File No: LTD/1713

June, 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-

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

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

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

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Director
NICNAS

TABLE OF CONTENTS

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/1713	Givaudan Australia Ltd.	Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-	ND*	≤ 1 tonne per annum	Fragrance ingredient

* Not Determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

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

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

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

When used at ≤ 0.067% in leave-on and wash-off cosmetic products and ≤ 0.003% in household products, the notified chemical is not considered to pose an unreasonable risk to public health.

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Enclosed, automated processes, where possible

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

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical
  - Coveralls
  - Impervious gloves

- Eye protection

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.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

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

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the concentration of the notified chemical exceeds or is intended to exceed ≤ 0.067% in leave-on and rinse-off cosmetics and ≤ 0.003% in household products;

or

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

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

(Material) Safety Data Sheet
The (M)SDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Givaudan Australia Limited (ABN: 87 000 470 280)
Unit 36/5 Inglewood Place
BAULKHAM HILLS NSW 2153

NOTIFICATION CATEGORY
Limited: Small Volume: Chemical other than polymer (≤1 tonne/year)

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
None

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Yes, previously assessed by NICNAS as an LVC permit.

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Javanol

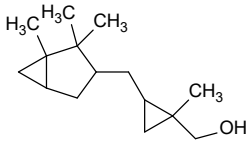
CHEMICAL NAME(S)
Cyclopropanemethanol, 1-methyl-2-[(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-

CAS NUMBER
198404-98-7

OTHER NAME(S)
GR-84-8282

MOLECULAR FORMULA
$C_{15}H_{26}0$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
222.37 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 85%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)

Chemical Name	cyclopropanemethanol, 1-methyl-2-[[(1R,3R,5S)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl)methyl]-, rel-		
CAS No.	1333973-173	*Weight %*	1.16

ADDITIVES/ADJUVANTS

Chemical Name	Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate)		
CAS No.	6683-19-8	*Weight %*	(500 ppm)

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless to pale yellow liquid

Property	Value	Data Source/Justification
Freezing Point	< -50 °C	Measured
Boiling Point	268 °C at 101.3 kPa	Measured
Density	946.97 kg/m^3 at 20 °C	Measured
Vapour Pressure	3.0 × 10^{-5} kPa at 20 °C	Measured
Water Solubility	3.8 x 10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	t½ > 1 year at 25 °C (pH 7 & 9) t½ = 342 days at 25 °C (pH 4)	Measured
Partition Coefficient (n-octanol/water)	Log Pow = 4.8 at 35 °C	Measured
Adsorption/Desorption	Log Koc = 3.36	Calculated using KOCWIN v2.00 (US EPA, 2009).
Dissociation Constant	Not determined	No readily dissociable functionality
Surface Tension	41.4mN/m at 20 °C ± 0.5 °C	Measured
Flash Point	136 °C at 101.325 kPa	Measured
Flammability	Not spontaneously flammable. Does not emit flammable gases in contact with water or moist air. Not expected to form flammable mixtures in air.	Not expected to be flammable based on flash point
Autoignition Temperature	255 ºC	Not expected to autoignite under normal conditions
Explosive Properties	Predicted negative	Does not contain explosophores
Oxidising Properties	Predicted negative	Does not contain oxidising groups

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

Reactivity
The notified chemical is expected to be stable under normal conditions of use.
It is not explosive, non-oxidising and not auto-ignitable under normal conditions. The notified chemical presents no significant reactivity hazard by itself or in contact with water.

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia as a component of compounded fragrances (at a maximum concentration of 0.33%).

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

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

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

IDENTITY OF RECIPIENTS
Givaudan Pty Ltd

TRANSPORTATION AND PACKAGING
Transportation of the notified chemical is restricted under requirements for Class 9 UN/D 3082 Group III.

The notified chemical (at ≤ 0.33% concentration) will be imported into Australia as a component of fragrance blends in glass, lacquer-lined containers. Standard packaging sizes of containers will be 1, 5, 10, 25, 100 and 190 kg. The fragrance blends containing the notified chemical will be transported by road to formulator sites within Australia for reformulation. The end-use products will contain the notified chemical at maximum concentrations of ≤ 0.067% in leave-on and rinse-off cosmetics and ≤ 0.003% in household products. The packaged consumer products will be transported to retail outlets for sale to the public.

USE
The notified chemical is a colourless liquid with a woody odour. It will be used as an aromatic blended fragrance ingredient and will be sold to industrial and commercial customers in formulated fragrance oils to be incorporated into cosmetic, fine fragrances, personal care, detergents and household consumer products. Product categories include fragrances, deodorant, hair spray, cosmetic rinse-off and leave-on products, personal care, air care (aerosol and candles), laundry detergents, fabric conditioners, and household cleaners. The notified chemical will be reformulated from fragrance oils at ≤ 0.33% concentration into final consumer products with proposed concentrations of ≤ 0.067% in leave-on and rinse-off cosmetics and ≤ 0.003% in household products.

OPERATION DESCRIPTION
The notified chemical will not be manufactured within Australia. The notified chemical will be imported in formulated fragrance oils at ≤ 0.33% concentration for reformulation into cosmetic and household products containing the notified chemical at a concentration of ≤ 0.067%.

No manufacturing, processing, reformulating or repackaging of the notified chemical will occur at the notifier facility. The finished fragrance oil containing the notified chemical will be stored at this facility until it is sold and shipped to customer facilities.

At the customer facilities, the procedures for incorporating the imported fragrance preparations (containing ≤ 0.33% notified chemical) into end-use products will likely vary depending on the nature of the cosmetic and household products formulated, and may involve both automated and manual transfer steps. However, in general, it is expected that the reformulation processes will involve blending operations that will be highly automated and occur in a fully enclosed environment, followed by automated filling of the reformulated products into containers of various sizes.

Cleaning and washing products.
Cleaning and washing agents containing the notified chemical (≤ 0.003% concentration) may be used by consumers and professional workers. The cleaning and washing agents may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines, or open processes and manually by rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush and followed by wiping. In some cases the cleaning product will be diluted with water prior to application. The label should indicate the appropriate dilution factor to be used, which is suggested based on the type of surface to be cleaned, the soil loading and the type and method of application. The cleaning and washing liquids should be completely discharged into industrial sewerage systems after use.

Cosmetics and hair care
The finished cosmetic and hair care products containing the notified chemical at ≤ 0.067% concentration 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.

