is estimated by the notifier that a maximum of 1% of the import volume of the notified chemicals (or up to 10 kg), may remain in containers once the consumer products are used up. Wastes and residues of the notified chemicals in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic formulations and household products in Australia, the majority of the notified chemicals is expected to enter the sewer system, before potential release to surface waters nationwide. Based on the result of the biodegradability study, the notified chemicals are not considered readily biodegradable (31% in 28 days). For details of the environmental fate studies, please refer to Appendix C. Based on its moderate water solubility and low adsorption coefficient (log K_{OC} = 2.08–2.42), release to surface waters may occur as limited partitioning to sludge and sediment is expected under environmental pH. Although the notified chemicals are not readily biodegradable, it is not expected to be bioaccumulative due to its low partition coefficient (log K_{OW} = 2.4). Therefore, in surface waters the notified chemicals are expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The majority of the notified chemicals will be released to sewer after use. A small proportion of the notified chemicals may be applied to land when effluent is used for irrigation, or when sewage sludge is used for soil remediation. The notified chemicals may also be applied to land when disposed of to landfill as collected spills and empty container residue. The notified chemicals in landfill, soil and sludge are expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume a worst case scenario, with 100% release of the notified chemical into sewer systems nationwide and no removal within sewage treatment plants (STPs).

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

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 L/m^2/year (10 ML/ha/year). The notified chemicals in this volume are assumed to infiltrate and accumulate in the top 10 cm of soil (density 1,500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemicals in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemicals in the applied soil in 5 and 10 years may be approximately 20.19 µg/kg and 40.39 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemicals are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 9.2 mg/L	Toxic to fish
Fish Toxicity	96 h LC50 = 10.5 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 31 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	96 h E_rC50 = 21 mg/L	Harmful to algae
	96 h NOE_rC = 2.5 mg/L	Not harmful to algae with long lasting effects

Based on the above ecotoxicological endpoints for the notified chemicals, it is expected to be toxic to fish and harmful to aquatic invertebrates and algae. Therefore, under the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* (United Nations, 2009), the notified chemicals are formally classified as 'Acute Category 2; Toxic to aquatic life'. Based on the low chronic toxicity and low bioaccumulation potential of the notified chemicals, they are not formally classified under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for fish. A safety factor of 100 was used given acute endpoints for three trophic levels and one chronic endpoint are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish, 96 h)	9.2	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	92	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated based on the predicted PEC and PNEC.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.61	92	0.007
Q - Ocean	0.06	92	0.001

The risk quotient for discharge of treated effluents containing the notified chemicals to the aquatic environment indicates that the notified chemicals are unlikely to reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity. Although the notified chemicals are not readily biodegradable, they are expected to have a low potential for bioaccumulation. On the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic formulations and household products, the notified chemicals are not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -50 °C

Method OECD TG 102 Melting Point/Melting Range (1995).
Remarks No congealing was noted down to the temperature of -50.0 ° in the preliminary test.
Test Facility Givaudan (2011a)

Boiling Point 205 °C at 101.3 kPa

Method OECD TG 103 Boiling Point (1995).
Remarks A capillary tube was used according to the Siwoloboff principle.
Test Facility Givaudan (2011b)

Density 961 ± 1 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids (1995).
Remarks The oscillating densitometer method was used.
Test Facility Givaudan (2011c)

Vapour Pressure 0.04 kPa at 20 °C

Method OECD TG 104 Vapour Pressure (2006).
Remarks The gas saturation method was used.
Test Facility Givaudan (2011d)

Water Solubility 1.05 g/L at 20 °C

Method OECD TG 105 Water Solubility.
Remarks Flask Method
Test Facility Givaudan (2011f)

Hydrolysis as a Function of pH $t_{½}$ > 1 year at 25 °C at pH 4, 7, 9

Method OECD TG 111 Hydrolysis as a Function of pH.

