File No: LTD/1817

November 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Benzoic acid, 2-hydroxy-5-(1-oxooctyl)-

(INCI name: Capryloyl salicylic acid)

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/1817	L'Oreal Australia Pty Ltd	Benzoic acid, 2-hydroxy-5-(1-oxooctyl)- (INCI name: Capryloyl salicylic acid)	Yes	≤ 1 tonne per annum	Cosmetic ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Skin sensitisation (Category 1)	H317 – may cause an allergic skin reaction
Serious eye damage/eye irritation (Category 1)	H318 – causes serious eye damage

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

R41: Risk of serious damage to eyes
R43: May cause sensitisation by skin contact

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

Hazard classification	*Hazard statement*
Acute Category 3	H402 – Harmful to aquatic life

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

Based on the available information, when used at ≤ 0.5% concentration in cosmetic 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

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:

- H317 – may cause an allergic skin reaction
- H318 – causes serious eye damage

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

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

Health Surveillance

- As the notified chemical is a skin sensitiser, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of skin sensitisation.

CONTROL MEASURES

Occupational Health and Safety

- 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:
  - Enclosed, automated processes, where possible
  - Local ventilation when handling the powder form of the notified chemical

- 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:
  - Avoid contact with skin and eyes
  - Avoid inhalation when handling the powder form of the notified chemical

- 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:
  - Coveralls
  - Impervious gloves
  - Eye protection
  - Respiratory protection, where necessary

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

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

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

Public Health

- Formulators should consider that cosmetic products containing the notified chemical should be formulated in a manner to avoid increased sun sensitivity.

Disposal

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

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified 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 0.5% in cosmetic products;
- information of the potential of the notified chemical to cause increased sun sensitivity becomes available;

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)SDSs of the notified chemical and a product containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the (M)SDSs remains the responsibility of the applicant.

ASSESSMENT DETAILS

This notification has been conducted under the cooperative arrangement with the Australian Therapeutic Goods Administration (TGA). The health hazard assessment component of the TGA report were provided to NICNAS and, where appropriate, used in this assessment report. The other elements of the risk assessment and recommendations on safe use of the notified chemical were carried out by NICNAS.

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
L'Oreal Australia Pty Ltd (ABN: 40 004 191 673)
564 St Kilda Road
MELBOURNE VIC 3004

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year) – Assessed by comparable agency

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: other names, analytical data, degree of purity, impurities 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 and dissociation constant

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Low Volume Chemical (LVC) Permit
TGA (2013)

NOTIFICATION IN OTHER COUNTRIES
EU (1995)

2. IDENTITY OF CHEMICAL

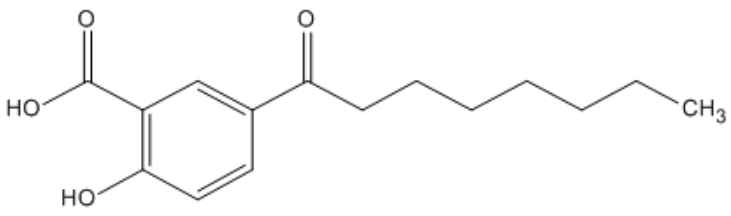
MARKETING NAME(S)
Mexoryl SAB
Capryloyl salicylic acid (INCI name)

CAS NUMBER
78418-01-6

CHEMICAL NAME
Benzoic acid, 2-hydroxy-5-(1-oxooctyl)-

MOLECULAR FORMULA
$C_{15}H_{20}O_4$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
264.32 Da

ANALYTICAL DATA
Reference IR spectrum was provided.