Air care products
The finished aerosol products containing the notified chemical at ≤ 0.003% concentration will be used by consumers. Depending on the nature of the product, application of products could be by pump or pressurised spray (manual or automatic) or through burning of candles.

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	4	2
Drum Handling	4	2
Drum Cleaning/washing	4	2
Maintenance	4	2
Quality Control worker	4	2
Packager	4	2
End users (professionals)	1–8	200

EXPOSURE DETAILS
The notifier estimates that 5–20 workers may be potentially exposed to blended fragrance oils containing the notified chemical during warehouse, production line, cleaning and sampling or analysis tasks. The potential exposure by these routes is anticipated to be minimal and irregular. The notifier estimates that the major occupational exposure of the notified chemical will be at the manufacturing plants of customers (manufacturers of the end products), where the import containers of the fragrance mixtures containing the notified chemical are opened.

Transport and storage
Transport and storage workers may come into contact with the notified chemical, as a component of the imported fragrance preparations (≤ 0.33% concentration) or end-use products (≤ 0.067% concentration), only in the event of accidental rupture of containers.

At the notifier facility, the primary work activity undertaken by transport and warehouse workers will include the handling, loading and off-loading of drums containing fragrance oils formulated with the notified chemical at ≤ 0.33% concentration. Exposures of these workers will be limited to situations involving products sampling for quality control or, in the event of a discharge, clean up from a spill or leaking drum. If such an event occurs, a worker may be exposed through dermal or ocular contact. Such exposures will be minimised through the use of personal protective equipment (PPE) including protective overalls, hard hats, chemical resistant gloves and safety glasses.

Formulation of end products
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 0.33% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation, local exhaust ventilation and/or enclosed systems, and through the use of PPE such as coveralls, goggles and impervious gloves. Due to the vapour pressure of the notified chemical, inhalation exposure may be expected especially where mists or aerosols may be generated. Self-contained breathing apparatus (local aspiration) will be used if ventilation is inadequate.

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic and personal care products (at ≤ 0.067% concentration) to clients (e.g. hair dressers, workers in beauty salons) or the use of household products (at ≤ 0.003% concentration) 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, but use is not expected. However, good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical through the use of the household products and the leave-on and rinse-off cosmetics (≤ 0.003–0.067% concentration in individual products). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

Data on typical use patterns of cosmetic and household cleaning product categories in which the notified chemical may be used are shown in the following tables (SCCS, 2010; Cadby *et al.*, 2002; SDA, 2005). For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In the absence of dermal absorption data, the default dermal absorption of 100% was assumed for calculation purposes (European Commission, 2003). For the inhalation exposure assessment (European Commission, 2003; SDA, 2005), an adult inhalation rate of 23 m^3/day (enHealth, 2004) was used and it was assumed that the bioavailability of the notified chemical via the inhalation route is 100%. An adult bodyweight of 60 kg was used for calculation purposes.

Cosmetic products (Dermal exposure)

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7,820	0.067	1	0.087323
Face cream	1,540	0.067	1	0.017197
Hand cream	2,160	0.067	1	0.024120
Fine fragrances	750	0.067	1	0.008375
Deodorant spray	1,430	0.067	1	0.015968
Shampoo	10,460	0.067	0.01	0.001168
Conditioner	3,920	0.067	0.01	0.000438
Shower gel	18,670	0.067	0.01	0.002085
Hand soap	20,000	0.067	0.01	0.002233
Hair styling products	4,000	0.067	0.1	0.004467
Total				**0.163374**

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

Household products (Indirect dermal exposure - from wearing clothes)

Product type	Amount (g/use)	C (%)	Product Retained (PR) (%)	Percent Transfer (PT) (%)	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	230	0.003	0.95	10	0.000109
Fabric softener	90	0.003	0.95	10	0.000043
Total					**0.000152**

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

Household products (Direct dermal exposure)

Product type	Frequency (use/day)	C (%)	Contact Area (cm^2)	Product Use C (g/cm^3)	Film Thickness (cm)	Time Scale Factor	Daily systemic exposure (mg/kg bw/day)
Laundry liquid	1.43	0.003	1980	0.01	0.01	0.007	0.000001
Dishwashing liquid	3	0.003	1980	0.0093	0.01	0.03	0.000008
All-purpose cleaner	1	0.003	1980	1	0.01	0.007	0.000069
Total							**0.000078**

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

Aerosol products (Inhalation exposure)

Product type	Frequency (use/day)	Amount (g/use)	C (%)	Inhalation rate (m^3/day)	Exposure duration (mins)	Airspace volume (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	2	10	0.067	23	15	2	0.026750
Total							**0.026750**

Daily systemic exposure = (Frequency × Amount × C × Inhalation rate × Exposure duration × bioavailability via the inhalation route)/(body weight × Airspace volume)

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 0.19 mg/kg bw/day. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative hair spray inhalation exposure assessment parameters, in particular assuming an airspace volume of 2 m^3, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposure factors (e.g. air fresheners).

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the table below. Details of these studies can be found in Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity (fixed dose method)	LD50 > 2,000 mg/kg bw;
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw;
Rabbit, skin irritation	non-irritant
Eye irritation – rabbit nucleation eye test	non-irritant
Guinea Pig, skin sensitisation – Maximisation test	non-sensitiser
Human, skin sensitisation – RIPT (4%)	no evidence of clinically significant skin irritation or allergic contact dermatitis
Rat, repeat dose oral gavage toxicity – 28 days	NOEL: 20 mg/kg bw/day
Hamster, genotoxicity – *in vitro* mammalian chromosome aberration	non-clastogenic
Mutagenicity – Bacterial Mutation assay	non-mutagenic

Toxicokinetics, metabolism and distribution.
The main route of exposure will be dermal, with the possibility of inhalation, ocular, and oral exposure. Based on the water solubility (0.0038 g/L at 20 °C), partition coefficient (log K_{ow} = 4.8) and the low molecular weight (223 Da) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are possible. However significant inhalation exposure is not expected as the notified chemical has a low vapour pressure (3.0×10^{-5} kPa).

Acute toxicity.
The notified chemical was found to have low acute oral toxicity in a study in rats where no systemic or local signs of toxicity were observed during the observation period.

The notified chemical was also found to have low acute toxicity via the dermal route. Test animals displaying clinical signs had recovered by Day 4 of the observation period. The dermal LD50 value of the notified chemical was established to exceed 2,000 mg/kg bw.

