File No: LTD/1925 and LTD/1952

January 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

LTD/1925: Ethanone, 1-(1-cycloocten-1-yl)-
LTD/1952: Ethanone 1-(3-cycloocten-1-yl)-

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:

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX:	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

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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/1925 & LTD/1952	Givaudan Australia Pty Ltd	LTD/1925: Ethanone, 1-(1-cycloocten-1-yl)- LTD/1952: Ethanone 1-(3-cycloocten-1-yl)-	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 following table.

Hazard classification	*Hazard statement*
Skin corrosion/irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1B)	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 3	H402 – Harmful to aquatic life

Human health risk assessment
Provided that the recommended controls are being adhered to, 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 ≤ 0.025% concentration in cosmetic and household 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 assessed 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:
Skin corrosion/irritation (Category 2): H315 – Causes skin irritation
Skin sensitisation (Category 1B): H317 – May cause an allergic skin reaction

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 isolation and engineering controls to minimise occupational exposure to the notified chemicals during reformulation:
Enclosed, automated processes, where possible
Adequate local exhaust ventilation

A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified 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 chemicals 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.

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 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 (each notified chemical);
the concentration of the individual notified chemicals exceeds or is intended to exceed 0.025% concentration in cosmetic and household products;
further information becomes available on the sensitisation potential of the notified chemical in LTD/1925 (i.e. the minor isomer);

or

(2) Under Section 64(2) of the Act; if
the function or use of the chemicals has changed from a fragrance ingredient, or is likely to change significantly;
the amount of chemical being introduced has increased, or is likely to increase, significantly;
the 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.

(Material) Safety Data Sheet
The (M)SDS of the isomer mixture containing the notified chemicals 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
Givaudan Australia Pty Ltd (ABN: 87 000 470 280)
Unit 36/5 Inglewood Place
BAULKHAM HILLS NSW 2153

NOTIFICATION CATEGORY
LTD/1925: Limited-small volume: Chemical other than polymer (1 tonne or less per year) – Group assessment
LTD/1952: Limited-small volume: Chemical other than polymer (1 tonne or less per year) – Group assessment

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
China (2008)
EU (2005)
Switzerland (2006)
USA (2006)

2. IDENTITY OF CHEMICAL

MARKETING NAME
Tanaisone (isomer mixture containing the notified chemicals)

CAS NUMBERS
LTD/1925: 17339-74-1
LTD/1952: 32669-00-4

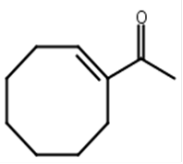
CHEMICAL NAMES
LTD/1925: Ethanone, 1-(1-cycloocten-1-yl)-
LTD/1952: Ethanone 1-(3-cycloocten-1-yl)-

OTHER NAMES
GR-85-4388 (isomer mixture containing the notified chemicals)
1-Cyclooct-3(1)-enylethanone (listed in the (M)SDS)

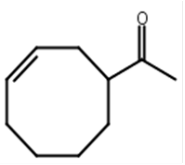
MOLECULAR FORMULA
LTD/1925 and LTD/1952: $C_{10}H_{16}O$

STRUCTURAL FORMULA

LTD/1925:



LTD/1952:



MOLECULAR WEIGHT
LTD/1925 and LTD/1952: 152.23 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 90% (sum of isomers)*

*The notified chemicals are manufactured as an isomer mixture and are not isolated

The typical composition of the notified chemicals in the isomer mixture (Tanaisone/GR-85-4388) is as follows:

Notified chemical	Weight %
Ethanone, 1-(1-cycloocten-1-yl)- (LTD/1925)	7-13
Ethanone 1-(3-cycloocten-1-yl)- (LTD/1952)	80-90

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None identified

OTHER IMPURITIES (> 1% BY WEIGHT)

Chemical Name Ethanone, 1-(*cis*-hexahydro-3a(1*H*)-pentalenyl)-
CAS No. 65682-11-3 *Weight %* 1.1 (in isomer mixture)

Chemical Name Cyclooctanol, 1-acetate
CAS No. 772-60-1 *Weight %* 4.4 (in isomer mixture)

ADDITIVES/ADJUVANTS
None

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: liquid

Property	Value	Data Source/Justification
Freezing Point	< -50 °C	Measured
Boiling Point	185 °C at 101.3 kPa	Measured
Density	960 kg/m^3 at 20 °C	Measured
Vapour Pressure	9.7 × 10^{-3} kPa at 20 °C	Measured
Water Solubility	1.039 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functionalities

Property	Value	Data Source/Justification
Partition Coefficient (n-octanol/water)	Log P_{OW} = 3.0 (LTD/1952)) Log P_{OW} = 3.2 (LTD/1925)	Measured; expected to partition to phase boundaries based on surface activity
Surface Tension	57.8 mN/m (90% concentration) at 20.1 °C	Measured
Adsorption/Desorption	Log K_{OC} = 2.78 (LTD/1952) Log K_{OC} = 2.89 (LTD/1925)	Calculated based on partition coefficient using KOCWIN v2.00 (US EPA, 2011); expected to adsorb to soil and sediment based on surface activity
Dissociation Constant	Not determined	Contains no dissociable functionalities
Flash Point	79 °C at 98.6 kPa	Measured
Flammability	Combustible liquid	Based on flash point
Autoignition Temperature	265 °C	Measured
Explosive Properties	Not explosive	Contain no functional groups that would infer explosive properties
Oxidising Properties	Not oxidising	Contain no functional groups that would infer oxidising properties

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. The notified chemicals are surface active.