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

Remarks HPLC method. A nominal concentration of 120 mg/L was prepared in acetone. The test was carried out at 50 °C with samples taken after 0, 18, 24, 120 and 144 hours. Less than 10% hydrolysis was observed after 120 h at 50°C at pH 4, 7 and 9 and therefore the estimated half-life at 25°C is > 1 year.
Test Facility Givaudan (2011g)

Partition Coefficient (n-octanol/water) log Pow = 2.4 at 35 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks HPLC Method
Test Facility Givaudan (2011h)

Surface Tension 60.9 mN/m at 19.5 °C

Method OECD TG 115 Surface Tension of Aqueous Solutions
Remarks Ring Method
Test Facility Harlan (2011a)

Adsorption/Desorption log K_{oc} = 2.08, 2.3 and 2.42 at 35 °C

Method	OECD TG 121 Estimation of the Adsorption Coefficient (K_{OC}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks	HPLC method
Test Facility	Givaudan (2011i)

Flash Point 59.0 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	The Pensky-Martens closed cup method was used.
Test Facility	Givaudan (2011e)

Autoignition Temperature 246 ± 5 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility	Harlan (2011b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (2001). EC Council Regulation No 440/2008 B.1 tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/RccHan:WIST(SPF)
Vehicle	Corn oil
Remarks - Method	GLP Certificate. No protocol deviations.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	No clinical signs were noted during acclimatisation. All animals showed clinical signs after test substance administration, including slightly to moderate decreased activity, slightly to moderately ruffled fur, swaying gait collapse and dragging of fore and hind limbs. These clinical signs were observed on test day 1 and 2 and lasted up to test day 6. No clinical signs were observed from test day 7 until termination on test day 15.
Effects in Organs	No macroscopic findings were noted at necropsy.
Remarks - Results	The body weight of the animals was within the usual range for this strain and age.

CONCLUSION	The test substance is of low toxicity via the oral route.
TEST FACILITY	Harlan (2011c)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 402 Acute Dermal Toxicity (1987). EC Council Regulation No 440/2008 B.3 Acute Toxicity (Dermal).
Species/Strain	Rat/RccHan:WIST(SPF)
Vehicle	Corn oil
Type of dressing	Semi-occlusive.
Remarks - Method	GLP Certificate. No protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2,000	0

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	No clinical signs were noted during acclimatisation. After treatment, 3 males showed slightly decreased activity on test day 3 to 5, and then no clinical signs were noted in these animals. Other animals did not show any clinical signs.
Signs of Toxicity - Systemic	Slight to moderate erythema was noted after the removal of the test substance on test day 2. From test day 6 until test day 13, focal crusts, desquamation, or both were noted in 5 males and 4 females. And then no

	local dermal signs were observed in any animal until termination on test day 15.
Effects in Organs	No macroscopic findings were noted at necropsy.
Remarks - Results	The body weight of the animals was within the usual range for this strain and age except that one female slightly lost body weight during the first week after treatment but recovered in the second week after treatment.
CONCLUSION	The test substance is of low toxicity via the dermal route.
TEST FACILITY	Harlan (2011d)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 403 Acute Inhalation Toxicity (2009). EC Council Regulation No 440/2008, 93/21/EEC B.2 Acute Toxicity (Inhalation).
Species/Strain	Rat/RccHan:WIST
Vehicle	None
Method of Exposure	Oro-nasal exposure.
Exposure Period	4 hours
Physical Form	Liquid aerosol
Particle Size	Mean mass median aerodynamic diameter = 3.02 μm with % < 4 μm being 62.2% and geometric standard deviation being 2.50
Remarks - Method	GLP Certificate. Minor deviation did not affect the validity of the study.

RESULTS

Group	*Number and Sex of Animals*	*Concentration (mg/L)*		*Mortality*
		Nominal	*Actual*	
1	5 per sex	16.9	5.20 ± 0.16	2 F

LC50	> 5.20 mg/L/4 hours
Signs of Toxicity	During exposure, all animals showed increased respiratory rate, decreased respiratory rate and laboured respiration. On removal from chamber all animals showed increased or decreased respiration rate. Occasional instances of laboured respiration, ataxia and lethargy, isolated instances of prostration were also observed. One female animal died at one hour after exposure. Little or no change in the condition of surviving animals was observed. One day after exposure, a further female animal was found dead, all surviving animals showed increased respiration rate, hunched posture and pilo-erection. There were frequent instances of noisy respiration, isolated occurrences of laboured respiration, sneezing, tip-top gait and red/brown staining around the snout observed. This incidence of these observations gradually receded over the recovery period, with animals appearing normal from days 8 to 11 after exposure.
Effects in Organs	No macroscopic abnormalities were detected amongst three surviving female animals. The remaining seven surviving animals (5 M and 3 F) exhibited abnormally dark lungs and/or dark patches on the lungs at necropsy. Abnormal dark lungs and/or dark kidneys were noted at necropsy for two female animals that died during the study. The deaths observed during the study were considered to be attributable to systemic toxicity of the test substance.

