File No: LTD/1798

May 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

9-Octadecenamide, N-[2-hydroxy-1-(hydroxymethyl)heptadecyl]-, (9Z)- (INCI Name: 2-Oleamido-1,3-Octadecanediol)

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
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TABLE OF CONTENTS

SUMMARY 3
CONCLUSIONS AND REGULATORY OBLIGATIONS 3
ASSESSMENT DETAILS 5
1. APPLICANT AND NOTIFICATION DETAILS 5
2. IDENTITY OF CHEMICAL 5
3. COMPOSITION 6
4. PHYSICAL AND CHEMICAL PROPERTIES 6
5. INTRODUCTION AND USE INFORMATION 6
6. HUMAN HEALTH IMPLICATIONS 7
6.1. Exposure Assessment 7
6.1.1. Occupational Exposure 7
6.1.2. Public Exposure 8
6.2. Human Health Effects Assessment 8
6.3. Human Health Risk Characterisation 10
6.3.1. Occupational Health and Safety 10
6.3.2. Public Health 10
7. ENVIRONMENTAL IMPLICATIONS 11
7.1. Environmental Exposure & Fate Assessment 11
7.1.1. Environmental Exposure 11
7.1.2. Environmental Fate 11
7.1.3. Predicted Environmental Concentration (PEC) 11
7.2. Environmental Effects Assessment 12
7.2.1. Predicted No-Effect Concentration 12
7.3. Environmental Risk Assessment 12
APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES 13
APPENDIX B: TOXICOLOGICAL INVESTIGATIONS 15
B.1. Acute toxicity – oral 15
B.2. Acute toxicity – oral 15
B.3. Acute toxicity – oral 16
B.4. Irritation – skin 16
B.5. Irritation – skin 16
B.6. Irritation – skin 17
B.7. Irritation – eye 17
B.8. Irritation – eye 18
B.9. Irritation – eye 19
B.10. Skin sensitisation 19
B.11. Repeat dose toxicity 20
B.12. Repeat dose toxicity 21
B.13. Genotoxicity – bacteria 22
B.14. Genotoxicity – bacteria 23
B.15. Genotoxicity – in vitro 24
B.17. Developmental toxicity 26
APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS 28
C.1. Environmental Fate 28
C.1.1. Ready biodegradability 28
C.2.1. Acute toxicity to fish 28
C.2.2. Acute toxicity to aquatic invertebrates 29
C.2.3. Algal growth inhibition test 29
C.2.4. Chronic toxicity to aquatic invertebrates 30
C.2.5. Chronic toxicity to fish 30
BIBLIOGRAPHY 32

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/1798	L'Oreal Australia Pty Ltd	9-Octadecenamide, N-[2-hydroxy-1-(hydroxymethyl)heptadecyl]-, (9Z)- (INCI Name: 2-Oleamido-1,3-Octadecanediol)	ND*	≤ 1 tonne per annum	Cosmetic 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).

Human health risk assessment
Provided that the recommended controls are being adhered to, under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

Based on the available information, when used at ≤ 1% in body lotions, ≤ 2.5% in other leave-on and aerosol spray products and ≤ 6% in rinse-off cosmetic products, the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment
On the basis of the low hazard and the assessed 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 during reformulation processes:
  - Enclosed, automated processes, where possible
  - Exhaust ventilation

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

- 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 during reformulation processes:
  - Coveralls, impervious gloves
  - Respiratory protection (if there is potential for inhalation exposure to the powdered chemical)

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

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

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

Disposal

- Where reuse or recycling are unavailable or impracticable, dispose of the chemical in an environmentally sound manner in accordance with relevant Commonwealth, State, Territory and local government legislation.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, 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 1% concentration in body lotions, 2.5% in other leave-on and aerosol spray products and 6% in rinse-off cosmetic products;

or

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

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

(Material) Safety Data Sheet
The (M)SDS of the notified chemical 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)
L'Oreal Australia Pty Ltd (ABN: 40 004 191 673)
564 St Kilda Rd
Melbourne VIC 3004

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: structural formulae (certain information), analytical data, degree of purity, impurities, additives/adjuvants and use details.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: hydrolysis as a function of pH, partition coefficient, adsorption/desorption, dissociation constant, flash point.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Low Volume Chemical (LVC) Permit.

NOTIFICATION IN OTHER COUNTRIES
France (2003).

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Mexanyl GZ
2-Oleamido-1,3-Octadecanediol (INCI name)

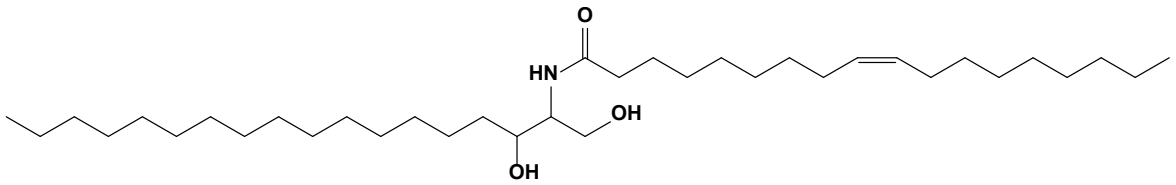
CAS NUMBER
54422-45-6

CHEMICAL NAME
9-Octadecenamide, N-[2-hydroxy-1-(hydroxymethyl)heptadecyl]-, (9Z)-

OTHER NAME(S)
DVS 603
71260

MOLECULAR FORMULA
$C_{36}H_{71}NO_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
565.95 Da

ANALYTICAL DATA
Reference IR spectrum was provided.

3. COMPOSITION

DEGREE OF PURITY
> 85%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: cream-coloured powder.

Property	Value	Data Source/Justification
Melting Point/Freezing Point	75.7 °C	Measured
Boiling Point	> 300 °C	Measured
Relative Density	0.519 ± 0.018 at 22 °C	Measured
Vapour Pressure	0.127 kPa at 20 °C	Measured*
Water Solubility	2×10^{-4} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functionality. However, the notified chemical is not expected to be hydrolysed significantly under normal environmental conditions (pH 4 – 9).
Partition Coefficient (n-octanol/water)	log Pow = 13.33	Calculated (WSKOW v1.42; US EPA, 2011).
Adsorption/Desorption	log K_{oc} = 6.9 (MCI method) log K_{oc} = 7.5 (Kow method)	Calculated (KOCWIN v2.0, EPI Suite v4.1 (US EPA, 2011).
Dissociation Constant	Not determined	Does not contain dissociable functionality
Particle Size	D_{10} = 0.105 µm D_{50} = 0.159 µm D_{90} = 0.285 µm	Measured
Flammability	Not considered highly flammable.	Measured
Autoignition Temperature	> 420 °C; not pyrophoric.	Measured
Explosive Properties	Not considered to present a danger of explosion.	Measured
Oxidising Properties	Not considered to present oxidising properties.	Measured

*Full study report in English not provided.