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 4	H227 – Combustible liquid

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemicals will not be manufactured in Australia. The notified chemicals will be imported as a component of fragrance compounds at ≤ 1.143% concentration (for the isomer mixture) for local reformulation into cosmetic and household products.

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

LTD/1925

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

LTD/1952

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

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

TRANSPORTATION AND PACKAGING
The notified chemicals will be imported as a component of fragrance formulations in glass, lacquer-lined containers of size ranging 1-190 kg. Finished consumer products containing the 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 fragrance ingredients. The notified chemicals are manufactured as an isomer mixture. The isomer mixture will be imported as a component of fragrance compounds (at ≤ 1.143% concentration) and incorporated into a variety of cosmetic and household products (at proposed usage concentrations of ≤ 0.025% in fine fragrances, ≤ 0.02% in other cosmetic products, ≤ 0.007% in fabric care products and ≤ 0.011% in cleaning products) in Australia.

OPERATION DESCRIPTION

Reformulation
The procedures for reformulating the fragrance formulations containing the notified chemicals will likely vary depending on the nature of the cosmetic and 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
Household cleaning products
Finished household cleaning products containing the notified chemicals (at ≤ 0.011% concentration for the isomer mixture) may be used by the general public and professional cleaners. The cleaning products will be generally applied with a cloth or sponge, mop or brush, or by spray followed by wiping. In some cases the cleaning product will be diluted with water prior to application.

Cosmetics
The finished cosmetic products containing the notified chemicals (at ≤ 0.025% concentration for the isomer mixture) will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application of products could be by hand, sprayed or through the use of an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse workers	Unknown	Unknown
Mixer (plant operator)	4	2
Drum handling	4	2
Drum cleaning/washing	4	2
Maintenance workers	4	2
Quality control workers	4	2
Packager	4	2
Professionals (end-product users)	1-8	200

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemicals at ≤ 1.143% concentration (for the isomer mixture) in fragrance mixtures or at ≤ 0.025% concentration (for the isomer mixture) in end-use products, only in the event of an unlikely accidental rupture of containers.

Reformulation
During reformulation into consumer products, workers may be exposed to the notified chemicals at ≤ 1.143% concentration (for the isomer mixture) via dermal, ocular and inhalation routes. 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 ≤ 0.025% concentration for the isomer mixture) may occur in professions where the services provided involve the application of cosmetics 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 the 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 ≤ 0.025% 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, 2010; 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 chemicals 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 chemicals inhaled is 50%. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes.

Cosmetic products (Dermal exposure):

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	0.020	1	0.0244
Face cream	1540	0.020	1	0.0048
Hand cream	2160	0.020	1	0.0068
Fine fragrances	750	0.025	1	0.0029
Deodorant spray	1430	0.020	1	0.0045
Shampoo	10460	0.020	0.01	0.0003
Conditioner	3920	0.020	0.01	0.0001
Shower gel	18670	0.020	0.01	0.0006
Hand soap	20000	0.020	0.01	0.0006
Hair styling products	4000	0.020	0.1	0.0013
Total				**0.0463**

C = concentration of isomer mixture; 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	0.011	0.95	10	0.0004
Fabric softener	90	0.007	0.95	10	0.0001
Total					**0.0005**

C = concentration of isomer mixture
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 Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.011	1980	0.01	0.01	0.007	0.0000
Dishwashing liquid	3	0.011	1980	0.0093	0.01	0.03	0.0000
All-purpose cleaner	1	0.011	1980	1	0.01	0.007	0.0002
Total							**0.0003**

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

Hairspray (Inhalation exposure):

Product type	Amount (g/use)	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	20	0.02	20	15	20	50	1	10	**0.0013**

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

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemicals. This would result in a combined internal dose of 0.0483 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.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the isomer mixture containing the notified chemicals are summarised in the following table. For the purpose of the risk assessment the results from the isomer mixture are assumed to represent the toxicity of the individual notified chemicals. 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 dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation (EC_3 = 32.4%)
Human, skin sensitisation – RIPT (15% of notified chemical isomer mixture)	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian chromosome aberration test (2 studies)	non genotoxic

Toxicokinetics
Given the low molecular weight (152.23 Da) and partition coefficient (Log Pow = 3.0-3.2) of the notified chemicals, there is potential for the chemicals to cross biological membranes.

Acute toxicity
The isomer mixture containing the notified chemicals was found to be of low acute oral and dermal toxicity in rats.