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

Irritation and sensitisation
In an acute dermal irritation study using three male New Zealand white rabbits, a single 4-hour, semi-occluded application of the notified chemical resulted in well-defined erythema and slight or moderate oedema and desquamation. All test animals had fully recovered after 7 days. The study authors concluded that the test substance did not meet the classification as irritant or corrosive.

In a rabbit eye irritation study, the notified chemical did not meet the criteria for classification as an eye irritant based on the testing of one rabbit as the animal had recovered from all symptoms within the 7 day test period.

The potential for cutaneous allergic reactions induced by the notified chemical was assessed in a Maximisation Test in 15 female albino guinea pigs. Slight to well defined erythema was noted at the 24 and 48 hour observations in both the control and test group (at 25% concentration) animals after the first challenge phase. However no skin reactions were observed at the second challenge in the same control group and test groups administered at the lower doses of 5% and 10% concentration. The study authors concluded that the notified chemical, when applied at 5% and 10% concentration, is not a skin sensitiser.

In a human repeat insult patch test (HRIPT) completed on 54 subjects, the notified chemical (at 4% concentration, used as supplied) did not induce clinically significant skin irritation or show any evidence of induced allergic contact dermatitis.

Repeated Dose Toxicity
In a 28 day repeat dose study by oral gavage rats were administered the notified chemical at 0, 20, 100 and 500 mg/kg bw/day. Adverse effects attributed to the notified chemical included increased liver and kidney weights and non-specific renal tubular damage observed at the 100 and 500 mg/kg bw/day. The study authors concluded that no toxicologically significant effects were detected in both sexes of test animals treated at 20 mg/kg bw/day. The No Observed Effect Level (NOEL) for systemic toxicity was established by the study authors as 20 mg/kg bw/day based on the absence of effects at this dose.

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

Health hazard classification
Based on the available information, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Transport and Storage
Workers may experience dermal and accidental ocular exposure to the notified chemical (at ≤ 0.33% concentration) where the fragrance oils are sampled for quality control purposes or in the event of a discharge via spill or drum leakage. The use of PPE (impervious gloves, goggles, coveralls, hard hats) should minimise the potential for exposure.

Therefore, provided adequate control measures are in place to minimise worker exposure, including PPE, the risk to workers from use of the notified chemical is not considered to be unreasonable.

Reformulation
Workers may experience dermal and accidental ocular and perhaps inhalation exposure to the notified polymer (at ≤ 0.33% concentration) during formulation processes. This exposure may occur during handling of the drums, cleaning and/or maintenance of the equipment. At these facilities, exposure may also extend to compounders and laboratory staff involved in the formulation of the end products containing the notified chemical and the sampling and quality control testing of these products.

The use of enclosed, automated processes and PPE (impervious gloves, goggles, coveralls and respiratory protection, if significant inhalation exposure is expected) should minimise the potential for exposure.

Therefore, provided that adequate control measures are in place to minimise worker exposure, including the use of automated processes and PPE, the risk to workers from use of the notified polymer is not considered to be unreasonable.

End-use
Workers involved in professions where the services provided involve the use of household products in the cleaning industry or application of cosmetic products to clients (e.g. beauty salon workers), may be exposed to

the notified chemical. Hairdressers may also be repetitively exposed to the notified chemical in their application of shampoo and hairspray to salon clients. The risk to these workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical on a regular basis (for details of the public health risk assessment, see Section 6.3.2.).

Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. For hairdressing salons, good ventilation would be recommended if hair spray is routinely used in a confined space. If PPE is used, the exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the various cosmetic and household products containing the notified chemical. Based on the information available, the risk to workers associated with use of the notified chemical at ≤ 0.067% concentration in leave-on and rinse-off cosmetics and ≤ 0.003% concentration in cleaning products is not considered to be unreasonable.

6.3.2. Public Health

Members of the public may be repeatedly exposed to the notified chemical during the use of leave-on and rinse-off cosmetics and household products containing the notified chemical at concentrations ≤ 0.067%.

The potential systemic exposure to the public from the use of the notified chemical in cosmetic products and household products was estimated to be 0.19 mg/kg bw/day. Using a NOEL of 20 mg/kg bw/day, which was derived from a 28-day repeated dose toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 105. A MOE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences. The MOE of 105 for the notified chemical is therefore considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.067% in leave-on and rinse-off cosmetics and ≤ 0.003% in household products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of fragrance preparations for local reformulation into a variety of consumer products (cosmetics and household products). Accidental spills during transport or reformulation are expected to be collected with inert material and disposed of to landfill. Import containers will either be recycled or disposed of through an approved waste management facility. The reformulation into consumer products will be a batch process where cleaning of the blending equipment may result in waste water generation. The wash water may contain up to 15 kg of the import volume of the notified chemical. It is expected that most sites will have closed, automated mixing and dosing equipment. The residues in import containers may be ≤ 1% of the import volume. The rinsate from the empty containers is expected to be added to the wash water. The wash water is expected to be sent to on-site waste water plant or to the sewer system. Therefore, up to 25 kg of the import volume is estimated to be released to sewer as a result of reformulation in Australia.

RELEASE OF CHEMICAL FROM USE

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

RELEASE OF CHEMICAL FROM DISPOSAL

It is estimated that a maximum of 1% of the consumer products containing the notified chemical will remain in end-use containers. These will be disposed of through domestic garbage disposal and will enter landfill or be recycled.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system before potential release to surface waters on a nationwide basis. The notified chemical is not readily biodegradable and, based on its calculated adsorption coefficient (log Koc = 3.36), partitioning to sludge is expected. The notified chemical is not likely to bioaccumulate based on its measured low bioconcentration factor (BCF < 100). In

surface waters, the notified chemical is expected to disperse and eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

The half-life of the notified chemical in air is calculated to be < 12 hours based on reactions with hydroxyl radicals (AOPWIN v1.92, US EPA, 2009). Therefore, in the event of release to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

A proportion of notified chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill. Notified chemical residues in landfill, soil and sludge are expected to have slight mobility based on its water solubility and its calculated soil adsorption coefficient (log K_{oc} = 3.36). In the soil compartments, the notified chemical is expected to slowly degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