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.

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 not be manufactured within Australia. The notified chemical will be imported into Australia either in neat form or already blended in finished cosmetic products.

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 or Melbourne

TRANSPORTATION AND PACKAGING
The notified chemical in its neat form will be imported to Australia by sea in pallets for reformulation. Products containing the notified chemical at ≤ 6% concentration, also imported to Australia by sea, will be packed in bottles and tubes (sizes up to 500 mL made mainly from HDPE) as follows: dozens inside a shipper, with multiple shippers per pallet and multiple pallets per shipping container. The containers will be taken from the wharf and transported to the appropriate central distribution centres and delivered to major retailer warehouses.

USE
The notified chemical will be used as an ingredient in cosmetic products (at proposed usage concentrations of ≤ 1% in body lotions, ≤ 2.5% in other leave-on and aerosol spray products and ≤ 6% in rinse-off cosmetic products).

OPERATION DESCRIPTION
Transportation and storage
Dockside and warehouse workers will transport the raw and finished products from the wharf to the central distribution centres and place the pallets of products into the warehouse.

Reformulation
The notified chemical will not be manufactured in Australia. It will be imported into Australia neat or already blended in finished cosmetic products. When reformulated, the notified chemical will be blended into end-use consumer products at customer sites. Procedures will vary depending on the nature of the cosmetic product being formulated. Both manual and automated steps will likely be involved. For example, a chemist will sample and test the notified chemical for QA purposes manually, a compounder will weigh an appropriate amount of the notified chemical into a container then add the amount directly into a flame proof mixing tank, with periodic sampling for quality control purposes also carried out during the manufacturing process. Automated processes may include mixing and filling of end-use containers with products.

End-use
Finished products containing the notified chemical (≤ 6% concentration) may also be used by consumers and professionals such as hairdressers and workers in beauty salons. Depending on the nature of the product, the application could be varied – by hand, using an applicator or sprayed.

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 Storage	4	12
Professional compounder	8	12
Chemist	3	12
Packers	8	12
End Users (workers)	8	365

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come in contact with the notified chemical either in neat form or at various concentrations in cosmetic products (≤ 6%), only in the event of accidental rupture of containers.

Reformulation
During reformulation into cosmetic products, dermal, ocular and inhalation exposure of workers (≤ 100% concentration) may occur when handling the notified chemical or products containing it. 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 chemical in end-use products (at ≤ 6% concentration) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (≤ 6% concentration) through the use of cosmetic products. The principal route of exposure would be dermal, while oral, ocular and inhalation exposures are also possible, particularly if products are applied by spray, or if products are applied to the lips.

A combined internal dose of 0.2976 mg/kg bw/day was estimated using data on typical use patterns of cosmetic product categories in which the notified chemical may be used (SCCS, 2012; Loretz *et al.*, 2006; specific use details of the notified chemical are considered as exempt information). This estimation assumed a worst case scenario and is for a person who is a simultaneous user of a selection of cosmetic products that may contain the notified chemical.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies (where full study reports in English were available), refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity*	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity**	LD50 > 2,000 mg/kg bw; low toxicity**
Rabbit, skin irritation*	slightly irritating
Rabbit, eye irritation*	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose dermal toxicity – 14 days	no evidence of toxicity or skin irritation
Rat, repeat dose oral toxicity – 28 days	NO(A)EL = 30 mg/kg bw/day
Mutagenicity – bacterial reverse mutation*	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic
Genotoxicity – in vitro mammalian cell gene mutation test	non mutagenic
Rat, reproductive and developmental toxicity screening	NOEL (mating/fertility) = 1,000 mg/kg bw/day NO(A)EL (maternal) = 1,000 mg/kg bw/day

* ≥ 2 studies included in Appendix B
** Full study report in English not provided

Toxicokinetics, metabolism and distribution.
Based on the molecular weight (565.95 Da), water solubility (2×10^{-4} g/L at 20 °C) and partition coefficient (calculated log Pow = 13.33) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption could occur, although the extent of absorption may be limited. The notified chemical may also be absorbed across the respiratory tract.

The limited dermal absorption is supported by the results of a percutaneous absorption study conducted on the notified chemical (L'Oreal Recherche Avancée, 1995; full study report in English not provided). The notifier has reported that when topically administered *in vivo* to female rats in a 1% oil in water emulsion for 4 hours and measured 96 hours following administration, 3.67 ± 0.39% of the average applied amount of the notified chemical penetrated the skin.

Acute toxicity.
The notified chemical was found to be of low acute toxicity by the oral route in studies conducted in rats. It is also reported to be of low toxicity via the dermal route; however, the full study report in English was not provided.

No inhalation toxicity data were provided for the notified chemical.

Irritation.
Two separate acute dermal irritation studies were performed in rabbits. Single 4-hour, semi-occluded applications of the notified chemical resulted in erythema in only one animal at the 1, 24 and 48 hour observations after patch removal. No oedema was noted. The effects noted in these studies were insufficient to warrant classification of the chemical as a skin irritant.

Three separate eye irritation studies were conducted in rabbits. Conjunctival irritation was noted in all treated eyes from 1 hour after treatment, persisting in some animals (duration < 9 days). Corneal opacity and/or iris lesions were seen in some of the animals. All signs of irritation had resolved by the end of the study period. The effects noted in these studies were insufficient to warrant classification of the chemical as an eye irritant.

Sensitisation.
A guinea pig maximisation test was conducted to determine the skin sensitisation potential of the notified chemical. Under the conditions of the study, the notified chemical was found to be a non-sensitiser, with no responses noted in any animals at both the 24 and 48 hour observations after challenge patch removal. While the study may not have been conducted in accordance with the procedures outlined in the test guideline (with respect to the intradermal induction phase), computational-based investigations on the notified chemical (conducted at NICNAS) support that sensitisation effects following exposure to the notified chemical are not expected.

Repeated dose toxicity.
A study to evaluate the repeated dose toxicity of the notified chemical was conducted in rats treated at 10, 30 and 100 mg/kg bw/day by oral gavage for 28 days. Mean absolute and relative thymus weights in male animals of the 100 mg/kg bw/day dose group were statistically significantly higher compared to control males. Despite the lack of microscopic abnormalities correlating with the increased weights, the study authors considered that a relationship to treatment could not be ruled out. Therefore, the No Observed (Adverse) Effect Level (NO(A)EL) was established by the study authors as 30 mg/kg bw/day.