Irritation
The isomer mixture containing the notified chemicals was found to be irritating to the skin and slightly irritating to the eyes in studies conducted in rabbits.

Sensitisation
The isomer mixture containing the notified chemicals was found to be sensitising in a Local Lymph Node Assay with stimulation indices of 1.9, 5.6 and 9.4 at 25%, 50% and 100%, respectively. The EC_3 value was calculated to be 32.4%. 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 15% concentration (with 97 subjects completing the study). No reactions were noted in subjects during the induction or challenge phases.

The EC_3 value derived for the isomer mixture is likely to reflect the potency of the major isomer (LTD/1952). The minor isomer is also expected to be a sensitiser given the presence of the ketone group, a structural alert for sensitisation, which is also present in the major isomer. However there is uncertainty as to the potency of the minor isomer given the ketone group is conjugated.

Repeated dose toxicity
A repeated dose oral (gavage) toxicity study on the isomer mixture containing the notified chemicals were conducted in rats, in which the test substance was administered at 0, 50, 200 and 1000 mg/kg bw/day for 28 consecutive days, with a 14-day recovery period for high dose and control animals.

Minimal to slight, mainly centrilobular hepatocellular hypertrophy was noted in all treatment groups in males and females that was reversible after recovery. This finding was considered by the study authors to be adaptive in nature. An increased incidence and severity of hyaline droplets, tubular basophilia and tubular cell necrosis was noted in males in all treatment groups. This adverse finding was not considered by the study authors to be relevant to humans. The No Observed Adverse Effect Level (NOAEL) was therefore established as 1000 mg/kg bw/day in this study.

Mutagenicity/Genotoxicity
The isomer mixture containing the notified chemicals was negative in a bacterial reverse mutation test.

When the isomer mixture was tested in an *in vitro* chromosome aberration test in Chinese hamster V79 cells, a statistically significant increase in the number of aberrant cells was observed in the presence of metabolic activation. However, as the increase was observed at a highly cytotoxic level and the finding was not corroborated in a confirmatory test, the study authors considered the genotoxicity was induced by general toxicity and therefore regarded as biologically irrelevant.

In a subsequent *in vitro* chromosome aberration test in Chinese hamster V79 cells with the isomer mixture, statistically significant increases in the number of aberrant cells were observed, in a dose-related manner, in the absence and presence of metabolic activation. However, since all values were clearly within the laboratory's historical control data, the results were regarded as biologically irrelevant.

Therefore, based on the available information, the isomer mixture containing the notified chemicals is not expected to be genotoxic.

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 corrosion/irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1B)	H317 - May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the toxicological information provided, the notified chemicals are skin sensitisers, irritating to skin and slightly irritating to eyes. Adverse effects could also occur after repeated exposure.

Reformulation

During reformulation, workers may be at risk of skin sensitisation effects when handling the notified chemicals at ≤ 1.143% concentration (for the isomer mixture). It is anticipated by the notifier that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible, and appropriate PPE (coveralls, imperious gloves, eye protection and respiratory protection) will be used to limit worker exposure.

Therefore, provided that control measures are in place to minimise worker exposure, 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

Workers involved in professions where the services provided involve the application of cosmetic and household products containing the notified chemicals to clients (*e.g.*, hairdressers, beauty salon workers and cleaners) may be exposed to the notified chemicals at ≤ 0.025% 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, the risk to such workers is expected to be of a similar or lesser extent than that experienced by consumers using the various products containing the notified chemicals.

6.3.2. Public Health

Cosmetic and household products containing the notified chemicals at ≤ 0.025% concentration (for the isomer mixture) will be available to the public. The main route of exposure is expected to be dermal and inhalation, with some potential for accidental ocular or oral exposure.

Irritation

The notified chemicals are irritating to skin and slightly irritating to eyes. However, irritation effects are not expected from use of the notified chemicals at the proposed low concentrations in cosmetic and household products.

Sensitisation

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 for products that may contain the notified chemicals (at 0.025% concentration for the isomer mixture), as a worst case scenario, the Consumer Exposure Level (CEL) for the isomer mixture is estimated to be 0.94 μg/cm^2/day (Cadby *et al.,* 2002). When tested in an LLNA study, the isomer mixture containing the notified chemicals was considered a skin sensitiser with an EC_3 value of 32.4%. Consideration of the study details and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 25.95 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.

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 lower expected exposure level from other cosmetic 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. However, 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.

Repeated dose toxicity

The repeated dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the isomer mixture containing the notified chemicals using the worst case exposure scenario from use of multiple products of 0.0483 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 1000 mg/kg bw/day derived from a 28 day repeated dose oral toxicity study on the isomer mixture, the MoE was estimated to be 20,704. A MoE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences. Therefore, the MoE for the isomer mixture containing the notified chemicals is considered to be acceptable

under the proposed use concentrations (i.e. ≤ 0.025% in fine fragrances, ≤ 0.02% in other cosmetic products, ≤ 0.007% in fabric care products and ≤ 0.011% in cleaning products). Based on the potential systemic exposure from the isomer mixture in cosmetic and household products, an MOE value greater than or equal to 100 is also expected where the isomer mixture is present at ≤ 0.025% concentration for all cosmetic and household product categories.