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

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

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.606 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 20.2 µg/kg and 40.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Acute Toxicity	96 h LC50 = 1.0 mg/L	Very toxic to fish
Fish Chronic Toxicity	30 d NOEC = 0.055 mg/L	Very Toxic to fish with long lasting effects
Daphnia Acute Toxicity	48 h EC50 = 0.38 mg/L	Very toxic to aquatic invertebrates
Daphnia Chronic Toxicity	21 d NOEC = 0.031 mg/L	Very toxic to aquatic invertebrates with long lasting effect
Algal Toxicity	72 h EC50 = 1.0 mg/L	Very toxic to algae
	72 h NOEC = 0.24 mg/L	Very toxic to algae with long lasting effect

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009) the notified chemical is considered to be very toxic to fish, aquatic invertebrates and algae and is formally classified as 'Acute Category 1: Very toxic to aquatic life'. On the basis of the chronic toxicity and the lack of ready biodegradability, the notified chemical is classified 'Chronic Category 1: Very toxic to aquatic life with long lasting effects'.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the chronic daphnia toxicity of the notified chemical and an assessment factor of 10 as three chronic measured endpoints are available.

7.3. Environmental Risk Assessment

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (Invertebrates).	0.031	mg/L
Assessment Factor	10	
PNEC:	3.1	µg/L

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	0.61	3.1	0.19
Q - Ocean:	0.06	3.1	0.019

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < -50 °C

Method OECD TG 102 Determination of freezing point.
EC Directive BS4633. 92/69/EEC A.1 Freezing Temperature.
Remarks No crystallisation of the test material could be observed when cooling down to a temperature of -50°C. Hence the congealing point is surmised to be below that value.
Test Facility Givaudan (1997a)

Density 947 kg/m^3 at 20 °C

Method OECD TG 109 Density of Liquids and Solids.
Directive 92/69/EEC A.3 Relative Density.
Remarks Oscillating density meter method
Test Facility Givaudan (1997b)

Vapour Pressure 3 x 10^{-5} kPa at 20 °C

Method OECD TG 104 Vapour Pressure.
Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Determined by the Static Technique
Test Facility NOTOX (1998a)

Water Solubility 3.8 x 10^{-3}g/L at 20 °C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Flask Method. Analysed by GC/FID.
Test Facility Givaudan (1998a)

Partition Coefficient (n-octanol/water) log Pow = 4.8 at 20 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks HPLC Method. Since the test substance is surface active in nature, this method is not applicable to determine the partition coefficient. However, the HPLC chromatogram of the test substance indicates two distinct peaks belonging to the two isomers of the notified chemical. Also the peak area of the test substance appears to be > 5% of the total area thus satisfying the method condition.
Test Facility Givaudan (1997c)

Hydrolysis as a function of pH t½ > 1 year at 25 °C (pH 7 & 9)
t½ = 342 days at 25 °C (pH 4)

Method OECD TG 111 Hydrolysis as a function of pH.
EC Directive 92/69/EEC C.7 Hydrolysis as a function of pH.

Results

pH	*T (°C)*	*t½*
4	25	342 days
7	25	> 1.0 year
9	25	> 1.0 year

Remarks A preliminary test (Tier 1) was conducted on the notified chemical at 50 °C. The degradation of the notified chemical was found to be < 10% after 5 days at pH 7 & 9. This is equivalent to a half life of > 1 year at 25 °C. However, at pH 4 the degradation was > 10%. Therefore, in order to calculate the half life at pH 4, the extent of hydrolysis was also evaluated at 35 °C.
Test Facility Givaudan (1998b)

Surface Tension 41.4 mN/m at 20 °C ± 0.5 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions. Directive 92/69/EEC A.5 Surface Tension.
Remarks	Concentration: 90% saturation
Test Facility	RCC (1999a)

Flash Point 136 °C at 101.3 kPa

Method	Pensky-Martens method according to DIN 51758 (Germany).
Remarks	Determined using a closed cup equilibrium method.
Test Facility	Givaudan (1998c)

Autoignition Temperature 255 °C

Method	Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility	Institute of Safety and Security (2000)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. Directive 92/69/EEC B.1 Acute Toxicity-Oral.
Species/Strain	Rat/WIST (SPF)
Number of Animals	10 (5M/5F)
Vehicle	PEG 400
Remarks - Method	No significant protocol deviations. GLP Ce. A single oral dose was delivered via gavage, followed by an observation period of 14 days. Clinical signs observed included general behaviour, motor susceptibility, body posture, motility, organ specific effects (eye, nose, skin) and bodily functions (respiration and secretions).

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2,000	0/10

LD50(rat)	> 2,000 mg/kg bw
Signs of Toxicity	No deaths occurred during the study. No systemic or local signs of toxicity were observed during the observation period. No macroscopic findings were observed at necropsy.
Effects in Organs	None- no abnormalities detected
Remarks - Results	The body weight of all animals was within the range commonly recorded for the strain/age.
Conclusion	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	RCC (1997a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity. Directive 92/69/EEC B.3 Acute Toxicity – Dermal.
Species/Strain	Rat/WIST (SPF)
Number of Animals	10 (5 per sex)
Vehicle	None- undiluted
Type of dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations. GLP Certificate. Single dermal administration and observed over a period of 14 days.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2,000	0/10

LD50(rat) > 2,000 mg/kg bw

Signs of Toxicity No deaths occurred during the study.
No systemic or local signs of toxicity were observed during the observation period.

Effects in Organs None- no abnormalities detected at necropsy.

Remarks - Results The body weights of all animals were within the range commonly recorded for the strain/age for the test period.

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

TEST FACILITY RCC (1999b)

B.3. Primary Irritation – eye

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
Directive 92/69 EEC B.5 Acute toxicity- Eye Irritation.

Species/Strain Rabbit/New Zealand White

Number of Animals 3 (1M/2F)

Observation Period 7 days

Remarks – Method No significant protocol deviations.
GLP Certificate.
A single undiluted 0.1mL dose of the test chemical was instilled into the left conjunctival sac of each test animal. The right eye was not treated and served as control. Ocular reactions were scored according to a numerical scale (0 to 4 spanning observations of zero reaction up to serious discernible reactions) observed approximately 1 hour, 24, 48 and 72 hours after the single administration. The criteria for irritation was considered to be significant or severe ocular lesions caused within 72 hours after exposure and which persist for 24 hours or more after treatment.