A 14 day repeat dose dermal toxicity study was conducted in rats (3/sex, 1000 mg/kg bw/day). At necropsy, the skin was sampled (microscopic analysis) and macroscopic analysis of the main organs of the abdominal and thoracic cavities was performed. There was no evidence of toxicity or skin irritation under the conditions of the test.

Mutagenicity/Genotoxicity.
Two separate reverse mutation assay tests were performed with the notified chemical, in which it was found to be non mutagenic. The notified chemical was also not clastogenic to Chinese hamster lung cells in an in vitro mammalian chromosome aberration test and non mutagenic to mouse lymphoma cells in an in vitro mammalian cell gene mutation test.

Reproductive/developmental toxicity
A study to evaluate the reproductive and developmental toxicity of the notified chemical was conducted in rats at 100, 300 and 1,000 mg/kg bw/day.

A female from the high dose group was prematurely sacrificed on day 52 (day 24 post coitum). Prior to death (towards the end of the gestation period), the animal showed a range of signs indicating poor clinical condition. At hysterectomy, the female was declared pregnant with 14 implantation sites consisting of 8 dead foetuses, 3 resorptions and 3 scars. A prolapse of the left uterine horn into the vagina lumen was also noted. At post-mortem examination, microscopic observations included thickening of the pericardium and pleura, adhesions, white deposits and serous content in the thoracic cavity. These findings were correlated to severe fibrinous and necrotic inflammation. The effects were deemed to be the major contributing factor to the poor clinical condition of the animal pre-death. However, they were considered by the study authors to be potentially caused by a gavage accident, not attributed to an effect of the test item.

A high dose male also showed some effects at macroscopic post mortem examination including several lesions (urinary lithiasis) of the urinary tract. On microscopic inspection, severe papillomatosis of the urinary bladder mucosa, inflammatory cells (neutrophils, mononuclear cells) and mineralized mineral material in the lumen, urethra lumen dilation, renal pyelic cavity lined by a slightly hyperplastic transitional epithelium, were noted. As bladder examination was not conducted for the remaining animals, a treatment-related conclusion for this finding could not be drawn. The study authors speculated that this finding could represent a random event or a treatment-related process.

Under the conditions of the study, a No Observed (Adverse) Effect Level (NO(A)EL) was established by the study authors as 1,000 mg/kg bw/day for maternal toxicity and a No Observed Effect Level (NOEL) of 1,000 mg/kg bw/day was established for mating/fertility.

Health 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).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Reformulation
Workers may experience dermal, ocular and inhalation exposure to the neat notified chemical during formulation processes. This exposure may occur during handling of the chemical, cleaning and/or maintenance of the equipment.

The notified chemical is a powder with particles in the respirable size range (D_{90} = 0.285 μm) and no data on the inhalation toxicity of the notified chemical is available. Therefore, caution should be exercised by workers when handling the chemical. The use of automated/enclosed processes (where possible), ventilated areas and PPE (such as gloves, coveralls and respiratory protection) should minimise the potential for exposure.

Provided that control measures are in place to minimise worker exposure, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Workers involved in professions where the services provided involve the application of cosmetic products containing the notified chemical to clients (*e.g.*, hairdressers and beauty salon workers) may be exposed to the notified chemical. If PPE is used, the risk to these workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical (for details of the public health risk assessment, see Section 6.3.2).

6.3.2. Public Health

Members of the public may experience repeated exposure to the notified chemical at ≤ 1% concentration in body lotions, ≤ 2.5% concentration in other leave-on and aerosol spray products and ≤ 6% concentration in rinse-off cosmetic products.

Based on the available information, acute toxicity effects are not expected from use of the notified chemical at the proposed concentrations. The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.2976 mg/kg bw/day (see Section 6.1.2) and the NO(A)EL of 30 mg/kg bw/day, which was established in a 28-day repeated dose toxicity study on the notified chemical. A MoE value ≥ 100 is considered acceptable to account for intra- and inter-species differences. Using the abovementioned NO(A)EL, a MoE of ~101 was estimated, which is considered to be acceptable.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 1% in body lotions, ≤ 2.5% in other leave-on and aerosol spray products and ≤ 6% in rinse-off cosmetic 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 manufactured overseas and imported into Australia either in neat form or already blended in finished cosmetic products. Blending is expected to take place under industrial settings in a closed system with adequate ventilation and engineering controls. Release of the notified chemical to the environment is unlikely except in the event of a transport accident or an accidental spill during handling. Accidental spills of formulated products containing the notified chemical are expected to be physically contained and then absorbed into inert material. The absorbed notified chemical is expected to be disposed of to landfill.

RELEASE OF CHEMICAL FROM USE

As the notified chemical will be used as an ingredient in cosmetic products, it is expected that effectively the entire annual import volume will be released to sewer through consumer use. A small proportion (estimated to be ≤ 3%) may remain as residues within the end-use containers.

RELEASE OF CHEMICAL FROM DISPOSAL

Expired wastes and residue of the notified chemical in the empty containers are likely either to share the fate of the container and be disposed of to landfill, or to be washed to sewer when containers are rinsed before recycling.

7.1.2. Environmental Fate

The notified chemical is considered not readily biodegradable based on the environmental fate study provided (53% biodegradation observed in 28 days). For the details of the environmental fate studies please refer to Appendix C. The majority of the notified chemical is expected to be released to the sewerage system. In waste water treatment processes in sewage treatment plants (STPs), a significant proportion of the notified chemical is expected to be removed from influent based on the high modelled log K_{oc} values and the low water solubility of the notified chemical. The notified chemical that partitions to sludge will be removed for disposal to landfill or used on land for soil remediation.

The notified chemical is expected to have high volatility from water (log H = 3.4×10^{-5} Pa/m^3/mol) and hence it is likely to volatilise to air during use or sewage treatment based on calculation for the notified chemical. In the event of release to atmosphere, the notified chemical is not expected to persist in the air compartment based on calculations (AOPWIN v1.92; US EPA, 2011) for the notified chemical.