3. COMPOSITION

DEGREE OF PURITY
> 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: white powder

Property	Value	Data Source/Justification
Melting Point/Freezing Point	115 °C	Measured
Boiling Point	Decomposes without boiling at > 260 °C	Measured
Density	354.8 kg/m^3 at 23 °C	Measured
Vapour Pressure	9.7 × 10^{-2} kPa at 21 °C 1.0 × 10^{-1} kPa at 40 °C	Measured*
Water Solubility	0.0297 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Limited solubility in water; contains no hydrolysable functionalities
Partition Coefficient (n-octanol/water)	log Pow = 0.32 at 20 °C	Measured
Surface tension	63.8 mN/m at 14.5 mg/L at 20 °C 63.5 mN/m at 20 mg/L at 20 °C 59.6 mN/m at 29 mg/L at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 3.3 at pH 1.3 at 25 °C log K_{oc} = 1.3 at pH 5.6 at 25 °C	Measured
Dissociation Constant	Not determined	Contains no dissociable functionalities
Particle Size	< 32 µm; 1.38% < 125 µm: 26.7%	Measured
Flammability	Not flammable	Measured
Flammability in contact with water	Not flammable	Measured
Autoignition Temperature	> 420.5 °C; not pyrophoric	Measured
Explosive Properties	Not explosive	Measured
Oxidising Properties	Not oxidising	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 of 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 as a component of finished cosmetic products at ≤ 0.5% concentration, or it may in the future be imported in the neat form for formulation of 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
Melbourne and Sydney

IDENTITY OF MANUFACTURER
Chimex (France)

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of finished cosmetic products in containers suitable for retail sale in ≤ 500 mL plastic/HDPE bottles or tubes.

USE
The notified chemical will be used as an ingredient in cosmetic products at ≤ 0.5% concentration.

OPERATION DESCRIPTION
The notified chemical will be imported into Australia as a component of finished cosmetic products at ≤ 0.5% concentration, or it may in the future be imported in the neat form for formulation of cosmetic products.

Reformulation
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 at ≤ 0.5% concentration will be used by the public and may also be used by professionals such as hairdressers and workers in beauty salons. Depending on the nature of the product, these could be applied by hand or by using an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and 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 into contact with the notified chemical either in neat form or at various concentrations in cosmetic products (≤ 0.5%), only in the event of an unlikely accidental rupture of containers.

Reformulation
During reformulation into cosmetic products, dermal, ocular and inhalation exposure of workers to the notified chemical at ≤ 100% concentration may occur. Exposure is expected to be minimised through the use of exhaust ventilation and/or automated/enclosed systems as well as through the use of personal protective equipment (PPE) such as coveralls, eye protection, impervious gloves and respiratory protection (as appropriate).

End use
Exposure to the notified chemical in end-use products at ≤ 0.5% 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 exposure is also possible. Inhalation exposure is not expected. 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 at ≤ 0.5% concentration through the use of cosmetic products. The principal route of exposure will be dermal, while accidental oral and ocular exposure (from the use of lip products) is also possible. Inhalation exposure is not expected based on the use pattern and low vapour pressure of the notified chemical.

A combined internal dose of 0.233 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; 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, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 = 3354 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	severely irritating
Guinea pig, skin sensitisation – adjuvant test	evidence of sensitisation (2% challenge)
Guinea pig, skin sensitisation – adjuvant test	limited evidence of sensitisation (2% challenge)
Guinea pig, skin sensitisation – non-adjuvant test	limited evidence of sensitisation (1% challenge)
Guinea pig, skin sensitisation – non-adjuvant test	no evidence of sensitisation (1% challenge)
Human, skin sensitisation – RIPT[1]	no evidence of sensitisation
Human, skin sensitisation – RIPT[2]	no evidence of sensitisation
Human, skin sensitisation – RIPT[3]	no evidence of sensitisation
Human, skin sensitisation – RIPT[4]	no evidence of sensitisation
Human, skin sensitisation – RIPT[5]	no evidence of sensitisation
Human, skin sensitisation – RIPT[6]	no evidence of sensitisation
Human, skin sensitisation – RIPT[7]	no evidence of sensitisation
Ocular acceptance – human volunteers[8]	good acceptance
Ocular acceptance – human volunteers[9]	good acceptance
Rat, repeat dose oral toxicity – 28 days	NOEL = 30 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberration	genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus test	non genotoxic
Genotoxicity – in vivo mammalian erythrocyte micronucleus test	non genotoxic
Genotoxicity – in vivo Unscheduled DNA Synthesis	non genotoxic
Rat, developmental toxicity	maternal LOAEL = 40 mg/kg bw/day developmental NOAEL = 40 mg/kg bw/day
Rat, reproductive and developmental toxicity	reproductive/developmental NOEL = 100 mg/kg bw/day