Therefore, based on the information available, the risk to the public associated with the use of the isomer mixture containing the notified chemicals at ≤ 0.025% concentration in cosmetic and household products, is not considered to be unreasonable.

Given the assumed similar toxicity of the notified chemicals, noting the uncertainty with regard to the individual sensitisation potencies, the risk to the public associated with the use of the individual notified chemicals at ≤ 0.025% 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 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 are 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. The process will be followed by automated filling of the formulated products into containers of various sizes suitable for retail and use. 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 each notified chemical) may be released from reformulation processes. These 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 each notified chemical), may remain in end-use 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 their use in cosmetic formulations and household products in Australia, the majority of the notified chemicals are expected to enter the sewer system, before potential release to surface waters nationwide. Based on the results of a ready biodegradability study, the notified chemicals are considered readily biodegradable (82% in 28 days). For details of the environmental fate study, please refer to Appendix C. Based on their surfactant properties and ready biodegradation, release to surface waters is unlikely to occur, as biodegradation and partitioning to sludge and sediment is expected under environmental pH. The notified chemicals are not expected to be bioaccumulative due to their surfactant properties. 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 notified chemicals are moderately volatile from water (vapour pressure = 9.7×10^{-3} kPa at 20 °C) and may slowly volatilise to air during sewage treatment. The half-lives of the notified chemicals in air is calculated to be 2.98-3.62 hours, based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, the notified chemicals are not expected to persist in the air compartment.

The majority of the notified chemicals will be released to sewer after use. A 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 chemicals into sewer systems nationwide and no removal within sewage treatment plants (STPs).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment			
	LTD/1925	**LTD/1952**	
Total Annual Import/Manufactured Volume	1,000	1,000	kg/year
Proportion expected to be released to sewer	100%	100%	
Annual quantity of chemical released to sewer	1,000	1,000	kg/year
Days per year where release occurs	365	365	days/year
Daily chemical release:	2.74	2.74	kg/day
Water use	200.0	200.0	L/person/day
Population of Australia (Millions)	22.613	22.613	million
Removal within STP	0%	0%	
Daily effluent production:	4,523	4,523	ML
Dilution Factor - River	1.0	1.0	
Dilution Factor - Ocean	10.0	10.0	
PEC - River:	0.606	0.606	µg/L
PEC - Ocean:	0.061	0.061	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 0.606 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg for each notified chemical. Assuming accumulation of the notified chemicals in soil for 5 and 10 years under repeated irrigation, the concentration of each notified chemical in the applied soil in 5 and 10 years may be approximately 20.20 µg/kg and 40.39 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the isomer mixture containing the notified chemicals are summarised in the table below. For the purpose of the risk assessment the results from the isomer mixture are assumed to represent the toxicity of the individual notified chemicals. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 38 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 48 mg/L	Harmful to aquatic invertebrates
Algal Toxicity	48 h EC50 = 78 mg/L	Harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 > 100 mg/L	Not inhibitory to microbial respiration

Based on the above ecotoxicological endpoints, the notified chemicals are considered to be harmful to aquatic life. 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 3; Harmful to aquatic life'. Based on the acute toxicity, ready biodegradability and low potential for bioaccumulation, the notified chemicals 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 endpoint for three trophic levels available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish, 96 h)	38	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	380	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
LTD/1925			
Q – River	0.606	380	**0.002**
Q – Ocean	0.061	380	**0.0002**
LTD/1952			
Q – River	0.606	380	**0.002**
Q – Ocean	0.061	380	**0.0002**

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 their maximum annual importation quantity. The notified chemicals are readily biodegradable, and 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

Freezing Point < -50 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	Determined using a crystallising apparatus
Test Facility	Givaudan (2004a)

Boiling Point 185 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point.
Remarks	Extrapolated from vapour pressure curve
Test Facility	Givaudan (2005a)

Density 960 kg/m^3 at 20°C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	Oscillating densitimeter method
Test Facility	Givaudan (2004b)

Vapour Pressure 9.7×10^{-3} kPa at 20 °C

Method	OECD TG 104 Vapour Pressure.
Remarks	Static method
Test Facility	NOTOX B.V. (2005a)

Water Solubility 1.039 g/L at 20 °C

Method	OECD TG 105 Water Solubility.
Remarks	Flask Method
Test Facility	Givaudan (2005b)

Partition Coefficient (n-octanol/water) log Pow = 3.0 (LTD/1952)
log Pow = 3.2 (LTD/1925)

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	Reverse Phase HPLC Method
Test Facility	Givaudan (2005c)

Surface Tension 57.8 mN/m at 20.1 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions.
Remarks	Ring Method Concentration: 90% saturation concentration.
Test Facility	NOTOX B.V. (2007a)