RESULTS

Lesion	Mean Score* Animal No.			Maximum Value	Maximum Duration of Any Effect	Maximum Value at End of Observation Period
	1	2	3			
Conjunctiva: redness	0.5	0.5	1.25	2	48 h	0
Conjunctiva: chemosis	0.5	0.5	0.75	2	24h	0
Corneal opacity	0	0	0	0	-	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 clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred.
Watery discharge, reddening and/or swelling of the conjunctivae and hyperemia of the sclera were noted in all animals after 24 hours. Reddening was noted after 48 hours in one animal only. All findings were reversible after 72 hours.
No staining of the sclera, conjunctivae or cornea, or corrosion was observed at any of the measuring intervals.

CONCLUSION Based on the referred classification criteria, the notified chemical is considered to be not irritating to the eye.

TEST FACILITY RCC (1997b)

B.4. Primary Irritation-skin

METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. Directive 92/69 EEC B.4 Acute Toxicity- Skin Irritation.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (1M/2F)
Observation Period	14 days
Type of dressing	Semi-occluded (Cotton gauze covered by elasticated corset)
Remarks – Method	No significant protocol deviations. GLP Certificate. A single 4 hour application of the test material was made and test sites were observed for evidence of primary irritation at 1, 24, 48 and 72 hours post patch removal.

RESULTS

Skin Reaction	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.5	0.7	0.7	1	≤ 7 days	0
Oedema	0.5	0.7	0.7	1	≤ 7 days	0

*Calculated on the basis of the scores at 1, 24, 48, and 72 hours, 7 and 14 days for EACH animal.

Remarks – Results	No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred. Diffuse erythema and oedema were noted in two animals after 24 hours and in all animals from 48 hours to Day 7 after application. All skin reactions were clear 14 days after treatment. No irreversible alterations or corrosive effects were evident on the treated skin.
CONCLUSION	Based on the referred classification criteria, the notified chemical is considered to be not irritating to rabbit skin.
TEST FACILITY	RCC (1997c)

B.5. Skin sensitisation – Maximisation test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation: Maximisation. EC Directive 96/54/EC B.6 Skin Sensitisation.
Species/Strain	Albino Guinea Pig
Number of Animals	15 F/3F (Main test/Pre-test)
Vehicle	PEG 400
Remarks – Method	No significant protocol deviations. GLP Certificate. Classification of allergenic potency was assigned according to Magnusson and Kligman Grading Scale (Grades 0-4). Dermal reactions at the injection sites and signs of systemic toxicity were evaluated at 24 and 48 hours after dressing removal. A positive control study was run in tandem to the main test using 2-Mercaptobenzothiazole at 25% concentration in mineral oil.
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: 5%, 3% and 1% in PEG 400 topical: 100%, 75%, 50% and 25% in PEG 400
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 5
INDUCTION PHASE	Induction Concentration: intradermal: 5% in PEG 400 5% in a mixture of FCA plus saline water (1:1) topical: 100% undiluted
CHALLENGE PHASE	

1st challenge	topical:	25% in PEG 400
2nd challenge	topical:	10% and 5% in PEG 400

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	25%	7/10	7/10		
	10%			0/10	0/10
	5%			0/10	0/10
Control Group		4/5	4/5	0/10	0/10

Positive skin reactions were observed in the control and test group after the first challenge performed with the test article at 25% and were considered to be of primary toxic origin. At the second challenge no skin reactions were observed in the same control and test group treated with the two lower concentrations of 10% and 5%. No oedema was noted in any test animal during the study.

No mortalities occurred during the study period.
No signs of systemic toxicity were observed in the animals of the control or test group. No skin reactions were noted at the rechallenge sites of the test and control group animals.
The body weight of the animals was within the range of physiological variability known for animals of this strain and age.
The positive control test rendered results confirming the validity of the study.

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

TEST FACILITY RCC (1997d)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified chemical (at 4% concentration)

METHOD Repeated Insult (occlusive) Patch Test (9-RIPT).
Species/Strain Human
Number of Animals 57 (7M/50F)
Observation period 14 day rest period
Type of dressing Occlusive patch (Parke-Davis Readi-Bandage)
Remarks- Method A panel of 57 healthy human subjects (devoid of any physical or dermatological conditions) was amassed. During the Induction phase, the test article was placed onto a Parke-Davis Readi-Bandage occlusive patch and applied to the back of each subject between the scapulae and waist. This application was repeated every Monday, Wednesday and Friday until 9 applications had been made. The subjects were instructed to remove the patches 24 hours after application.

After a rest period of 2 weeks, the Challenge phase patch was applied to a virgin test site. The site was scored 24 and 72 hours after application. Dermal responses were scored according to a 6-point scale (0, +, 1 to 4).

RESULTS

Skin Reaction	*Reaction observed in Test subjects*	*Maximum Value **	*Maximum Duration of Any Effect **	*Maximum Value at End of Observation Period*
Erythema/Eschar	0/54**	0	-	0

*Calculated on the basis of the scores at 24 and 72 hours for test subjects.
** 3 subjects discontinued for personal reasons unrelated to the conduct of the study. Data from these subjects up to the point of discontinuation was not used in the conclusions of the final report.

Remarks - Results	No clinical signs of systemic toxicity were noted by any of the test subjects during the study and no mortality occurred. 54 subjects satisfactorily completed the test procedure. There were no responses on any subject during the Test phase. During the Induction phase, a barely perceptible (+) to moderate (2) non-specific response and mild oedema was observed on one test panelist. By the 72 hour evaluation, no response was noted. These non-specific responses were not considered to be related to the potential irritant or allergic nature of the test article.
CONCLUSION	Under the conditions of the test procedure, the notified chemical was found to not induce clinically significant skin irritation or show any evidence of induced allergic contact dermatitis in human subjects.
TEST FACILITY	Essex Testing Clinic (1998)

B.7. Repeat dose toxicity

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain	Rat/HanIbm:Wistar (SPF)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week
Vehicle	Used as supplied
Remarks - Method	No significant protocol deviations. GLP Certificate. Doses selected on the basis of a 5 day preliminary study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0/0
low dose	5 per sex	20	0/0
mid dose	5 per sex	100	0/0
high dose	5 per sex	500	0/0

Mortality and Time to Death
There were no unscheduled deaths during the study.