Remarks - Results	All male animals and two surviving female animals exhibited body weight losses on the first day post-exposure. Two male animals and two surviving female animals showed further body weight losses or no body weight gains from day 1 to 3 post-exposure. Reasonable body weight gains were observed in all surviving animals during the remainder of the recovery period except one female animal exhibited no body weight gain during the final week of recovery.
CONCLUSION	The test substance is of low toxicity via inhalation.
TEST FACILITY	Harlan (2013)

B.4. Irritation – skin

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion (2002). EC Council Regulation No 440/2008 B.4 Acute Toxicity (Skin Irritation). EC Directive 2004/73/EC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive.
Remarks - Method	GLP Certificate. No protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	1.67	2	1.33	2	< 14 d	0
Oedema	0.33	0.33	0.33	2	< 48 h	0

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

Remarks - Results	No deaths occurred during the study. No clinical signs or stating of the treated skin was noted. The body weight was within the usual range. No necropsy was performed. Well-defined erythema was observed in all animals at the 1- and 24-hour reading. The erythema persisted as very slight to slight in all three animals up to the 72 hours before disappearing from 7 to 14 days after the treatment. Slight oedema at the 1-hour reading to very slight oedema at the 48-hour reading were observed in all animals. Scaling appeared in all animals 10 and 14 days after treatment. The scaling was moderate for one animal and severe for two animals 10 days after treatment and decreased on the last day of observation to be slight for one animal and moderate for two animals.
CONCLUSION	The test substance is irritating to the skin.
TEST FACILITY	Harlan (2011e)

B.5. Irritation – eye

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion (2002). EC Council Regulation No 440/2008 B.5 Acute Toxicity (Eye Irritation).

	EC Directive 2004/73/EC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Observation Period	17 days
Remarks - Method	GLP Certificate. No protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	2.67	2.67	0.67	3	< 14 d	0
Conjunctiva: chemosis	1.67	1	0.33	3	< 10 d	0
Conjunctiva: discharge	0.67	0.67	0	2	< 48 h	0
Corneal opacity	0.33	0.33	0	1	< 48 h	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks – Results	No deaths occurred during the study. No clinical signs, corrosion, staining of the treated eyes, test substance remnants or abnormal findings for iris light reflex were noted. The body weight was within the usual range. No necropsy was performed. Moderate to marked reddening of the conjunctivae and sclerae in all animals 1 hour after treatment was observed. The severity of the conjunctivae and sclerae reddening decreased in all animals and two animals were still slightly to moderately affected 72 hours after treatment. The reddening persisted as slight in one animal 7 and 10 days after treatment. A slightly to marked conjunctival chemosis was seen in all animals 1 and 24 hours after treatment. The severity decreased and was still slight in one animal 7 days after treatment. A moderate to marked ocular discharge was observed in all animals at the 1-hour reading and persisted as moderate in two animals at the 1- and 24-hour reading, being described with diffuse areas of opacity (grade 1). These effects were reversible and were no longer evident from 72 hour to 14 days after treatment.
CONCLUSION	The test substance is irritating to the eye.
TEST FACILITY	Harlan (2011f)

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

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010) EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)
Species/Strain	Mouse/CBA/CaOlaHsd
Vehicle	Acetone:olive oil = 4:1
Preliminary study	Yes
Positive control	Alpha-Hexyl Cinnamaldehyde
Remarks - Method	GLP Certificate. Minor deviation did not affect the validity of the study.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			

0 (vehicle control)	5 F	661.8 ± 353.9	1.00
1	5 F	938.6 ± 4141.8	1.42
10	5 F	1,109.8 ± 414.9	1.68
50	5 F	4,363.0 ± 2,127.7	6.59
Positive Control			
25	5 F	6,328.0 ± 1,240.2	9.56

EC3	20.8%
Remarks - Results	No deaths occurred during the study. The body weight of the animals was within the usual range for this strain and age. Animals treated with 50% test concentration showed an erythema of the ear skin (score 1) on application days 4 and 5. A statistically significant increase in ear weight was seen in the groups treated with 50 and 10% text substance concentration. A relevant increase in ear thickness was not observed.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance.
TEST FACILITY	Harlan (2011g)

B.7. Repeat dose toxicity

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents (2008).
Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Corn oil
Remarks - Method	GLP Certificate. No protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0
low dose	5 per sex	50	1 M
mid dose	5 per sex	150	0
high dose	5 per sex	450	0
control recovery	5 per sex	0	0
high dose recovery	5 per sex	450	0

Mortality and Time to Death

One male animal in the low-dose group died on the day of necropsy immediately after the blood sampling. No clinical signs were observed during the treatment period for this animal and therefore its death was not considered to be related to the treatment of test substance.