Flash Point 79 °C at 98.6 kPa

Method	Commission Directive 92/69/EEC, Method A.9.
Remarks	Closed cup method
Test Facility	Givaudan (2004c)

Autoignition Temperature 265 °C

Method	Commission Directive 92/69/EEC, Method A.15.
Remarks	Tested in an Auto Ignition Temperature apparatus
Test Facility	NOTOX B.V. (2005b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	GR-85-4388 (isomer mixture containing the notified chemicals)
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Wistar Brl:Wist (SPF)
Vehicle	Polyethylene glycol 300 (PEG 300)
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3F	2000	0/3
2	3F	2000	0/3

LD50	> 2000 mg/kg bw
Signs of Toxicity	Clinical signs included ataxia, ruffled fur, hunched posture, sedation and tremors.
Effects in Organs	No abnormalities were noted at macroscopic examination.
Remarks - Results	The animals showed expected body weight gain over the observation period.
CONCLUSION	The test substance is of low toxicity via the oral route.
TEST FACILITY	RCC (2005a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Tanaisone (isomer mixture containing the notified chemicals)
METHOD	OECD TG 402 Acute Dermal Toxicity.
Species/Strain	Rat/HanRCC:WIST (SPF)
Vehicle	Polyethylene glycol 300 (PEC 300)
Type of dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	Slight erythema was noted in 9 animals on Days 2-6 and persisted up to Day 9 in 1 female animal. Slight scaling was observed in all female animals on Days 5-8 and persisted up to Day 9 in 1female animal. Four male animals also showed slight scaling on Days 6-9.
Signs of Toxicity - Systemic	No signs of systemic toxicity were noted.
Effects in Organs	No abnormal macroscopic findings were noted at necroscopy.
Remarks - Results	The body weight of the animals was within the range commonly recorded for this strain and age.
CONCLUSION	The test substance is of low toxicity via the dermal route.
TEST FACILITY	RCC (2007a)

B.3. Irritation – skin

TEST SUBSTANCE	GR-85-4388 (isomer mixture containing the notified chemicals)
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (1 M and 2 F)
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks - Method	No significant 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	3.0	1.0	2.0	3	< 10 days	0
Oedema	1.0	0	0.7	2	< 7 days	0

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

Remarks - Results

No mortality or signs of systemic toxicity were noted.

Very slight to well-defined erythema was noted in all animals at the 1-hour observation. Very slight to marked erythema was noted in all animals up to the 72-hour observation. Very slight erythema was noted in one (male) animal at the 7-day observation. Very slight oedema was noted in two animals at the 48-hour observation and slight oedema was noted in one (male) animal at the 72-hour observation.

Scaling persisted in one animal up to the 10-day observation and in 2 other animals up to the 14-day observation.

Changes in body weight gain were within the range expected for rats used in this type of study.

CONCLUSION The test substance is irritating to the skin.

TEST FACILITY RCC (2005b)

B.4. Irritation – eye

TEST SUBSTANCE	GR-85-4388 (isomer mixture containing the notified chemicals)
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (1M and 2F)
Observation Period	7 days
Remarks - Method	No significant 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	1.3	1.7	1.3	2	< 7 days	0
Conjunctiva: chemosis	0.3	0.7	0	2	< 72 hours	0

Corneal opacity	0	0.3	0	1	< 48 hours	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	Moderate reddening of the conjunctivae noted in all animals at the 1-hour observation and slight reddening persisted up to the 72-hour observation. Moderate chemosis was observed in all animals at the 1-hour observation and persisted in two animals in one animal at the 48-hour observation. Moderate ocular discharge noted in all animals at the 1-hour observation and one animal showed slight ocular discharge at the 24-hour observation. Moderate to marked reddening of the sclerae was noted in all animals at the 1-hour observation. All animals showed slight to moderate sclerae at the 24-hour observation and persisted up to the 72-hour observation in one animal. All signs of irritation were resolved at the 7-day observation. There was no unscheduled mortality or clinical signs of systemic toxicity.
CONCLUSION	The test substance is slightly irritating to the eye.
TEST FACILITY	RCC (2005c)

B.5. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	GR-85-4388 (isomer mixture containing the notified chemicals)
METHOD	OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain	Mouse/CBA/Ca
Vehicle	Acetone/olive oil (4:1)
Preliminary study	Yes
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using α-hexylcinnamaldehyde.
Remarks - Method	Not significant protocol deviations

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	4F	322	-
25	4F	622	1.9
50	4F	1819	5.6
100	4F	3027	9.4

EC3	32.4 %
Remarks - Results	In the main study, there were no mortality or signs of systemic toxicity observed in the test or control animals. Slight to moderate ear erythema was observed in all the treated animals on Days 2-3. Animals treated with 100% test substance also showed slight ear swelling on Days 3-5. The auricular lymph nodes of the animals in control and 25% concentration groups were considered normal in size while the nodes of the animals in 50% and 100% concentration groups were considered enlarged. The test substance elicited a SI ≥ 3 and is therefore considered a skin sensitiser. All treated animals showed body weight changes comparable to those of

	the vehicle control group.
CONCLUSION	There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the test substance.
TEST FACILITY	RCC (2005d)