In surface waters, the notified chemical will partition to suspended solids and organic matter. Based on its calculated high log Kow value, the notified chemical has potential to bioaccumulate. However, due to its biodegradability and high potential to partition to sludge/sediment, it is not expected that a significant amount of the notified chemical is bioavailable. In soil, landfill or aquatic compartments, the notified chemical is expected to be degraded by abiotic and biotic processes to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

Since most of the notified chemical will be washed into the sewer, under a worst case scenario, with no removal of the notified chemical in the sewage treatment plant, the resultant Predicted Environmental Concentration (PEC) in 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 4.03 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 20.19 µg/kg and 40.39 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 the studies of the analogue can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Acute Toxicity		
Fish Toxicity (96 hours)	LC_{50} > 100 mg/L	Not harmful at saturation to fish
Daphnia Toxicity (48 hours)	EC_{50} > 100 mg/L	Not harmful at saturation to aquatic invertebrates
Algal Toxicity (96 hours)	E_rC_{50} > 100 mg/L	Not harmful at saturation to algae
Chronic Toxicity		
Fish Chronic Toxicity (35 days)	NOEC > 1.1	Not harmful at saturation to fish
Daphnia Chronic Toxicity (21 days)	NOEC > 1.2	Not harmful at saturation to aquatic invertebrates

The ecotoxicological data indicates that the notified chemical has no toxicological effects at the limit of its water solubility. Therefore, the notified chemical is not expected to be harmful at the limit of its water solubility, and is not be formally classified under the Globally Harmonised System of Classification of Chemicals (GHS; United Nations, 2009) for acute and chronic effects.

7.2.1. Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) has not been calculated as the notified chemical is not expected to be harmful to aquatic organisms up to the limit of its water solubility.

7.3. Environmental Risk Assessment

A risk Quotient (Q = PEC/PNEC) value was not calculated since the PNEC was not derived. The notified chemical is not expected to pose an unreasonable risk to the environment based on the assessed use pattern and the low toxicity to the aquatic organisms.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 75.7 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	Determined using the Kofler hot bar method.
Test Facility	SEPC (1994a)

Boiling Point > 300 °C

Method	OECD TG 103 Boiling Point.
Remarks	Determined using the distillation method. Boiling temperature was not observed (barometric pressure ~ 96 kPa). The study authors noted that the low volume of distillate indicated that impurities were present in the distillate. A previously conducted study indicating a boiling temperature of 99.3 °C (distillation method) was considered to be invalid by the notifier.
Test Facility	SEPC (1994b)

Relative Density 0.519 ± 0.018 at 22 °C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	Determined using the pycnometer method.
Test Facility	SEPC (1994a)

Water Solubility 2×10^{-4} g/L at 20 °C

Method	OECD TG 105 Water Solubility. EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Column Elution Method
Test Facility	Pharmakon (1995)

Particle Size D_{10} = 0.105 µm
D_{50} = 0.159 µm
D_{90} = 0.285 µm

Method	Static light scattering
Remarks	Determined after dispersion (1% test substance) in 1% aqueous sodium dodecyl sulfate. Distribution determined in volume and number: *Volume*: D_{10} = 0.201 µm; D_{50} = 1.45 µm; D_{90} = 30.3 µm *Number:* D_{10} = 0.105 µm; D_{50} = 0.159 µm; D_{90} = 0.285 µm
Test Facility	L'Oreal Recherche Avancée (2015)

Flammability Not considered highly flammable.

Method	EEC Directive 92/69 A.10 Flammability (Solids).
Remarks	No ignition was noted and no burning rate could be measured.
Test Facility	SEPC (1994c)

Autoignition Temperature > 420 °C; not pyrophoric.

Method	EEC Directive 92/69 A.13 (1992)
Remarks	Determined by measurement of the minimum temperature of the inner surface of an oven that will result in ignition of the test substance; no self-ignition was observed (from 19 to 420 °C). Any ignition during dropping (1 m height) and within 5 minutes of settling also determined.
Test Facility	SEPC (1994d)

Explosive Properties Not considered to present a danger of explosion.

Method	EEC Directive 92/69 A.14 Explosive Properties.
Remarks	3 part method of thermal sensitivity (flame test) and mechanical sensitivity (with respect to shock and friction).
Test Facility	SEPC (1994c)

Oxidizing Properties Not considered to present oxidising properties.

Method	Similar to EEC Directive 92/69 A.17 Oxidizing Properties (Solids).
Remarks	The maximum burning rate was determined via comparison with the maximum burning rate of the reference mixture.
Test Facility	SEPC (1994c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical.

METHOD
- Species/Strain: Rat/ Sprague-Dawley (Crl: CD (SD) BR)
- Vehicle: 0.2% carboxymethyl cellulose aq. and 14% Tween 80.
- Remarks - Method: GLP Compliance.
  No significant protocol deviations.

RESULTS

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

- LD_{50}: > 2,000 mg/kg bw
- Signs of Toxicity: There were no treatment related signs of systemic toxicity noted in any of the animals over the study period. The only noted observation was that some animals were occasionally seen produce pasty faeces.
- Effects in Organs: No macroscopic abnormalities were observed at necropsy.
- Remarks - Results: All animals survived until the scheduled termination and showed gains in bodyweight over the study period.

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

TEST FACILITY: CIDAC (1997a)

B.2. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical.

METHOD: Similar to OECD TG 401 Acute Oral Toxicity – Limit Test.
- Species/Strain: Rat/ Sprague-Dawley SPF
- Vehicle: 0.5% carboxymethyl cellulose aq.
- Remarks - Method: No significant protocol deviations.

  Control animals (5 per sex) were included in the study.

RESULTS

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

- LD_{50}: > 2,000 mg/kg bw
- Signs of Toxicity: There were no treatment related signs of systemic toxicity noted in any of the animals over the study period.
- Effects in Organs: Congestive point was noted on the glandular zone of the stomach of 1 animal of each sex.
  No other macroscopic abnormalities were observed at necropsy.
- Remarks - Results: All animals survived until the scheduled termination and showed gains in bodyweight over the study period (reduced mean body weight gain was noted in female animals on day 7) relative to control animals.

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

TEST FACILITY CERB (1991a)

B.3. Acute toxicity – oral

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 420 Acute Oral Toxicity - Fixed Dose Method.
Species/Strain Rat/ Sprague-Dawley (Rj: SD)
Vehicle 0.5 % methylcellulose aq.
Remarks - Method GLP Compliance.
No significant protocol deviations.

RESULTS

Sighting Study

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

Signs of Toxicity None.
Effects in Organs None.

Main Study

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	4 F	2,000	0/4

Discriminating Dose 2,000 mg/kg bw
Signs of Toxicity There were no treatment related signs of systemic toxicity noted in any of the animals over the study period.
Effects in Organs No macroscopic abnormalities were observed at necropsy.
Remarks - Results All animals survived until the scheduled termination.

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

TEST FACILITY CIT (2005a)

B.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3 M
Vehicle Moistened with water.
Observation Period 72 hours
Type of Dressing Semi-occlusive.
Remarks - Method No significant protocol deviations.
GLP Compliance.

RESULTS
Remarks - Results Very slight erythema was observed in 1 animal, 1 hour after patch removal, however this effect had cleared by the 24 hour observation. No other clinical signs were noted during the study.

CONCLUSION The notified chemical is slightly irritating to the skin.