[1] tested on a facial product containing 0.5% notified chemical (concentration provided by the notifier)

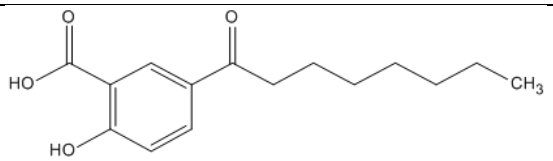
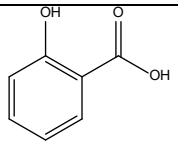
[2] tested on a facial serum product containing 0.5% notified chemical (concentration provided by the notifier)
[3] tested on a cream product containing 0.5% notified chemical (concentration provided by the notifier)
[4] tested on a fluid cream product containing 0.5% notified chemical (concentration provided by the notifier)
[5] tested on a cosmetic product containing 2% notified chemical (concentration provided by the notifier)
[6] tested on a facial powder product containing 2% notified chemical (concentration provided by the notifier)
[7] tested on a deodorant aerosol product containing 2% notified chemical (concentration provided by the notifier)
[8] tested on a facial product containing 0.3% notified chemical (concentration provided by the notifier)
[9] tested on an eye contour product containing 0.3% notified chemical (concentration provided by the notifier)

Toxicokinetics.
No toxicokinetic data on the notified chemical were submitted. Based on the low molecular weight of the notified chemical, absorption across biological membranes may occur. However, dermal absorption may be limited by the relatively low partition coefficient (log Pow = 0.32). This is supported by the low dermal absorption (20%) derived from studies on an analogue of the notified chemical (analogue 1; salicylic acid) (SCCNFP, 2002).

Analogue 1 has similar structure to the notified chemical but has a greater potential for dermal absorption based on its partition coefficient and lower molecular weight. Therefore analogue 1 is considered acceptable to estimate the dermal absorption potential of the notified chemical.

Based on analogue 1, a dermal absorption of 20% is considered a reasonable worst case scenario for exposure calculation purposes (see Section 6.1.2).

Comparison of structural and physicochemical properties of analogue 1 with notified chemical

	Notified Chemical	**Analogue 1**
Chemical Name	Benzoic acid, 2-hydroxy-5-(1-oxooctyl)-	Benzoic acid, 2-hydroxy-
INCI Name	Capryloyl salicylic acid	Salicylic acid
CAS Number	78418-01-6	69-72-7
Structural Formula		
Molecular Weight	264.32 Da	138.12 Da
Water Solubility	2.97×10^{-2} g/L at 20 °C	Slightly soluble in cold water (CIR, 2003)
Partition Coefficient (Log Pow)	0.32	2.25 (CIR, 2003)

Acute toxicity.
The notified chemical is of low acute oral and dermal toxicity based on studies conducted in rats.

Irritation.
The notified chemical is not irritating to the skin but is severely irritating to eyes based on studies conducted in rabbits.

In the skin irritation study no skin reactions were observed during the 72 hour observation period.

In the eye irritation study, diffuse corneal opacity, iridial inflammation and moderate or severe conjunctival irritation were observed in all treated eyes 1 hour after treatment and persisted in 2 treated eyes at the subsequent 24-, 48- and 72-hour observations. One animal was killed for humane reasons following the 72-hour observation. For the remaining animals, irritation effects persisted to the end of the 14-day study period.

Sensitisation.
The skin sensitising potential of the notified chemical has been investigated in guinea pigs (with and without adjuvant) and in human repeat insult patch tests (HRIPT).

In a guinea pig maximisation test (GPMT), the notified chemical (at 0.5% induction concentration; 2% challenge concentration) was found to be a sensitiser with responses noted in 14/20 and 5/20 animals at 24 and 48 hours after patch removal, respectively.

In a second GPMT study, the notified chemical (at 10% induction concentration; 2% challenge concentration) elicited a positive response (responses noted in 5/20 animals at 24 and 48 hours after patch removal); however the response was not sufficient to warrant classification.