Clinical Observations
Analysis of clinical appearance, functional observations, body weight and water consumption did not reveal any toxicologically significant abnormalities between the treated and the control groups. Specifically, hind and forelimb grip strength and locomotor activity of the test article treated animals were deemed similar to that of the controls.

Females treated with 20 mg/kg/day were significantly less active than the control group females, however in the absence of a similar finding in the animals at higher dose levels, this observation was considered to be incidental.

Breathing noises and salivation was evident in one animal respectively from the 500 mg/kg/day groups; however, these findings were considered by the study authors to be unrelated to the treatment.

A transient reduction in food consumption was noted in females treated at 500 mg/kg/day, which was deemed test article-related by the study authors. However males at this dose were unaffected.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No changes of toxicological significance were noted in the haematology parameters of the test article-treated animals. Significantly lower absolute reticulocyte counts were noted in males treated with 500 mg/kg/day and considered to be incidental by the test authors.

All individual values were within the normal ranges for rats of the strain and age used and lacked a discernible dose response relationship, therefore the intergroup differences were considered not to be of toxicological importance.

Various changes in metabolism were noted during the study. Plasma glucose was reduced in males treated at 100 mg/kg/day and both sexes dosed at 500 mg/kg/day. Lipid metabolism was altered in females treated at 500 mg/kg/day. Increased activity of gamma glutamyltransferase, increased calcium levels and decreased potassium levels was noted in animals of both sexes at 500 mg/kg/day.

Effects in Organs

Changes in organ weights which were deemed test article-related were noted in the liver for both sexes at 500 mg/kg/day, males only in the kidney at 500 mg/kg/day and in the thymus for male animals in both the 100 mg/kg/day and 500 mg/kg/day groups.

Females dosed at 20 mg/kg/day did show increased relative liver weights (organ to body weight ratio). But as no findings were ascertained in the clinical biochemistry parameters of these animals, the differences in organ weights were considered to be adaptive changes rather than signs of test article-induced toxicity. All other organ weights compared favourably with those of the controls.

Only one gross lesion was attributed to the test article by study authors, which was the enlarged liver of one male animal in the 500 mg/kg/day group. The remaining macroscopic findings included incompletely collapsed lungs, renal pelvis dilation, cysts in the ovaries and discolouration and/or foci in several organs. However these were considered to be within the range of spontaneous background alterations typical to rats of this strain and age.

Microscopic changes consisting of tubular basophilia and tubular mineralization at the corticomedullary junction were noted in the kidneys of males in the 100 mg/kg/day and 500 mg/kg/day groups. This finding was accompanied by hyaline tubular cast in a single male treated at 500 mg/kg/day. These findings were considered by the test authors to be indicative of non-specific renal tubular damage induced by the test article.

Remarks – Results

Toxicity in this study was based on the observation of increased liver and kidney weights and renal macroscopic changes seen at the higher doses. The study authors deemed that no significant effects were detected in both sexes of test animals treated at 20 mg/kg/day.

CONCLUSION

Both the No Observed Effect Level (NOEL) was established as 20 mg/kg bw/day in this study.

TEST FACILITY RCC (2000a)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EEC Directive 92/69 B.10 Mutagenicity – In Vitro.
Species/Strain	Hamster/Chinese
Cell Type/Cell Line	V79
Metabolic Activation System	S9 fraction from phenobarbital/β-naphthoflavone induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks - Method	GLP Certificate. A preliminary cytogenetic assay (Test 1a & 1b) were performed: tested both with and without the metabolic activation system (at 1.8% v/v) for concentrations between 17.4 and 2,230 µg/mL with 4 hour exposure time

and 24 hour fixation time. Precipitation was noted in the culture medium at this dose level. Precipitation and cell lysis were noted at ≥ 1,000 µg/mL.

Tests 1 (with and without metabolic activation) and 2a (without metabolic activation), as shown in the table below, represent repeat assays. The tests were repeated as appropriate cytotoxicity was not achieved using the initially selected test substance concentrations.

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

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	5, 10, 20	4 h	18 h
Test 2a	2.5, 5, 10	18 h	18 h
Test 2b	2.5, 7.5, 15	28 h	28 h
Present			
Test 1	15, 30, 45	4 h	18 h
Test 2	15, 30, 45	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	≥ 34.9	≥ 20	> 20	negative
Test 2a		≥ 10	> 10	negative
Test 2b		≥ 15	> 15	negative
Present				
Test 1	≥ 69.7	≥ 45	> 45	negative
Test 2		≥ 45	> 45	negative

Remarks - Results

There were no toxicologically (or statistically) significant increases in the number of cells with aberrations, with or without metabolic activation. The study authors also note that there were no effects on the number of polyploid cells and cells with endoreduplicated chromosomes, with or without metabolic activation. The study authors claim the test material does not disturb mitotic processes and cell cycle progression.

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

Precipitation of the test item in culture medium was not observed.

CONCLUSION

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

TEST FACILITY

RCC (2000b)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test

using Bacteria.
Plate incorporation procedure/Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver
Concentration Range in Preliminary Test	With metabolic activation: 3–5,000 µg/plate
Concentration Range in Main Test	a) With metabolic activation: 3–5,000 µg/plate b) Without metabolic activation: 1–5,000 µg/plate
Vehicle	Dimethyl formamide
Remarks - Method	GLP Certificate. A preliminary test was conducted using all 5 strains in the presence of metabolic activation between 3 – 5,000 µg/plate. The notified chemical caused reduced background growth and reduction in the number of revertants at higher concentrations in strains TA 1535, TA 1537, TAA 98 and TA 100.

RESULTS

METABOLIC ACTIVATION	Test Substance Concentration (µg/plate) Resulting in:			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 100		≥ 2,500	negative
Test 2		≥ 100	≥ 2,500	negative
Present				
Test 1	≥ 1,000		≥ 1,000	negative
Test 2		≥ 333	≥ 2,500	negative

Remarks - Results	No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose material, either with or without metabolic activation. The test material did not induce gene mutations by base pair changes or frame shifts in the genome of the strains used. The positive controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.
CONCLUSION	The notified chemical was considered to be not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Harlan (2012)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sewage sludge from a predominantly domestic sewage treatment plant.
Exposure Period	38 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (TOD) Method
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Notified chemical		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
5	-1	5	77
7	-1	7	86
14	-0	14	94
21	-0	21	95
28	-0	28	97
38	-0	-	-

Remarks - Results	The validity criteria for the test were met. The toxicity control attained 40% degradation by day 14 of the study thereby confirming that the notified chemical was not toxic to the sewage treatment micro-organisms used in the study. After 28 days the toxicity control had attained 65% degradation. The notified chemical attained 0% degradation after 38 days and, therefore, cannot be considered as readily biodegradable under the conditions of OECD Guideline 301B.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Givaudan (1997d).