TEST FACILITY CIDAC (1997b)

B.5. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 F
Vehicle	Moistened with water.
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. GLP Compliance.
RESULTS	
Remarks - Results	No skin reactions were observed in any animal during the study period.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	CERB (1991b)

B.6. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3M
Vehicle	None
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. GLP Compliance. The test substance was initially applied to 1 animal for a period of 3 minutes, 1 hour and 4 hours, before being applied to the remaining 2 animals for 4 hours (the results shown below are based on the 4 hour exposure in the animals).

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	0.7	0	0	1	< 72 h	0
Oedema	0	0	0	0	NA	0

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

Remarks - Results	Very slight erythema was noted in 1 animal (1/3) after a 4 hour exposure, which was observed at the 1, 24 and 48 hour observations.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	CIT (2005b)

B.7. Irritation – eye

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Observation Period	5 days

Remarks - Method
No significant protocol deviations.
GLP Compliance.

At 24 and 48 hours after instillation, 2% aqueous sodium fluorescein solution was applied to the treated eyes.

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	0.3	1.3	1.3	2	< 5 days	0
Conjunctiva: chemosis	0	0	0	1	< 24 hours	0
Conjunctiva: discharge	-	-	-	-	-	-
Corneal opacity	0	0.7	0.3	1	< 5 days	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
All animals presented with conjunctival redness and oedema at the 1 hour observations, with irritation effects being observed at the subsequent 24 and/or 48 and 72 hour observations.

An additional reading was made at 5 days for the 2 animals still showing signs at the 72 hour observations. By this time, all signs had resolved.

CONCLUSION
The notified chemical is slightly irritating to the eye.

TEST FACILITY
CIDAC (1997c)

B.8. Irritation – eye

TEST SUBSTANCE
Notified chemical.

METHOD
OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain
Rabbit/New Zealand White
Number of Animals
3 M
Observation Period
9 days
Remarks - Method
No significant protocol deviations.
GLP Compliance.

0.5% sodium fluorescein was applied at the 24 hour observation.

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	1	0.3	2	< 9 days	0
Conjunctiva: chemosis	1	1.3	0.7	3	< 7 days	0
Conjunctiva: discharge	0	0	0	2	< 24 hours	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	1	< 24 hours	0

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

Remarks - Results
All animals presented with chemosis at the 1 hour observations, ranging from above normal to swelling with half closed eye lids. Conjunctival redness, discharge and iris lesions were also seen in animals at the 1 hour observations, with all signs of irritation resolved by the end of the study period.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY CIT (2005c)

B.9. Irritation – eye

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3F
Observation Period 72 hours
Remarks - Method No significant protocol deviations.
GLP Compliance.

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	0.7	0	0	2	< 48 hours	0
Conjunctiva: chemosis	0.3	0	0	1	< 48 hours	0
Conjunctiva: discharge	-	-	-	-	-	-
Corneal opacity	0.3	0	0	1	< 48 hours	0
Iridial inflammation	0.3	0	0	1	< 48 hours	0

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

Remarks - Results All animals presented with slight chemosis and slight to clearly visible reddening at the 1 hour observations. Corneal and iris lesions were also noted in all animals.

All signs of irritation had resolved by the end of the study period.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY CERB (1991c)

B.10. Skin sensitisation

TEST SUBSTANCE Notified chemical.

METHOD Similar to OECD TG 406 Skin Sensitisation – Maximisation Test.
Species/Strain Guinea pig/Hartley
PRELIMINARY STUDY Maximum Non-irritating Concentration:
topical: 100% (skin moistened with 0.5 mL thick paraffin oil)
MAIN STUDY
Number of Animals Test Group: 10 per sex Control Group: 5 per sex (Negative and Positive Control Groups)
INDUCTION PHASE Induction Procedure (for the test substance treated animals):
D_0: epicutaneous application of 100% 0.5 mL on a 8cm gauze square, with an intradermal injection of 0.05mL Complete Freund's Adjuvant (50%)
D_7: topical application of 10% 0.5 mL sodium lauryl sulphate in paraffin oil
D_8: topical application of 100% moistened with 0.5 mL thick paraffin oil
Signs of Irritation None.
CHALLENGE PHASE
1st challenge topical: 100% (skin moistened with 0.5 mL thick paraffin oil)
Remarks - Method The preliminary study used 4 animals per sex.
A concurrent positive control study was conducted using dinitrochlorobenzene.

Non occlusive dressings were used.

The intradermal induction phase was not conducted in accordance with the procedures outlined in the guideline.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: Challenge*	
		24 h	*48 h*
Test Group	100%	0/20	0/20
Control Group			
negative	-	0/10	0/10
positive	1%	10/10	0/10

Remarks - Results: No skin reactions (after challenge) were observed in any animal treated with the test substance.

CONCLUSION: There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: CERB (1992a)

B.11. Repeat dose toxicity

TEST SUBSTANCE: Notified chemical.

METHOD: Similar to OECD TG 410 Repeated Dose Dermal Toxicity: 21-28-day Study – Limit Test.
Directive 87/18 EEC Recommendation CC 81/30 Appendix 2

Species/Strain: Rat/Sprague-Dawley
Route of Administration: Dermal – semi-occluded
Exposure Information: Total exposure days: 14 days
Dose regimen: 7 days per week
Duration of exposure (dermal): 6 hours/day
Post-exposure observation period: None.
Vehicle: None (powdered substance was applied to moistened skin).
Remarks - Method: GLP Compliance.

Following the 6 hour exposure period, the application area was washed using a swab soaked with distilled water.

Animals were monitored daily.
Body weights were recorded at Days 1, 7 and 14.
At necropsy, the skin was sampled for analysis.
Macroscopic examination of the main organs of the abdominal and thoracic cavities was performed.

Full study report was not provided (with individual animal results).

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	3 per sex	0	0/6
Test substance	3 per sex	1,000	0/6

Histological evaluation of the skin did not reveal any signs of treatment related skin irritation.

Remarks – Results

No deaths occurred and all animals gained weight over the course of the study. No functional (behavioural) observations, skin irritation effects or structure changes (including skin appearance, suppleness and fur regrowth) were reported during the study period. No macroscopic abnormalities were reported.

CONCLUSION	The notified chemical showed no evidence of skin irritation or toxicity under the conditions of the test.
TEST FACILITY	CERB (1992b)

B.12. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/ Sprague-Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period:
Vehicle	0.5% carboxymethyl cellulose aq.
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0/10
low dose	5 per sex	10	0/10
mid dose	5 per sex	30	0/10
high	5 per sex	100	0/10

Mortality and Time to Death

There were no unscheduled deaths or moribund/debilitated animals that needed to be sacrificed before necropsy.