B.6. Skin sensitisation – human volunteers

Test Substance	Notified chemical (tested at 15% concentration)
Method	Repeated insult patch test
Study Design	Induction Phase: The test substance (approximately 0.2 mL) was added onto an occlusive patch and applied to the upper arm and was allowed to remain in direct skin contact for a period of 24 hours. Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications. Rest Period: 24 hour rest periods for Tuesday and Thursday removals and 48 hour rest periods for Saturday removals. Challenge Phase: After a rest period of approximately 2 weeks, the challenge patches were applied to previously untreated test sites. After 24 and 72 hours, the test sites were evaluated for dermal reactions.
Study Group	90 F, 20 M; age range 18 – 74 years
Vehicle	Not stated
Remarks - Method	The test substance was volatilized for at least 10 minutes but less than 20 minutes on the patch prior to the application on the skin.
Results	
Remarks - Results	This study was initiated with 110 subjects. Thirteen subjects discontinued for reasons unrelated to the test substance. A total of 97 subjects completed the study. During challenge phase, a subject showed barely perceptible (minimal, faint, uniform or spotty) erythema at the 24 hour evaluation. No adverse events were reported during the study.
Conclusion	The test substance at 15% concentration was non-sensitising under the conditions of the test.
Test Facility	Essex Testing Clinic (2006)

B.7. Repeat dose toxicity

TEST SUBSTANCE	Tanaisone (isomer mixture containing the notified chemicals)
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Polyethylene glycol 300 (PEG 300)
Remarks - Method	No significant protocol deviations.

RESULTS

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

control	5 per sex	0	0/10
control recovery	5 per sex	0	0/10
low dose	5 per sex	50	0/10
mid dose	5 per sex	200	0/10
high dose	5 per sex	1000	2/10
high dose recovery	5 per sex	1000	0/10

Mortality and Time to Death

There were two mortalities in the high dose group during the study (one male died on Day 15 and a female died on Day 21). The cause of death was considered by the study authors to be likely due to a dosing error.

Clinical Observations

No treatment-related clinical signs of toxicological relevance were noted throughout the treatment and recovery periods.

Treatment-related findings were generally restricted to slightly lower mean daily food consumption (days 15-28 of treatment and on days 1-14 of recovery), and slightly reduced mean body weights and mean body weight gain (during treatment period) in male animals treated with 1000 mg/kg/day.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Treatment-related changes in haematology parameters included elevated mean thromboplastin times and reduced mean activated partial thromboplastin in female and male animals treated with 1000 mg/kg/day. However, only mean thromboplastin times noted in male animals were marginally exceeded the historical control values. No differences were considered by the study authors to represent changes of toxicological relevance after recovery.

Treatment-related changes in biochemistry parameters were only noted in animals treated with 1000 mg/kg/day, including elevated sodium, calcium and protein levels, reduced albumin/globulin ratio, reduced glucose level, increased cholesterol and triglyceride levels in both sexes, elevated globulin level in male animals, and reduced creatinine level in female animals. The protein and globulin levels in both sexes exceeded the upper limits of the historical control data and the albumin/globulin ratio exceeded the lower limit. The study authors stated that these changes were considered to coincide with the microscopic changes in the kidneys and to be treatment-related.

Animals of both sexes treated with 1000 mg/kg/day showed increased urinary output and presence of ketones.

Effects in Organs

Treatment-related organ weight changes were noted in liver and kidney of male animals treated with 50 mg/kg/day and of both sexes treated with 200 and 1000 mg/kg/day. No treatment-related differences were noted after the recovery period.

Increased incidence and severity of hyaline droplets, tubular basophilia and tubular cell necrosis (commensurate with hydrocarbon-induced α-2-microglobulin nephropathy) were noted in male animals of all treatment groups. This nephropathy did not completely resolve in the recovery group, and correlated with increased organ weights/organ weight ratios. The study authors considered the observed test substance induced nephropathy to be human irrelevant as little or no α-2-microglobulin is present in humans.

Minimal to slight hepatocellular (mainly centrilobular hypertrophy) was noted in treated animals of both sexes. This finding was not accompanied by inflammatory or degenerative lesions of the liver and was reversible after recovery.

Remarks – Results

The hepatic and nephropathic changes were considered by the study authors to be adaptive and human irrelevant, respectively.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day in this study, based on the absence of test substance related adverse effects at all doses tested.