Clinical Observations

No test substance-related adverse findings were noted for daily observations, weekly behaviour observations, functional observations battery including grip strength and locomotor activity (for males), food consumption and body weights.

Female in the high does group had significantly reduced locomotor activity values during 20–30 minutes ($p < 0.05$), 30-40 minutes ($p < 0.05$) and 40-50 minutes ($p < 0.05$) when compared with control animals. This change was considered to be related to the test substance.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

The mean cell haemoglobin concentration of treated males at all dose levels were significantly higher than that of control males (all $p < 0.01$), but these differences were not dose related and all were considered to be related to the low value seen in the control males. The females were not affected.

The mean relative eosinophil count in females in the high dose group was significantly reduced ($p < 0.01$) but remained within the range of historical control values.

All other statistically significant differences (i.e. reduced red cell count and haematocrit in males in the low dose group and increased platelet count in male in the mid dose group) were not evident at higher dose levels and therefore not considered to be related to the test substance.

After two weeks recovery, significant higher mean cell haemoglobin concentration was seen in the same males after the treatment period. This finding was considered to be related to the similar low value seen in the control males. No differences were seen in the remaining parameters and the females were unaffected.

Significantly higher mean potassium levels were observed in males in the mid and high dose groups (both $p < 0.05$) after treatment, but remained in the range of historical control data. In females, some deviations from control electrolyte levels with increasing dose were noted: there were significantly reduced sodium in females in the mid- and high-dose groups (both $p < 0.01$, but in range) and significantly reduced calcium in the high dose group ($p < 0.01$, and out of range), but no consistent pattern and a clear relationship with the test substance could not be established.

Females after four weeks treatment showed dose-unrelated reduced mean blood glucose in the mid- and high-dose groups (both $p < 0.05$) when compared to the controls. As these changes may have been influenced by a slightly high control value and remained within the ranges of the historical control values, no toxicological relevance was associated by study authors with this finding. Reduced mean blood urea was also seen in females at in the mid- and high-dose groups; they were not related to dose and therefore considered to be incidental. Females also showed significantly reductions of total protein ($p < 0.01$), as a results of significantly lower albumin ($p < 0.01$) and globulin ($p < 0.05$) in the high dose group. Total protein and albumin levels remained within the historical control ranges whereas globulin exceeded the lower limit. All other differences were either dose-unrelated or without toxicological relevance.

After two weeks' recovery, very slight yet statistically significant changes in aspartate and alanine aminotransferase activities (both $p < 0.05$) were noted in males previously treated with 450 mg/kg/day. In the absence of such changes after the treatment period, these minor differences were considered to be incidental.

Females showed only significantly reduced glucose ($p < 0.01$), significantly increased alanine aminotransferase activity ($p < 0.05$) and increased calcium ($p < 0.05$). All of these differences remained within the ranges of the historical control data.

After the treatment, no test substance related differences in the urinalysis parameters of males or females were noted. Males in the mid dose group had significantly lower volume ($P < 0.05$) and significantly higher relative density ($p < 0.05$), but these changes were without dose dependence and considered to be isolated. The females were not affected. After two weeks' recovery, no differences were observed in all animals.

No other effects on the parameters of haematology, clinical biochemistry and urinalysis observed were considered to be related to the test substance.

Effects in Organs

After 4 weeks treatment, significantly reduced mean absolute thymus weights ($p < 0.05$) were observed in males in the high dose group. No other differences in the mean absolute weights were noted in males. Significantly increased mean liver-to-body weight ratio ($p < 0.01$) and the mean liver-to-brain ratio ($p < 0.05$) were observed, as was a reduced thymus-to-body weight ratio ($p < 0.05$), and significantly increased kidney-to-body weight ratio ($p < 0.05$). The mean absolute and relative organ weights of the females were unaffected.