In two guinea pig tests without adjuvant (Buehler method), the notified chemical (at 1% induction concentration; 1% challenge concentration) was found not to be a sensitiser. In one study no evidence of reactions indicative of skin sensitisation to the notified chemical were noted whilst in the second study there was only limited evidence with responses noted in 2/20 and 0/20 animals at 24 and 48 hours after patch removal, respectively.

In seven human repeat insult patch tests (HRIPT), four cosmetic product formulations containing 0.5% notified chemical and three cosmetic product formulations containing 2% notified chemical did not elicit a positive response.

Ocular acceptance.
Two formulations each containing 0.3% notified chemical were tested in two separate studies for ocular acceptance by applying to the face and eye contour of human volunteers. The studies showed that the products were well tolerated.

Repeated dose toxicity.
A No Observed Effect Level (NOEL) of 30 mg/kg bw/day was established for the notified chemical in a 28-day repeated dose oral gavage toxicity study in rats, based on treatment related effects in the stomach. Due to the death of 5 animals, the highest dose tested was reduced during the course of this study from 300 mg/kg bw/day to 200 mg/kg bw/day from day 13 onwards. The cause of death was not clear. Hyperplasia of the non-glandular stomach accompanied by chronic inflammation and ulceration was observed in animals dosed at 200/300 mg/kg bw/day. At a dose level of 100 mg/kg bw/day, slight hyperplasia of the non-glandular stomach was observed in one male.

Mutagenicity/Genotoxicity.
The notified chemical was negative in a bacterial reverse mutation assay but positive (in the presence of activation system) in an *in vitro* chromosomal aberration study in Chinese hamster ovary cells. The notified chemical was negative in two *in vivo* mouse micronucleus assays and in an *in vivo* unscheduled DNA synthesis test with mammalian liver cells. Overall, based on the available evidence, the notified chemical is not expected to be genotoxic.

Developmental toxicity.
A No Observed Adverse Effect Level (NOAEL) of 40 mg/kg bw/day was established for the notified chemical in a dermal developmental toxicity study in rats, based on an increase in the incidence of foetuses with incomplete ossification of the sacral neural arch at 100 mg/kg bw/day. The NOAEL was not established for maternal toxicity as treatment related effects (local reaction at the site of administration and reductions in bodyweight gain) were observed at both doses tested.

Reproductive toxicity.
A NOEL of 100 mg/kg bw/day was established for the notified chemical in an oral gavage reproduction/developmental toxicity screening study in rats, based on the absence of treatment related adverse effects at all doses tested.

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

Hazard classification	***Hazard statement***
Skin sensitisation (Category 1)	H317 – may cause an allergic skin reaction
Serious eye damage/eye irritation (Category 1)	H318 – causes serious eye damage

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

R41: Risk of serious damage to eyes
R43: May cause sensitisation by skin contact

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the available information the critical health effects of the notified chemical are as a severe eye irritant and skin sensitiser.

Reformulation

During reformulation workers may be at risk of sensitisation and eye irritation effects when handling the notified chemical at ≤ 100% concentration. It is anticipated by the notifier that engineering controls such as enclosed and automated processes and local ventilation will be implemented where possible and appropriate PPE (coveralls, imperious gloves, eye protection and respiratory protection) will be used to limit workers exposure.

Therefore, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

End-use

Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic products (at ≤ 0.5% concentration) to clients (e.g. hair dressers, workers in beauty salons). Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. 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 products containing the notified chemical.

6.3.2. Public Health

Cosmetic products containing the notified chemical at ≤ 0.5% concentration will be available to the public. The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

Salicylates such as the notified chemical act as exfoliants and as such there are concerns that their repeated use may increase exposure of the dermis and epidermis to UV radiation (CIR, 2003). On the other hand, salicylates are known to absorb UV radiation, which would decrease exposure. However, data is not currently available to determine the balance of these two effects. Therefore in the absence of such evidence, the Cosmetic Ingredient Review Expert Panel recommended that when used in cosmetics, salicylates should be formulated to avoid increased sun sensitivity or, where sun sensitivity would be expected, the daily use of sun protection should be included in the directions for use (CIR, 2003). The U.S. Food and Drug Administration (FDA) advises similar precautions for the use of beta hydroxy acids (BHA) (which include salicylates) in cosmetic products and include avoiding using BHA-containing products on infants and children, and using sun protection if a BHA product is used. The US FDA has also initiated a project to determine the long-term effects of salicylic acid on the skin's response to ultraviolet light.