TEST FACILITY RCC (2007b)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE	GR-85-4388 (isomer mixture containing the notified chemicals)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure (Test 1)/Pre incubation procedure (Test 2)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Concentration Range in Main Test	With and without metabolic activation: 10-5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	A preliminary test at a concentration range of 3-5000 µg/plate was conducted and this test was reported as part of main Test 1 because the criteria "evaluable plates (> 0 colonies) at five concentrations or more in all strains used" was met. Tests 1 and Test 2 were carried out at a concentration range of 10-5000 µg/plate. Positive control: With metabolic activation: 2-aminoanthracene Without metabolic activation: sodium azide (TA 1535 and TA 100), 4-nitro-o-phenylene-diamine (TA 1537 and TA 98), methyl methane sulfonate (TA 102)

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 333	> 5000	Negative
Test 2	> 333	> 5000	Negative
Present			
Test 1	> 1000	> 5000	Negative
Test 2	> 333	> 5000	Negative

Remarks - Results	No significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation. The positive and negative controls gave a satisfactory response confirming the validity of the test system.
CONCLUSION	The test substance was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	RCC (2005e)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE	GR-85-4388 (isomer mixture containing the notified chemicals)
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Chinese hamster
Cell Type/Cell Line	V79
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Ethanol
Remarks - Method	A dose range-finding study was conducted at 12.5 - 1600 µg/mL with 4 hour and 24 hour treatments. The dose selection for the main experiments was based on toxicity observed in the range-finding study. Vehicle and positive controls (ethyl methanesulfonate and

cyclophosphamide) were run concurrently with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	12.5, 25, 50*, 100*, 200*, 400	4 h	18 h
Test 2a	12.5, 25, 50*, 100*, 200*, 400	18 h	18 h
Test 2b	50, 100, 200*, 400	28 h	28 h
Present			
Test 1	25, 50*, 100*, 200*, 400, 800	4 h	18 h
Test 2	12.5, 25, 50, 100*, 200*, 400*	4 h	28 h
Test 3	150, 200, 250*, 300*, 350*, 400	4 h	28 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	> 200	> 200	> 400	Negative
Test 2a	> 200	> 100	> 400	Negative
Test 2b		> 100	> 400	Negative
Present				
Test 1	> 400	> 200	> 800	Negative
Test 2		> 200	> 400	Positive
Test 3		> 400	> 400	Negative

* Toxicity indicated by reduced cell numbers of below 50% of the control.

Remarks - Results

In Test 2b, a single statistically significant increase (2.5%) of aberrant metaphase cells was noted at the concentration of 200 µg/mL, in the absence of metabolic activation. This finding was considered by the study authors to be biologically irrelevant as it was within the testing facility's historical control data range.

In Test 2, in the presence of metabolic activation, a statistically significant increase of aberrant metaphase cells (17.5% aberrant cells, exclusive gaps) was noted at the highest scored test concentration of 400 µg/mL, with a strongly cytotoxic level as indicated by the reduced cell number (22.9% of the control). In Test 3 (a confirmatory test for Test 2 in the presence of metabolic activation), the aberration rates were close to the control value and within the test facility's historical control data. Therefore, the genotoxic finding in Test 2 in the presence of metabolic activation was assumed by the study authors to be induced by strong general toxicity and biologically irrelevant.

The positive and negative controls gave a satisfactory response confirming the validity of the test system.

CONCLUSION

The test substance was not clastogenic to Chinese hamster V79 cells treated *in vitro* under the conditions of the test.

TEST FACILITY

RCC (2006a)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE

Tanaisone (isomer isomer mixture containing the notified chemicals)

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Species/Strain

Chinese hamster

Cell Type/Cell Line	V79
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Ethanol
Remarks - Method	A dose range find study was conducted at 12.7 - 1620 µg/mL with 4 hours and 24 hours treatments. The dose selection for the main experiments was based on toxicity observed in the range-finding study. Vehicle and positive controls (ethyl methanesulfonate and cyclophosphamide) were run concurrently with the test substance.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	25, 50*, 100*, 200*, 400, 800	4 h	18 h
Test 2a	25, 50*, 100*, 200*, 400, 800	18 h	18 h
Test 2b	25, 50, 100*, 200*, 400, 800	28 h	28 h
Present			
Test 1	25, 50*, 100*, 200*, 400, 800	4 h	18 h
Test 2	25, 50, 100*, 200*, 400*, 800	4 h	28 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	> 202.5	> 200	> 800	Negative
Test 2a	> 202.5	> 200	> 800	Negative
Test 2b		> 100	> 800	Negative
Present				
Test 1	> 202.5	> 200	> 800	Negative
Test 2		> 400	> 800	Negative

* Toxicity indicated by reduced cell numbers of below 50% of the control.