In the mid dose group, the mean absolute liver weight and mean liver-to-body weight ratio ($p < 0.05$) significantly increased in males ($p < 0.05$ and $p < 0.01$, respectively) when compared with controls. No differences were noted in the absolute or relative organ weights of females.

In the low dose group, no differences were observed in the mean absolute or relative organ weights in either males or females.

After two weeks recovery, the combined mean absolute and/or relative organ weights of the prostate gland and seminal vesicles of males in the high dose group were significantly lower ($p < 0.05$) than those of the control males. The intergroup variations were relatively high, and the differences may be due to drainage of the seminal vesicles during necropsy. In females, the mean absolute and relative ovary weights were significantly reduced ($p < 0.05$) when compared with the controls, and the adrenal-to-body weight ratio was significantly higher ($p < 0.05$). As no findings were evident at the end of the treatment period, these differences were considered to be unrelated to the treatment with the test substance.

After 4 weeks treatment, in the control males, accentuated lobular pattern of the liver was recorded in three of five males at the end of the treatment period. One of these males also had bilateral renal pelvis dilation. In the control females, one had reddish foci on the thymus and enlarged mandibular lymph nodes. A second control female had black punctate foci on both Harderian glands. All other control animals were unaffected.

In the low dose group, two males had accentuated lobular pattern of the liver and unilateral renal pelvis dilation. A third male had many tan foci on the right ex-orbital lacrimal gland. A fourth male had reddish foci on the thymus, but as this was the male which died accidentally after blood sampling, this finding was considered by study authors to be a typical agonal change in rats and of no toxicological relevance. The fifth rat was unaffected. Two females showed changes in the mandibular lymph nodes: enlarged in one female and with reddish foci in the other. All other females were unaffected.

In the mid dose group, one male had a cyst on the pituitary gland. All other males and all females at this dose level were without macroscopic findings.

In the high dose group, one male had accentuated lobular pattern of the liver. Three males had unilateral renal pelvis dilation. In the females, one had unilateral discoloration on the ovary, and a second female had reddish foci on the thymus. All other females were without macroscopic findings.

After 2 weeks recovery, diaphragmatic hernias were recorded in two males in the control group, whereas ocular discoloration was seen in one male and thymic foci in another male. Control females were not affected.

In the animals in the high dose group, thymic foci was noted in one male and enlarged mandibular lymph nodes in a second male. All females were unaffected.

There were no microscopic findings that could be attributed to treatment with the test substance. All findings recorded were within the range of normal background lesions which may be recorded in animals of this strain.

No differences on the oestrus stages of the vagina were recorded between controls and high dose animals.

No other test substance related differences in mean absolute or relative organ weights, macroscopic findings and microscopic changes were noted.

CONCLUSION
Based on the observations in this study, the No Observed Effect Level (NOEL) was established as 150 mg/kg bw/day and the No Observed Adverse Effect Level (NOAEL) was established as 450 mg/kg bw/day.

TEST FACILITY	Harlan (2012a)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997). Plate incorporation procedure/Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Rat S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver

Concentration Range in Main Test	a) With metabolic activation: 0, 3, 10, 33,100, 333, 1,000, 2,500 and 5,000 µg/plate b) Without metabolic activation: 0, 3, 10, 33,100, 333, 1,000, 2,500 and 5,000 µg/plate
Vehicle	DMSO
Remarks - Method	GLP Certificate. No protocol deviations. There was no preliminary test.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:* *Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 1,000	≥ 1,000	negative
Test 2	≥ 1,000	≥ 1,000	negative
Present			
Test 1	≥ 2,500	≥ 2,500	negative
Test 2	≥ 1,000	≥ 1,000	negative

Remarks - Results	No substantial increase in revertant colony numbers of any of the five tester strains was observed either in the standard plate test or in the pre incubation test in the presence or absence of metabolic activation. There was no tendency of higher mutation rates with increasing concentrations on the range below the generally acknowledged border of biological relevance. The positive and negative controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.
CONCLUSION	The test substance was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Harlan (2011h)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Chinese Hamster
Cell Type/Cell Line	V79 cells
Metabolic Activation System	Rat S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Vehicle	DMSO
Remarks - Method	GLP Certificate. Minor deviation did not affect the validity of the study. There was no preliminary test. Only one experiment was conducted.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 15.6*. 31.3*, 62.5*, 93.4*, 125.0, 187.5, 250.0, 375.0, 500.0	4	18
Present			
Test 1	0*, 0.02, 0.04, 0.08*, 0.16*, 0.31*, 0.63, 1.25, 2.50, 5.00	4	18

*Cultures selected for metaphase analysis.