Clinical Observations

No behavioural signs of toxicity were observed in animals of any dose groups.

From day 10 until the end of the dosing period, a decrease in mean body weight was noted in mid dose females, compared to the equivalent control animals. At the day 28 observation, this difference was statistically significant. No other significant body weight changes were noted for male animals or the other female groups.

Some effects on food and water consumption were noted during the study period. The slight variation in food consumption values in animals of both sexes in all dose groups compared to controls did not show any dose response relationship. Water consumption was reduced in male animals from the mid dose group during week 2 to week 4 and in the low dose group in week 4 only. Females showed an increase in water consumption during the study, seen in the low dose group during weeks 2 and 3, and during week 1 and 2 for the mid and high dose animals.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Various effects were seen in the clinical chemistry of the study animals. A single female of the high dose group presented with elevated ASAT and ALAT levels. A single female of the mid dose group showed slightly elevated potassium levels. Females of the mid dose group showed statistically significant lower mean urea levels compared to the control animals, however the study authors deemed individual results scored in the physiological range.

Some statistically significant differences were noted in specific haematological parameters. Mean white cell count in low dose group females was lower than the equivalent control animals. In addition a single male from the control group had slightly elevated white cell (neutrophils and lymphocytes) counts. Significantly reduced

mean neutrophil levels were seen in low and high dose group males and reduced mean lymphocytes in low dose group females. However the study authors deemed individual results scored in the physiological range.

Effects in Organs

Macroscopic abnormalities noted at necropsy included stomach effects (ulceroid fissures and points on glandular zone) and were deemed minor by the study authors.

The below effects were seen on organ weights:

Treatment	Females	Males
100	↑ absolute & relative thymus weight (1/5 animals)	↓mean relative heart* ↑ mean absolute & relative thymus weight*
30	-	↓mean absolute & relative heart*
10	-	-

* Statistically significant changes

With respect to the decreased heart weights, the study authors considered that the individual results were within the physiological range.

The high dose group female showing anomalies in hepatic clinical chemistry parameters was found at histopathological examination to have a moderate lesion of single cell necrosis, believed to be associated with inflammatory cell infiltration and a sinusoidal cell vacuolation.

Treatemnt related effects on the thymus (or other organs) were not detected at histopathological examination.

Remarks – Results

Despite the lack of microscopic abnormalities correlated with the increased thymus weights seen in high dose males at histological observation. The study authors considered that a relationship to treatment could not be excluded.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) was established by the study authors as 30 mg/kg bw/day in this study. The study authors considered the effects to be potentially indicative of test substance toxicity with respect to the increased thymus weights.

TEST FACILITY CERB (1992c)

B.13. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD

	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure /Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S9 fraction from Aroclor 1254-induced rat liver
Concentration Range in Main Tests	a) With metabolic activation: 312.5 – 5,000 µg/plate b) Without metabolic activation: 312.5 – 5,000 µg/plate
Vehicle	Ethanol
Remarks - Method	No significant protocol deviations. GLP Compliance. All experiments were performed using the direct plate incorporation method, except for test 2 & 3 in the presence of S9-mix. A preliminary toxicity test (10-5,000 µg/plate; plate incorporation) was performed for strains TA98, TA100 and TA102 (with and without S9-mix) to determine the toxicity of the test material. A moderate to marked emulsion was noted in plates at ≥ 1,000 µg/plate. A confirmatory test was conducted (with S9-mix) using the TA100 strain.

Positive control tests were conducted in parallel to the main test using sodium azide, 9-aminoacridine, 2-nitrofluorene and mitomycin C in the absence of S9-mix, and 2-aminoanthracene with S9-mix.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5,000	> 5,000	> 5,000	negative
Test 2		> 5,000	> 5,000	negative
Test 3		> 5,000	> 5,000	negative
Present				
Test 1	> 5,000	> 5,000	> 5,000	negative
Test 2		> 5,000	> 5,000	negative
Test 3		> 5,000	> 5,000	negative

Remarks - Results

No visible reduction in the growth of the bacterial background lawn was seen at any dose level, with and without metabolic activation.

Slight increases in the frequency of revertant colonies were noted in strains TA1535 (Test 2) and TA100 (Test 2). However this was not considered to be relevant by the study authors as the increases were not dose-related, not seen in Test 1(TA1537) or in Tests 1 and 3 (TA100).

No precipitate formation was observed. However a moderate to marked emulsion was observed at all dose levels ≥ 1,250 µg/plate.

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 not mutagenic to bacteria under the conditions of the test.

TEST FACILITY

CIT (2005d)

B.14. Genotoxicity – bacteria

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure /Pre incubation procedure

Species/Strain

S. typhimurium: TA1535, TA1537, TA98, TA100
Escherichia. coli: WP2uvrA

Metabolic Activation System

S9 fraction from Aroclor 1254-induced rat liver

Concentration Range in Main Test

a) With metabolic activation: 312.5 – 5,000 µg/plate
b) Without metabolic activation: 312.5 – 5,000 µg/plate

Vehicle

Dimethylsulfoxide

Remarks - Method

No significant protocol deviations.
GLP Compliance.
All experiments were performed using the direct plate incorporation method, except for test 2 in the presence of S9-mix.

A preliminary toxicity test (10 – 5,000 µg/plate) was performed for the TA100 strain (with and without S9-mix) to determine the toxicity of the test material. A moderate to strong precipitate was observed at doses ≥ 2,500 µg/plate.

Positive control tests were conducted in parallel to the main test using

sodium azide, 9-aminoacridine, 2-nitrofluorene and N-ethyl-N-nitro-nitrosaguanidine in the absence of S9-mix, and 2-anthramine with S9-mix.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5,000	> 5,000	≥ 1,250	negative
Test 2		> 5,000	≥ 625	negative
Present				
Test 1	> 5,000	> 5,000	≥ 1,250	negative
Test 2		> 5,000	≥ 312.5	negative

Remarks - Results

No visible reduction in the growth of the bacterial background lawn was seen at any dose level, with and without metabolic activation.

No increases in the frequency of revertant colonies were recorded for any of the bacterial strains.

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 not mutagenic to bacteria under the conditions of the test.

TEST FACILITY

CIT (1994)

B.15. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Hamster/Chinese

Cell Type/Cell Line: Lung/JCRB0030

Metabolic Activation System: S9 fraction from Aroclor 1254-induced rat liver

Vehicle: Test substance suspended in the culture medium (MEM with 10% FCS)

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

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

100 cells/culture were analysed.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	9.8, 19.5, 39.1, 78.1, 156, 313, 625, 1250*, 2500*, 5000*	6 h	24 h
Test 2	9.8, 19.5, 39.1, 78.1, 156, 313, 625, 1250*, 2500*, 5000*	24 h	24 h
Test 3	9.8, 19.5, 39.1, 78.1, 156, 313, 625, 1250*, 2500*, 5000*	48 h	48 h
Present			
Test 1	9.8, 19.5, 39.1, 78.1, 156, 313, 625, 1250*, 2500*, 5000*	6 h	24 h

*Cultures selected for metaphase analysis.