Remarks - Results	Precipitation was noted only in the range finding study in the presence of metabolic activation after 4 hours treatment at ≥ 810 µg/mL. In Test 1 (in the presence of metabolic activation) and Test 2b (in the absence of metabolic activation), two statistically significant increases of aberrant cells were noted at the concentration of 200 µg/mL. In addition, in Test 2 (in the presence and absence of metabolic activation), dose-dependent increases in cells carrying aberrations were noted. These findings were considered by the study authors to be biologically irrelevant as they were within the testing facility's historical control data range. The positive and negative controls gave a satisfactory response confirming the validity of the test system.
CONCLUSION	The test substance was not clastogenic to V79 cells treated *in vitro* under the conditions of the test.
TEST FACILITY	RCC (2007c)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	GR-85-4388 (isomer mixture containing the notified chemicals)
METHOD	OECD TG 301 A Ready Biodegradability: DOC Die-Away Test.
Inoculum	Activated sewage sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	19	7	81
14	60	14	89
21	76	21	92
29	82	29	94

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound surpassed the threshold level of 60% by 5 days (75%). Therefore, the tests indicate the suitability of the inoculum. The degree of degradation of the test substance after 28 days was 82%. As the test substance is surface active, the 10-day window is not applicable. Therefore, the test substance is considered to be readily biodegradable according to the OECD (301 F) guideline.
CONCLUSION	The test substance is readily biodegradable.
TEST FACILITY	Givaudan (2005d)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Tanaisone (isomer mixture containing the notified chemicals)
METHOD	OECD TG 203 Fish, Acute Toxicity Test - Static.
Species	*Cyprinus carpio* (carp)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
10	8.8	7	0	0	0	0	0
18	16	7	0	0	0	0	0
32	27	7	0	0	0	0	0

56	53	7	100	100	100	100	100
100	95	7	100	100	100	100	100

LC50	38 mg/L (95% CI 27-53 mg/L) at 96 hours
NOEC (or LOEC)	16 mg/L at 96 hours.
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were not renewed during the 96 h test period. The actual concentrations of the test substance were measured at the start and end of the 96 h test period. The 96 h LC50 and NOEC for fish were determined to be 38 mg/L (95% CI 27-53 mg/L) and 16 mg/L, respectively, based on measured concentrations.

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

TEST FACILITY NOTOX B.V. (2007b)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE GR-85-4388 (isomer mixture containing the notified chemicals)

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

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h [acute] 14 d [chronic]*	*48 h [acute] 21 d [chronic]*
Control	Control	20	0	0
10	8.55-11.1	20	0	0
18	19.5-20.4	20	0	0
32	33.8-41.4	20	0	15
56	51.9-64.1	20	15	55
100	110-113	20	100	100

EC50	48 mg/L (95% CI 42-57 mg/L) at 48 hours
NOEC (or LOEC)	18 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The test solutions were not renewed during the 48 h test period. The actual concentrations of the test substance were measured at the start and end of the 48 h test period. As measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. The 48 h EC50 and NOEC for daphnids were determined to be 48 mg/L (95% CI 42-57 mg/L) and 18 mg/L, respectively, based on nominal concentrations.

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

TEST FACILITY NOTOX B.V. (2005c)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Tanaisone (isomer mixture containing the notified chemicals)
METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test – Static.
Species	*Pseudokirchneriella subcapitata* (green alga)
Exposure Period	48 hours
Concentration Range	Nominal: 4.6-100 mg/L Actual: 4.16-95.5 mg/L
Auxiliary Solvent	None
Water Hardness	24 mg $CaCO_3$/L
Analytical Monitoring	GC
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Biomass		*Growth*	
EC50 *mg/L at 48 h*	*NOEC* *mg/L*	*EC50* *mg/L at 48 h*	*NOEC* *mg/L*
24 (95% CI 12-48)	< 4.6	78 (95% CI 51-110)	4.6

Remarks - Results	At the end of the test, the appearance of the algal cells was not checked. However, this was not deemed to have significantly impacted the validity or integrity of the test. All other validity criteria for the test were satisfied. The test solutions were not renewed during the 48 h test period. The actual concentrations of the test substance were measured every 24 hours during the 48 h test period. As measured concentrations were within 20% difference of the nominal concentrations, the nominal concentrations were used. The 48 h EC50 and NOEC for algae were determined to be 78mg/L (95% CI 51-110 mg/L) and 4.6 mg/L, respectively, based on nominal concentrations.
CONCLUSION	The test substance is considered to be harmful to algae.
TEST FACILITY	NOTOX B.V. (2007c)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Tanaisone (isomer mixture containing the notified chemicals)
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.
Inoculum	Activated sewage sludge
Exposure Period	3 hours
Concentration Range	Nominal: 1-100 mg/L Actual: Not determined
Remarks – Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported. As the test substance was not soluble enough in water to prepare a stock aqueous solution, the test substance was dissolved in ethanol to produce the relevant test concentrations. 3,5-Dichlorophenol was used as the reference control. The respiration rate was determined by measurement of Biochemical Oxygen Demand during the test after 3 hours of exposure.
RESULTS	
IC50	> 100 mg/L
NOEC	Not determined
Remarks – Results	The stock solution for the reference control was prepared using 100 mL of 0.1 M NaOH instead of 10 mL of 1 M NaOH. However, this was not

	deemed to have significantly impacted the validity or integrity of the test. All other validity criteria for the test were satisfied. The 3 h IC50 was determined to be > 100 mg/L, based on nominal concentrations.
CONCLUSION	The test substance is not considered to be inhibitory to microbial respiration.
TEST FACILITY	Givaudan (2008)

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