Irritation

The notified chemical is a severe eye irritant. Eye irritation effects are not expected from use of the notified chemical at the proposed concentrations in cosmetic products.

Sensitisation

A number of animal and human sensitisation studies were provided for the notified chemical and based on the results of one GPMT study the notified chemical is considered a sensitiser.

Proposed methods for the quantitative risk assessment of dermal sensitisation have been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). As is shown in the table below, the Consumer Exposure Level (CEL) from use of the notified chemical in leave-on and rinse-off cosmetic products may be estimated (SCCS, 2012 and Cadby *et al*, 2002). When tested at up to 2% concentration in human repeat insult patch studies, the notified chemical was not a skin sensitiser. Consideration of each of the studies and application of appropriate safety factors, allowed the derivation of an Acceptable Exposure Level (AEL) of

33.33 µg/cm^2. In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (1), a use and time factor (3.16) and a database factor (1), giving an overall safety factor of ~30.

Product type	Proposed usage concentration (%)	CEL (µg/cm^2)	AEL (µg/cm^2)	Recommended usage concentration (%)
Leave-on cosmetics (assumed: fine fragrances)	0.5	18.75	33.33	≤ 0.5
Rinse-off cosmetics (assumed: conditioner)	0.5	0.14	33.33	≤ 0.5

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical at ≤ 0.5% concentration in leave-on (using fine fragrances as a worst case example) and rinse-off cosmetic products (using conditioner as a worst case example) is not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Repeated-dose toxicity
The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products of 0.233 mg/kg bw/day (see Section 6.1.2). Using a NOEL of 30 mg/kg bw/day derived from a 28-day repeated dose oral toxicity study on the notified chemical, the margin of exposure (MOE) was estimated to be 128.7. A MOE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 0.5% concentration in 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 not be manufactured in Australia. The notified chemical will be imported neat for reformulation into cosmetic products, or as a component of finished cosmetic formulations. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills. Accidental spills are unlikely, given the imported product containing the notified chemical will be containerised. In the event of spills, the product containing the notified chemical is expected to be collected with inert material, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated, and is expected to occur within a fully enclosed environment. Therefore, significant release of the notified chemical from this process to the environment is not expected. The process will be followed by automated filling of the formulated products into containers of various sizes suitable for retail. Wastes containing the notified chemical generated during reformulation include equipment wash water, empty import containers, and spilt materials. Wastes may be collected and released to sewers in a worst case scenario, or disposed of to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE
The notified chemical is a component of rinse-off and leave-on cosmetic formulations. The formulated products will be applied to the body, and will either be removed with tissues and disposed of to domestic garbage, or washed off the body with ultimate release to the sewer.

RELEASE OF CHEMICAL FROM DISPOSAL
It is estimated that a maximum of 4%, or up to 40 kg of the notified chemical, may remain in end-use containers once the consumer products are used up. Wastes and residue of the notified chemical in empty containers are likely either to share the fate of the container and be disposed of to landfill, or to be released to sewer when containers are rinsed before recycling, through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic formulations, the majority of the notified chemical is expected to enter the sewer system, before potential release to surface waters nationwide. The notified chemical is not considered readily biodegradable, but shows inherent biodegradability (≥ 64% in 28 days). For details of the environmental fate studies, please refer to Appendix C. Based on its low water solubility and calculated adsorption coefficient (log K_{OC} = 1.3 at pH 5.6), release to surface waters may occur as only partial partitioning to sludge and sediment is expected under environmental pH. The notified chemical is not expected to bioaccumulate due to its low n-octanol/water partition coefficient (log P_{OW} = 0.32) and inherent biodegradability. This is supported by a low bioconcentration factor (BCF = 3.162), calculated using EPI Suite v 4.10 (US EPA, 2011). Therefore, in surface waters the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon.