RESULTS

Metabolic	*Test Substance Concentration (µg/mL) Resulting in:*

Activation	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 93.4	> 500.0	positive
Present			
Test 1	> 0.31	> 5.00	positive

Remarks - Results

No precipitation or phase separation was observed at the end of treatment period.

Cytotoxic effects indicated by reduced cell numbers and/or mitotic indices to approximately 50% of control cells were observed in all experimental parts. In the highest evaluable does of 93.4 µg/mL in the absence of S9 mix the mitotic index was reduced to 60.1% of control cells. In the presence of S9 mix reduced cell numbers were observed after 4 hour treatment with 0.31 µg/mL (54.7% of control). However, in both experimental parts high concentrations were not evaluated for cytogenetic damage due to exceedingly strong cytotoxicity.

In the absence of S9 mix the aberration rates (9.5 and 12.5%) were statistically significantly increased after treatment with 15.6 and 31.3 µg/mL as compared to the corresponding controls (4.0% aberrant cells excluding gaps). In addition, the number of cells carrying exchanges were distinctly increased (6.0 and 7.5) as compared to the solvent controls (1.0%). The treatment with higher concentration (62.5 and 93.4 µg/mL) resulted in chromosomal aberrations rates still exceeding the laboratories historical data range, but not being statistically significant. This may be due to rather high aberration rate in the solvent control. In the presence of S9 mix a statistically significant increase in the aberration rate (11.3% aberrant cells excluding gaps) was noted following treatment with 0.31 µg/mL. The number of cells carrying exchanges (4.3% versus 0.5% in the solvent control) provided an additional evidence for the clastogenic potential of the test substance. The noted statistically significant values were clearly exceeding the laboratory's historical solvent control data (0.0–4.0% aberrant cells excluding gaps).

No evidence of an increase in polyploidy metaphases was noted after treatment with the test substance compared with controls.

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

CONCLUSION

The test substance was clastogenic to V79 cells of the Chinese hamster treated in vitro under the conditions of the test.

TEST FACILITY

Harlan (2011i)

B.10. Genotoxicity – in vivo

TEST SUBSTANCE

Mixture of notified chemicals

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test (1997).
EC Directive 2000/32/EC B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test.

Species/Strain: Mouse/NMRI
Route of Administration: Oral – gavage
Vehicle: Corn oil
Remarks - Method: GLP Certificate. Minor deviation did not affect the validity of the study.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*

I (vehicle control)	7 M	0	24
II (low dose)	7 M	500	24
III (mid dose)	7 M	1,000	24
IV (high dose)	7 M	2,000	24
	7 M	2,000	48
V (positive control, CP or M)	7 M	40	24

CP=cyclophosphamide. M=mitomycin C.

RESULTS

Doses Producing Toxicity	The mean number of polychromatic erythrocytes (PCE) was not substantially decreased after treatment with the test substance as compared to the mean value of PCEs of the negative control indicating the test substance did not have any cytotoxic properties in the bone marrow.
Genotoxic Effects	A statistically significant increase in micronucleated PCEs was not observed at any dose level. The positive control induced statistically significant increases in micronucleated PCEs.
Remarks - Results	All 7 animals from each treatment and control group were selected for bone marrow analysis. It was not possible to confirm that the notified chemical reached the bone marrow.

CONCLUSION The test substance was not clastogenic under the conditions of the in vivo test.

TEST FACILITY Harlan (2011j)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sewage sludge
Exposure Period	34 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	7	5	73
14	22	7	81
21	26	14	89
28	31	21	95
34	32	28	94

Remarks - Results	All validity criteria of the test guideline were satisfied. The percentage degradation of the reference compound (sodium benzoate) surpassed the threshold level of 60% after 5 days (73%), and attained 94% degradation in 28 days. Therefore, the tests indicate the suitability of the inoculums. The toxicity test showed no toxic effects of the test substance to the micro-organisms at the test concentration of 20 mg/L. The degree of degradation of the test substance after 28 days was 31%. Therefore, the test substance is not considered to be readily biodegradable according to the OECD (301 F) guideline.
CONCLUSION	The test substance is not readily biodegradable.
TEST FACILITY	Givaudan (2011j)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Mixture of notified chemicals
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi Static.
Species	*Brachydanio rerio* (zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	125 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*