RESULTS

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

Activation	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 5,000	≥ 156	negative
Test 2	> 5,000	≥ 156	negative
Test 3	> 5,000	≥ 156	negative
Present			
Test 1	> 5,000	≥ 156	negative

Remarks - Results

No statistically significant increases in the proportion of polyploidy cells or the proportion of metaphase cultures containing chromosomal aberrations were seen at any dose level, with and without metabolic activation.

The positive controls produced satisfactory responses, thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.

It is noted that precipitate was seen at the analysed concentrations at the stages of dosing, medium change and/or cell harvest.

CONCLUSION

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

TEST FACILITY

Huntingdon Research Centre (1992)

B.16. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 476 In vitro Mammalian Cell Gene Mutation Test.

Species/Strain: Mouse

Cell Type/Cell Line: L5178Y $TK^{+/-}$ (3.7.2C) Mouse Lymphoma

Metabolic Activation System: S9 fraction from Aroclor 1254-induced rat liver

Vehicle: Acetone

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

A preliminary toxicity study was performed (3 hour exposure, with and without activation) at concentrations 4.688 – 150 µg/mL. Precipitate was noted at the end of the treatment periods at ≥ 75 µg/mL, with samples > 75 µg/mL discarded prior to analysis.

Vehicle and positive controls (methyl methane sulphonate without metabolic activation and benzo[α]pyrene with metabolic activation) were used in parallel with the test material.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	0*, 5*, 10*, 20*, 30*, 40*, 50*	3 h	2 days	12-13 days
Test 2	0*, 5*, 10*, 20*, 30*, 40*, 50, 80, 100	3 h	2 days	12-13 days
Present				
Test 1	0*, 5*, 10*, 20*, 30*, 40*, 50*, 60, 75, 100	3 h	2 days	12-13 days
Test 2	0*, 5*, 10*, 20*, 30*, 40*, 50, 80, 100	3 h	2 days	12-13 days

*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	> 75	> 50	≥ 50	negative
Test 2		> 40	≥ 40	negative
Present				
Test 1	> 75	> 50	≥ 50	negative
Test 2		> 40	≥ 40	negative

Remarks - Results: No increases in the mutant frequency were recorded.

The positive and vehicle control values confirmed the validity of the test system.

CONCLUSION: The notified chemical was not mutagenic to mouse lymphoma cells treated in vitro under the conditions of the test.

TEST FACILITY: Covance (2009)

B.17. Developmental toxicity

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 421 Reproduction/Developmental Toxicity Screening Test
- Species/Strain: Rat/ Sprague-Dawley
- Route of Administration: Oral – gavage
- Exposure Information: Exposure days: 42-56 days
  Post-exposure observation period: None
- Vehicle: 0.5% carboxymethyl cellulose aq.
- Remarks - Method: No significant protocol deviations.
  GLP Compliance.

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
1	10 per sex	0	0/20
2	10 per sex	100	0/20
3	10 per sex	300	0/20
4	10 per sex	1,000	1/20

Mortality and Time to Death

A female from the high dose group was prematurely sacrificed on day 52 (day 24 post coitum (*p.c*)). Prior to death (towards the end of the gestation period), the animal showed signs of poor clinical condition. These included emaciated appearance (corresponding with a significant body weight loss from day 14 to 24 *p.c*), dyspnea, abdominal breathing, piloerection, round back, half-closed eyes and thick brownish vaginal discharge. At hysterectomy, the female was declared pregnant with 14 implantation sites consisting of 8 dead foetuses, 3 resorptions and 3 scars. A prolapse of the left uterine horn into the vagina lumen was also noted. At post-mortem examination, microscopic observations included thickening of the pericardium and pleura, adhesions, white deposits and serous content in the thoracic cavity. These findings were correlated to severe fibrinous and necrotic inflammation. The effects were deemed to be the major contributing factor to the poor clinical condition of the animal pre-death. However, they were considered by the study authors to be potentially caused by a gavage accident, not attributed to an effect of the test item.

2 females from the mid dose group were sacrificed on day 52 as no evidence of mating was detected. The lack of impregnation was confirmed at hysterectomy. One of these animals had shown thick brownish vaginal discharge on days 27 to 29.

Effects on Dams

In addition to the abovementioned observed effects (and corresponding mortalities) a female from the high dose group presented with signs of poor clinical condition towards the end of the gestation period. The signs included

emaciated appearance, dyspnea, chromorhinorrhea and abdominal breathing. While the animal successfully delivered after 22 days of gestation, it continued to show the aforementioned signs during lactation.

Two pairs treated at 300 mg/kg bw/day didn't mate. The test item was not deemed to affect fertility (2 low dose group females and 1 control group female failed to fall pregnant), with all high dose females falling pregnant.

Effects on Males

A high dose male showed some effects at macroscopic post mortem examination. These included several lesions (urinary lithiasis) of the urinary tract, thickening and reddening of the bladder mucosa, dilation of the right ureter and pelvic cavity of the right kidney. On microscopic inspection, severe papillomatosis of the urinary bladder mucosa, inflammatory cells (neutrophils, mononuclear cells) and mineralized mineral material in the lumen, urethra lumen dilation, renal pyelic cavity lined by a slightly hyperplastic transitional epithelium, were noted. As bladder examination was not conducted for the remaining animals, a treatment-related conclusion for this finding could not be drawn. The study authors speculated that this finding could represent a random event or a treatment-related process.

Other microscopic findings were dismissed as common to rats of the chosen species and age and therefore not considered to be treatment-related.

Effects on Foetus

The test item was not deemed to affect the number of pups delivered per litter, sex ratio, the mean number of live pups per litter on day 1 post-partum (*p.p*), or attributed as the cause of the deaths of pups from day 1 to 5 *p.p*.

No treatment-related clinical signs or mean body weight changes dissimilar to the control animals were noted for any pup during the lactation period. At necropsy, no treatment-related macroscopic observations were noted in the pups found prematurely dead or sacrificed at the end of the study period.

Remarks - Results

The study authors considered that the effects seen in the prematurely euthanized high dose group female were isolated and were considered to be unrelated to treatment with the test item.

CONCLUSION

In this study, the No Observed (Adverse) Effect Level (NO(A)EL) for maternal toxicity was established by the study authors as 1,000 mg/kg bw/day and the No Observed Effect Level (NOEL) for mating and fertility was established as 1,000 mg/kg bw/day.