The majority of the notified chemical will be released to sewer after use. A small proportion of the 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 as collected spills and empty container residue. The notified chemical residues in landfill, soil and sludge are expected to eventually degrade to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

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

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.606	µg/L
PEC - Ocean:	0.061	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 4.039 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the 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 these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 10-16 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 = 26.1 mg/L	Harmful to *Daphnia*
Algal Toxicity	72 h E_rC50 = 75 mg/L	Harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 = 413 mg/L	Not inhibitory to bacterial respiration

Based on the ecotoxicological endpoints for the notified chemical, it is expected to be harmful to fish, daphnids, and algae. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as “Acute Category 3; Harmful to aquatic life”. Based on the acute toxicity, inherent biodegradability, and low bioaccumulation potential of the

notified chemical, it is not expected to be harmful to aquatic life on a long term basis, and is therefore not formally classified under the GHS.

7.2.1. Predicted No-Effect Concentration

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

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish, 96 h)	10	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	100	µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.606	100	**0.006**
Q - Ocean	0.061	100	**0.001**

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 115 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	Determined using Kofler the hot bar method
Test Facility	SEPC (1993a)

Boiling Point Decomposes without boiling at > 260 °C

Method	OECD TG 103 Boiling Point.
Remarks	Differential scanning calorimetry method
Test Facility	Siemens (2010)

Density 354.8 kg/m^3 at 23 °C

Method	EC Directive92/69/EEC A.3 Relative Density.
Remarks	Pycnometer method
Test Facility	SEPC (1993a)

Vapour Pressure 9.7×10^{-2} kPa at 21 °C
1.0×10^{-1} kPa at 40 °C

Method	OECD TG 104 Vapour Pressure.
Remarks	Report in French
Test Facility	INERIS (1994)

Water Solubility 0.0297 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 Europe (1994a)

Partition Coefficient (n-octanol/water) log Pow = 0.32 at 20 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	Stock solution was 20 mg/L instead of the standard 1-100 mg/L due to limited solubility in water of the test substance. Determined using the shake flask method.
Test Facility	Pharmakon Europe (1994b)

Surface Tension 63.8 mN/m at 14.5 mg/L at 20 °C
63.5 mN/m at 20 mg/L at 20 °C
59.6 mN/m at 29 mg/L at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions.
Test Facility	SEPC (1994a)

Adsorption/Desorption – screening test log K_{oc} = 3.3 at pH 1.3 at 25 °C
log K_{oc} = 1.3 at pH 5.6 at 25 °C

Method	OECD TG 121 Adsorption/Desorption (log K_{OC}). EC Council Regulation No 440/2008 C.19 Adsorption/Desorption.
Remarks	HPLC method
Test Facility	Harlan (2011)

Particle Size

Method CIPAC Handbook Volume F, Method MT 59 Sieve Analysis.

Range (μm)	*Mass (%)*
< 32	1.38
32-45	0.06
45-63	2.13
63-75	3.8
75-90	5.85
90-125	13.48
125-250	32.37
> 250	40.92

Remarks Sieve Analysis
Test Facility Dr U Noack (2010)

Flammability Not flammable

Method EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks No ignition was noted and no burning rate could be measured.
Test Facility SEPC (1993b)

Flammability Not flammable

Method EC Directive 92/69/EEC A.12 Flammability in Contact with Water.
Remarks No ignition or development of gas in contact with water
Test Facility SEPC (1993b)

Autoignition Temperature > 420.5 °C; not pyrophoric

Method EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
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 22 to 420.5 °C).
Any ignition during dropping (1 m height) and within 5 minutes of settling also determined.
Test Facility SEPC (1993b)

Explosive Properties Not explosive

Method EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks Determined by heat sensitivity test and mechanical sensitivity test (shock and friction)
Test Facility SEPC (1993b)

Oxidizing Properties Oxidising

Method EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks Tested with mixtures containing the test substance and cellulose at 3:7, 2:3 and 1:1. The burning rates of the test substance/cellulose mixtures were faster than the values of burning rate than the reference mixture barium nitrate/cellulose (60/40%).
Test Facility SEPC (1993b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Sprague-Dawley
- Vehicle: Arachis oil
- Remarks - Method: No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5M/5F	2530	1/10
2	5M/5F	3000	6/10
3	5M/5F	3557	6/10
4	5M/5F	4217	8/10
5	5M/5F	5000	7/10