Control	ND	7	0	0	0	0	0
3.2	ND	7	0	0	0	0	0
7.0	6.1	7	0	0	0	0	0
15	14	7	0	0	29	100	100
32	28	7	0	100	100	100	100
70	ND	7	0	100	100	100	100

LC50	9.2 mg/L (95% CI 6.1–14 mg/L) at 96 h
NOEC	6.1 mg/L at 96 hours
Remarks – Results	All validity criteria of the test guideline were satisfied. The fish were exposed to the control and test solutions for a period of 96 hours with daily batch renewal of the media. The 96 h LC50 and NOEC for fish were determined to be 9.2 mg/L (95% CI 6.1–14 mg/L) and 6.1 mg/L, respectively, based on mean measured concentrations.

CONCLUSION The test substance is considered to be toxic to fish.

TEST FACILITY Harlan (2012b)

C.2.2. Acute toxicity to fish

TEST SUBSTANCE Mixture of notified chemicals

METHOD OECD TG 203 Fish, Acute Toxicity Test – Semi Static.

Species	*Gobiocypris rarus* (Chinese rare minnow)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	165 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography
Remarks – Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	ND	7	0	0	0	0	0
8	6.69	7	0	0	0	0	0
12	10.4	7	0	0	29	29	43
17	15.0	7	0	14	71	86	100
24	22.6	7	0	71	100	100	100
35	36.4	7	0	86	100	100	100
50	52.1	7	100	100	100	100	100

LC50	10.5 mg/L (95% CI 9.0–12.2 mg/L) at 96 h
NOEC	Not reported
Remarks – Results	All validity criteria of the test guideline were satisfied. Daily renewal of exposure medium was performed. The 96 h LC50 for fish was determined to be 10.5 mg/L (95% CI 9.0–12.2 mg/L) based on measured concentrations.

CONCLUSION The test substance is considered to be harmful to fish.

TEST FACILITY BSAL (2012)

C.2.3. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Mixture of notified chemicals

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction

	Test – Semi Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	150 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Concentration mg/L		*Number of D. magna*	*Immobilised (%)*	
Nominal	*Actual*		*24 h [acute]*	*48 h [acute]*
Control	ND	20	0	0
6.5	ND	20	0	0
13	12	20	0	0
25.0	23	20	0	10
50.0	47	20	100	100
100.0	99	20	100	100

LC50	31 mg/L (95% CI 27-37 mg/L) at 48 h
NOEC	12 mg/L at 48 h
Remarks - Results	All validity criteria of the test guideline were satisfied. The test solutions were renewed daily during the 48 h test period. The 48 h EC50 and NOEC for Daphnia were determined to be 31 mg/L (95% CI 27–37 mg/L) and 12 mg/L, respectively, based on mean measured concentrations.

CONCLUSION The test substance is considered to be harmful to aquatic invertebrates.

TEST FACILITY Harlan (2012c)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE Mixture of notified chemicals

METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test – Static.
Species	*Pseudokirchneriella subcapitata* (green alga)
Exposure Period	96 hours
Concentration Range	Nominal: 2.2–35 mg/L Actual: 0.99–34 mg/L
Auxiliary Solvent	None
Water Hardness	15 mg $CaCO_3$/L
Analytical Monitoring	Gas chromatography
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Biomass		*Growth*	
EC50 mg/L at 96 h	NOEC mg/L	EC50 mg/L at 96 h	NOEC mg/L
11 (95% CI 10-13)	2.5	21 (95% CI 19-25)	2.5

Remarks - Results	All validity criteria of the test guideline were satisfied. The actual concentrations of the test item were measured at the start of the test period. Over the 96 hours test period, the test item concentrations in the test media decreased. Thus, the mean measured time-weighted exposure concentrations were calculated taking into account the

	'adsorption factor'. The 96 h EC50 and NOEC for algae were determined to be 21 mg/L (95% CI 19–25 mg/L) and 2.5 mg/L, respectively, based on mean measured concentrations.
CONCLUSION	The test substance is considered to be harmful to algae.
TEST FACILITY	Harlan (2012d)

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