C.1.2. Inherent biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 302 C Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sewage sludge from a predominantly domestic sewage treatment plant.
Exposure Period	48 days
Auxiliary Solvent	None
Analytical Monitoring	Biological Oxygen Demand (BOD) Method
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles.

RESULTS

Notified chemical		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
8	-24	5	83
16	-50	7	87
24	-55	14	97
32	-32	-	-
40	-36	-	-
48	-30	-	-

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

The negative biodegradation levels could be interpreted in term of toxicity of the notified chemical to the inoculum. However, a previous test showed that, at a higher concentration (100 mg/L) of the notified chemical was used did not show inhibition to activated sludge microorganisms. Therefore, the effect observed in the present test cannot be assigned to toxicity of the notified chemical.

CONCLUSION: The notified chemical is not inherently biodegradable.

TEST FACILITY: Givaudan (1998d).

C.1.3. Bioaccumulation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 305 Bioconcentration: Flow-through Fish Test.
EC Directive 98/73/EC C.13 Bioconcentration: Flow-Through Fish Test.

Species: *Cyprinus carpio* (Carp)

Exposure Period: Exposure: 28 days Depuration: 7 days

Auxiliary Solvent: Dimethyl Sulfoxide (DMSO) 0.02 mL/L

Concentration Range: Nominal: 9.44 and 0.944 µg/L.

Analytical Monitoring: GC-MS

Remarks - Method: Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. Based on the results of the range finding test, the test was conducted at nominal concentrations of 0.944 and 9.44 µg notified chemical/L. No significant deviations to the test protocol were reported

Test fish of a solvent control (containing 0.02 mL/L DMSO) were analysed before the exposure, at the end of exposure, and at the end of the depuration phase. A water dilution control was not used.

The test substance (500 mg) was dissolved in DMF to give a 472 mg/L stock solution. The required nominal concentrations of the test substance were prepared from this stock solution.

RESULTS

Bioconcentration Factor: $BCF_{(Edible\ fraction)}$ = 27 at low concentration (0.944 µg/L) and 53 at higher concentration (9.44 µg/L).

$BCF_{(Non\text{-}edible\ fraction)}$ = 41.5 at low concentration (0.944 µg/L) and 64 at higher concentration (9.44 µg/L).

Bioconcentration Factor Lipid Normalised: BCF_L = 48.5 at low concentration (0.944 µg/L) and 47.5 at higher concentration (9.44 µg/L).

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

A steady state of bioaccumulation was not attained. However, at days 9–14, the bioconcentration factor (BCF) reached its peak value and progressively decreased through to day 28. Therefore, day 14 was

assigned to have achieved a steady state of bioaccumulation.

A rapid depuration was observed, with an elimination half-life of 0.17 and 1.96 days. All defects in the fish tissue decreased to below the level of quantification (LOQ) by day 6.6 of the depuration phase.

CONCLUSION Under the conditions of this test, the notified chemical is not considered to be bioaccumulative.

TEST FACILITY CERI (2014)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE Notified chemical

Method OECD TG 203 Fish, Acute Toxicity Test – Static.

Species *Cyprinus carpio* (Carp)

Exposure Period 96 hour

Auxiliary Solvent Acetone (0.1 mL/L)

Water Hardness 250 mg $CaCO_3$/L

Analytical Monitoring GC/FID

Remarks – Method After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to the test protocol were reported.

The test substance (100 mg/mL) was prepared in acetone. The stock solution (0.1mL) was mixed with 1 L of test medium and stirred overnight. This mixture was filtered through a 0.2 µmm filter. The filterate was further diluted to prepare the final test concentrations.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*			
Nominal	*Measured*		*24 h*	*48 h*	*72 h*	*96 h*
Control		7	0	0	0	0
Dilution control		7	0	0	0	0
0.496	0.485	7	0	0	0	0
0.893	0.840	7	0*	0*	0*	0
1.59	1.55	7	1*	1*	1*	1*
2.78	2.79	7	7	7	7	7
10	4.96	7	7	7	7	7

*Fish showed clinical effects rather than mortality observed

LC50 1 mg/L at 96 hours

NOEC < 0.86 mg/L

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

The analytical measurements showed that the actual concentrations were not stable during the exposure period and could not be maintained at 80% of the initial concentration. Therefore, the measurement of LC50 values were based on the average concentrations i.e. the geometric means of the measured concentrations at the start and end of the test.

CONCLUSION The notified chemical is very toxic to fish.

TEST FACILITY NOTOX (1998b)

C.2.2. Chronic toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 210 Fish Early Life Stages Toxicity Test – Flow Through.
Species	*Danio rario* (Zebra fish)
Exposure Period	30 days
Auxiliary Solvent	Acetone (0.1 mL/L)
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	GC/FID

Remarks - Method

After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to the test protocol were reported.

The test substance (100 mg/mL) was prepared in acetone. The stock solution (0.1mL) was mixed with 1 L of test medium and stirred overnight. This mixture was filtered through a 0.2 µmm filter. The filterate was further diluted to prepare the final test concentrations.

The test included a solvent control with a concentration of acetone (0.1mL/L) corresponding with the concentration in the treated solutions. A water dilution control was not used.

Fresh healthy fertilized eggs (60) between 2-4 hours old were exposed per concentration. The fertilised eggs were randomly distributed and divided equally over two Petri dishes each containing 30 eggs. The control group contained 120 eggs distributed between four Petri dishes.

Results

Concentration tested, cumulative mean number of offspring released, number of larvae released per egg, mean length and survival of larvae.

	Concentration (mg/L)					
	Solvent Control	*0.012*	*0.022*	*0.055*	*0.104*	*0.225*
Total no. of larvae hatched on day 4	100	49	53	50	52	45
Total no. of larvae survived on day 30	89	45	33	37	40	6
Mean length (mm) of larvae at the end of test period	9.21	8.47	8.59	9.52	8.25	7.05
% Survival	89	91.8	62.2	74	76.9	13.3

LC 50 (overall) 0.14 mg/L
NOEC (overall) 0.055 mg/L

Remarks – Results

The analytical measurements showed variation in measured concentrations. This was due to deviations in the stock concentrations which varied from 4.0 to 6.7 mg/L. The solutions were stirred continuously to maintain the concentrations as stable as possible.