- LD50: 3354 mg/kg bw
- Signs of Toxicity: Mortalities as indicated in the table above occurred starting from 1 h and up to 13 days post-dose. Typical major signs of toxicity were hunched posture, piloerection, lethargy and hypoventilation with gasping, with isolated signs of ptosis, increased salivation, red/brown stains around snout/mouth, distended abdomen, emaciation, tiptoe gait and pallor of the extremities. Body weight gain was reduced or bodyweight loss occurred in all other than the LD group.
- Effects in Organs: At necropsy, decedents showed haemorrhagic or abnormally red lungs, dark liver or patchy pallor of the liver, pale spleen, pale or dark kidneys, haemorrhagic or sloughing of the glandular gastric epithelium and haemorrhage of the small and/or large intestines. However, no such abnormalities were seen at the necropsy of survivors given test substance at ≥ 3000 mg/kg.
- Remarks - Results: LD50 and 95% confidence limits of the test substance were calculated by a probit method of Finney D. J. to be 3354 (2834-3970) mg/kg bw.

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

TEST FACILITY: Safepharm (1989a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Sprague-Dawley
- Vehicle: None
- Type of dressing: Semi-occlusive
- Remarks - Method: Application site was moistened with Arachis BP oil prior to treatment with test substance.

RESULTS

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

- LD50: > 2000 mg/kg bw

Signs of Toxicity - Local	Oedema, blanching and hard, light brown coloured scabs were noted at the site of application with loss of the upper layers of skin and fur resulting in purple/pink areas.
Signs of Toxicity - Systemic	Clinical signs noted one day after treatment were hunched posture, lethargy and piloerection.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	One male animal showed a small loss in bodyweight over the first week and all other animals showed expected bodyweight gain over the study period.

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

TEST FACILITY Safepharm (1989b)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion (1981).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	Test substance (0.5 g) moistened with distilled water (0.5 mL)
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations

RESULTS The test substance did not cause any skin irritation.

CONCLUSION The notified chemical is non-irritating to the skin.

TEST FACILITY Safepharm (1989c)

B.4. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 405 Acute Eye Irritation/Corrosion (1987).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	14 days
Remarks - Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*[#]	*Maximum Value at End of Observation Period*[#]
	1	2	3			
Conjunctiva: redness	2.7	2.7	2.3	3	> 14 days	1
Conjunctiva: chemosis	2.7	2.7	3	3	> 14 days	1
Conjunctiva: discharge	2.3	2	2	3	< 14 days	0
Corneal opacity	1	1	2.7	3	> 14 days	3
Iridial inflammation	1	1	1	1	> 7 days[+]	?

* Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.
[+] Evaluation of one of the two surviving animals was precluded by corneal opacity and pannus formation at the 14-day observation. The other animal had an iridial inflammation score of 0 at the 14-day observation.
[#] For the 2 animals that survived to the end of the 14-day observation period.

Remarks - Results One animal was killed for humane reasons following 72-hour observation.

CONCLUSION The notified chemical is severely irritating to the eye.

TEST FACILITY Safepharm (1989d)

B.5. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD OECD TG 406 Skin Sensitisation – Magnusson and Kligman Maximisation Test (1981).

Species/Strain Guinea pig/albino Dunkin-Hartley

PRELIMINARY STUDY Maximum Non-irritating Concentration:
intradermal: 1%
topical: 0.5%

MAIN STUDY

Number of Animals Test Group: 20F Control Group: 10F

Vehicle Arachis oil BP

INDUCTION PHASE Induction Concentration:
intradermal: 1%
topical: 0.5%

Signs of Irritation Scattered mild redness (grade 1) or moderate and diffuse redness (grade 2) at application sites 1 hour after patch removal following topical induction were observed. Scattered mild redness was commonly noted at the 24-hour observation. Small superficial scattered scabs at 1 test site precluded accurate assessment of the erythema.