TEST FACILITY CIT (2009)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 310 Ready Biodegradability: CO_2 in Sealed Vessel Test.
Inoculum	Activated sewage sludge from a predominantly domestic sewage treatment plant.
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Total Inorganic Carbon (TIC)
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Notified chemical		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
8	9	7	70
15	23	14	78
21	40	21	83
28	53	28	79

Remarks - Results	All validity criteria for the test were satisfied. The reference compound, sodium benzoate, reached the 60% pass level by day 7 indicating the suitability of the inoculum. The toxicity control exceeded 25% biodegradation within 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the test substance was 53% after 28 days. Therefore, the test substance is not considered to be readily biodegradable based on the test outcome.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Dr. U Noack (2010)

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish
Species	*Branchydanio rerio*
Exposure Period	96 hours
Auxiliary Solvent	Ethanol.
Water Hardness	Not reported.
Analytical Monitoring	Not reported.
Remarks – Method	No significant protocol deviations. GLP Compliance.

RESULTS

Nominal Concentration (mg/L)	*Number of Fish*	*Accumulative Mortality (%)*			
		24h	*48h*	*72h*	*96h*
Control	10	0	0	0	0
Solvent control	10	0	0	0	0
100	10	0	0	0	0

LC_{50}	> 100 mg/L at 96 hours.

NOEC	100 mg/L at 96 hours.
Remarks – Results	All validity criteria for the test were satisfied. The test was conducted as a limit test. The dispersion of the test substance was improved by manual stirring, four times a day since the second study day. The 96-hour LC_{50} was determined by visual observations
CONCLUSION	The notified chemical is not harmful to fish
TEST FACILITY	SEPC (1994e)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static Test
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Ethanol.
Water Hardness	130 mg $CaCO_3$/L
Analytical Monitoring	None reported.
Remarks - Method	No significant protocol deviations. GLP Compliance.

RESULTS

Nominal Concentration (mg/L)	*Number of D. magna*	*Cummulative % Immobilised 48 h*
Control	20	0
Solvent control	20	5
100	20	10

EC50	> 100 mg/L at 48 hours
NOEC	100 mg/L at 48 hours
Remarks - Results	All validity criteria for the test were satisfied. The test was conducted as a limit test. The 48hour EC_{50} was determined by visual observations
CONCLUSION	The notified chemical is not harmful to aquatic invertebrates
TEST FACILITY	SEPC (1994f)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L
Auxiliary Solvent	None reported
Analytical Monitoring	None reported
Remarks - Method	No significant protocol deviations. GLP Compliance. Due to the very low water solubility of the test substance, a saturated suspension of the test substance was prepared and particles removed by filtration.
RESULTS	Growth E_rC_{50} = 100 mg/L at 72 hours
Remarks - Results	All validity criteria for the test were satisfied. The test was conducted as a

limit test. The 48hour EC_{50} was determined by visual observations

CONCLUSION The notified chemical is not harmful to algae

TEST FACILITY SEPC (1994g)

C.2.4. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD 211 *Daphnia magna* Reproduction Test – Semi Static
Species *Daphnia magna*
Exposure Period 21 days
Auxiliary Solvent N,N-Dimethylformamide (DMF)
Water Hardness 250 mg $CaCO_3$/L
Analytical Monitoring HPLC-MS/MS
Remarks – Method No significant protocol deviations.
GLP Compliance.

Due to low solubility of the test substance in test water, the organic solvent DMF was used to dose the test substance.

Test Day 21	*Control*	*Solvent*	*Nominal Concentration (µg/L)*				
			0.1	*0.22*	*0.46*	*1.0*	*2.2*
Total no. of offspring released by survived daphnid	752	824	806	694	719	697	796
Total no. of offspring released per survived daphnid	75.2	82.4	80.6	72.8	75.1	69.7	79.6
% No of adult daphnids immobilised	0	0	0	1	1	0	0
% Survival	100	100	100	90	90	100	100

21 day EL_{50} (Immobilization) > 1.2 µg/L (WAF)
21 day EL_{50} (Reproduction) > 1.2 µg/L (WAF)
21 day NOEL = 1.2 µg/L (WAF)

Remarks – Results The survival of the test animals at the end of the test was in the range of 90% or above in controls, solvent controls and treatments. This was observed at all test concentrations including the highest test concentration of 1.2 µg/L (nominal 2.2 µg/L). Thus, the survival of *Daphnia magna* was not affected by the test substance up to and including the highest test concentration.

The 21 day EL_{50} for immobilization and reproduction were determined to be > 1.2 µg/L as the mean measured concentration (nominal concentration of 2.2 µg/L). The NOEL was determined to be = 1.1 µg/L as a mean measured concentration (nominal concentration of 2.2 µg/L). All the endpoints were determined by the study author and are considered acceptable. Since no effect was observed at the top nominal concentration of 1.1 µg/L which is above the water solubility, the notified chemical is considered not harmful to *Daphnia* up to the limit of water solubility.

CONCLUSION The notified chemical is considered not harmful to daphnia on a chronic basis

TEST FACILITY RCC (2002a)

C.2.5. Chronic toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD OECD TG 210 Fish Early Life Stages Toxicity Test – Flow Through.

Species	*Brachydanio rerio* (Zebra fish)
Exposure Period	35 days
Auxiliary Solvent	N,N-Dimethylformamide (DMF)
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	GC/FID
Remarks - Method	No significant protocol deviations. GLP Compliance. Due to low solubility of the test substance in test water, the organic solvent DMF was used to dose the test substance.

Results

	Concentration (µg/L)						
	Control	*Solvent Control*	*0.1*	*0.22*	*0.46*	*1.0*	*2.2*
Total no. of larvae hatched on day 5	52	50	45	47	48	50	45
Total no. of larvae survived on day 30	38	36	27	35	40	45	37
Mean length (mm) of larvae at the end of test period	17.5 (± 3.5)	18.1 (± 3.0)	16.5 (± 4.4)	15.8 (± 3.2)	19.0 (± 2.3)	17.9 (± 3.2)	19.5 (± 3.2)
% Survival	73	72	60	74	83	90	82

LC_{50} (overall) > 1.1 µg/L (nominal 2.2 µg/L)
NOEC (overall) = 1.1 µg/L (nominal 2.2 µg/L)

Remarks – Results The LC_{50} value for survival of the larvae was determined to be > 1.1 µg/L (mean measured concentration). The NOEC was determined to be > 1.1 µg/ (mean measured concentration). All the endpoints were determined by the study authors and are considered acceptable.

CONCLUSION The notified chemical is considered not harmful to fish on a chronic basis

TEST FACILITY RCC (2002b)

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