The validity criteria was not met as the concentrations of the test substance could not be maintained within ± 20% as per OECD TG 210 (adopted July 1992). However, OECD TG 210 (adopted July 2013) requires a mandatory analytical measurement of test concentrations, which is provided by the

notifier. Additionally, the test substance showed a tendency to form unstable solutions during the test. Therefore, even though the test validity criteria of OECD TG 210 (adopted July 2013) was met, the results should be treated with caution.

The survival of the larvae at the end of the test was 89 % in the control.

The first young larva released from the egg was recorded in the control and at all test concentrations at day 2. Thus, the time of first brood was not affected by the test substance up to and including the highest test concentration.

The 30 day EC50 for survival of the larvae was determined to be ≥ 0.14 mg/L as the mean measured concentration. The NOEC was determined to be 0.055 mg/L as a mean measured concentration. All the endpoints were determined by the study author and are considered acceptable.

CONCLUSION The notified chemical is considered very toxic to fish larvae on a chronic basis.

TEST FACILITY NOTOX (1999a)

C.2.3. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static.

Species *Daphnia magna*

Exposure Period 48 hours

Auxiliary Solvent Acetone (0.1 mL/L)

Water Hardness 250 mg $CaCO_3$/L

Analytical Monitoring GC/FID

Remarks - Method After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to the test protocol were reported.

The test substance (100 mg/mL) was prepared in acetone. The stock solution (0.1mL) was mixed with 1 L of test medium and stirred overnight. This mixture was filtered through a 0.2 µmm filter. The filterate was further diluted to prepare the final test concentrations.

RESULTS

Concentration mg/L Measured	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
Control	20	0	0
Solvent Control	20	0	0
0.05	20	0	0
0.11	20	0	0
0.24	20	0	1
0.47	20	1	5
1.02	20	10	19
2.04	20	10	20

EC50 0.38 mg/L at 48 hours

NOEC < 0.38 mg/L

Remarks - Results The validity criteria for the test were met.

The analytical measurements showed that the actual concentrations were not stable during the exposure period and could not be maintained at 80% of the initial concentration. Therefore, the values were based on the

	average concentrations i.e. the geometric means of the measured concentrations at the start and end of the test.
CONCLUSION	The notified chemical is very toxic to aquatic invertebrates
TEST FACILITY	NOTOX (1998c)

C.2.4. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 211 *Daphnia* sp. Reproduction test – Flow Through.
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	Acetone (0.1 mL/L)
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	GC/FID
Remarks - Method	After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to the test protocol were reported. The test substance (100 mg/mL) was prepared in acetone. The stock solution (0.1 mL) was mixed with 1 L of test medium and stirred overnight. This mixture was filtered through a 0.2 µmm filter. The filterate was further diluted to prepare the final test concentrations.

Results

Concentration tested, cumulative mean number of offspring released, number of offspring released per female daphnid (*Daphnia magna*), mean length and survival of parental daphnids.

	Concentration (mg/L)					
Test Day 21	*Control*	*0.009*	*0.018*	*0.031*	*0.069*	*0.13*
Total no. of offspring released by survived *Daphnia*	487	477	555	545	269	451
Total no. of offspring released per survived daphnid	92.38	81.23	94.5	95.35	46.08	70.18
Mean length (mm)	4.61	4.58	4.43	4.2	4.21	4.51
No. of adult daphnids Immobilised	2	1	4	2	2	2
% Survival	95	97.5	90	95	95	95

21 day NOEC	0.031 mg/L
Remarks – Results	The validity criteria for the test were met. The analytical measurements showed that the actual concentrations were not stable during the exposure period and could not be maintained within ± 20% of the average measured value. This was attributed to the presence of algal cells in the medium. The survival of the test animals at the end of the test was in the range of 90 to 95% in the controls. This was observed at all test concentrations including the highest test concentration of 0.131 mg/L. Thus, the survival of *Daphnia magna* was not affected by the test substance up to and including the highest test concentration. The first young offspring released from their parent animals were recorded in the control, solvent control and at all test concentrations at

day 8. Thus, the time of first brood was not affected by the test substance up to and including the highest test concentration.

The NOEC was determined to be 0.031 mg/L as a mean measured concentration. All the endpoints were determined by the study author and are considered acceptable.

CONCLUSION The notified chemical is considered very toxic to daphnids on a chronic basis.

TEST FACILITY NOTOX (1999b)

C.2.5. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.
EC Council Regulation No 440/2008 C.3 Algal Inhibition Test.

Species *Selenastrum capricornutum*

Exposure Period 72 hours

Concentration Range Nominal: 0.24, 0.53, 1.11 and 2.42 mg/L
Actual: 0.14, 0.31, 0.84 and 2.07 mg/L

Auxiliary Solvent Acetone (0.1 mL/L)

Water Hardness 24 mg $CaCO_3$/L

Analytical Monitoring GC/FID

Remarks - Method After a range finding test, a definitive test was conducted in accordance with the guidelines above and in compliance with GLP standards and principles. No significant deviations to the test protocol were reported.

The test substance (100 mg/mL) was prepared in acetone. This was diluted to 10 mg/L with test medium and stirred for 24 hours. This mixture was filtered through a 0.2 µmm filter. The filtrate was further diluted to prepare the final test concentrations.

RESULTS

Biomass		*Growth*	
EyC50	*NOEC*	*ErC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
0.33	0.14	0.74	0.14
95% confidence interval ranging from 0.13 – 0.88 mg/L		95% confidence interval ranging from 0.32 – 0.1.7mg/L	

Remarks - Results The validity criteria for the test were met.

Analysis of the sample taken from the solution prepared at nominal 10 mg/L at the start of the test showed a concentration of 3.5-3.8 mg/L. Concentrations in the dilutions were in agreement with the expected values. At the end of the test period the concentration measured in the filtrate without algae had decreased to 76% of the initial concentration. The lower concentrations were all decreased by more than 20%. Therefore, the measurement of EC50 values were based on the average concentrations i.e. the geometric means of the measured concentrations.

CONCLUSION The notified chemical is very toxic to algae

TEST FACILITY NOTOX (1998d)

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