CHALLENGE PHASE

challenge topical: 2%

Remarks - Method No significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	2%	14/20	3/20
Control Group	2%	0/10	0/10

Remarks - Results Positive sensitisation responses (redness grade 1 or 2) were noted at the application sites of 12 test animals at the 24-hour observation, and a further two animals showed haemorrhage of dermal capillaries and oedema at the application sites. Redness (grade 1) persisted in 3 test animals at the 48-hour observation. Desquamation was commonly noted at this time.

No animals in the control group exhibited adverse skin reactions.

Bodyweight gains of animals in the test group were comparable to those observed in the control group animals.

CONCLUSION There was evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY Safepharm (1989e)

B.6. Skin sensitisation

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 406 Skin Sensitisation – Magnusson and Kligman Maximisation Test.

Species/Strain Guinea pig/albino Dunkin-Hartley

PRELIMINARY STUDY	Maximum Non-irritating Concentration: topical: 2%
MAIN STUDY	
Number of Animals	Test Group: 20F Control Group: 10F
Vehicle	Ethanol
Positive control	Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using ethyl para-aminobenzoate.
INDUCTION PHASE	Induction Concentration: intradermal: 0.5% topical: 10%
Signs of Irritation	Not reported
CHALLENGE PHASE	
challenge	topical: 2%
Remarks - Method	No significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	2%	5/20	5/20
Control Group	2%	0/10	0/10

Remarks - Results	Positive sensitisation responses were noted at the application sites of 5 test animals at the 24-hour and 48-hour observation. No animals in the control group exhibited adverse skin reactions.
CONCLUSION	There was limited evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Toxicol (1993)

B.7. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation – Buehler Method.
Species/Strain	Guinea pig/albino Dunkin-Hartley (1992)
PRELIMINARY STUDY	Maximum Non-irritating Concentration: topical: 10%
MAIN STUDY	
Number of Animals	Test Group: 20F Control Group: 10F
Vehicle	PEG 300
INDUCTION PHASE	Induction Concentration: topical: 25%
Signs of Irritation	Several test animals exhibited erythema scores of 2 or more at the application site. Due to the severity of skin reaction after the first application, the concentration of the test substance was reduced to 15% for the second application, and then, to 10 % for the last application.
CHALLENGE PHASE	
challenge	topical: 5%
Remarks - Method	No significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	5%	2/20	0/20

Control Group	5%	0/10	0/10

Remarks - Results: Positive sensitisation responses were noted at the application sites of 2 test animals at the 24-hour observation. No positive responses were noted at the 48-hour observation.

No animals in the control group exhibited adverse skin reactions.

CONCLUSION: There was limited evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: Toxicol (1995)

B.8. Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 406 Skin Sensitisation – Buehler Method.
- Species/Strain: Guinea pig/albino Dunkin-Hartley (1992)
- PRELIMINARY STUDY: Non-irritating Concentration: topical: 1%
- MAIN STUDY
  - Number of Animals: Test Group: 10M/10F Control Group: 5M/5F
  - Vehicle: 0.5% aqueous methylcellulose
  - Positive control: Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using 2,4-dinitro chlorobenzene.
- INDUCTION PHASE: Induction Concentration: topical: 1%
  - Signs of Irritation: None was noted.
- CHALLENGE PHASE
  - challenge: topical: 1%
- Remarks - Method: No significant protocol deviations.

RESULTS

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

Remarks - Results: One animal was found dead on Day 18, but microscopic examination revealed no apparent abnormalities. None of the other animals showed any clinical signs; body weight gains were comparable to the control group animals. None of the test animals showed any skin reaction during the induction or challenge phase. In the positive control group, positive response was observed in 3/10 animals.

No animals in the control group exhibited adverse skin reactions.

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

TEST FACILITY: CIT (1998)

B.9. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation (face product) containing 0.5% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.02 mL test substance were applied 3 times per week (Tuesday, Thursday and Saturday) for a total of 9 applications. Patches were removed after 48 hours (or 72 hours for patches applied on Saturday) and sites were graded 15-20 minutes after removal of the patches. Rest Period: 13 days Challenge Procedure: Patches containing 0.02 mL test substance was applied to the treated site and a naïve site for 48 hours. A patch alone was applied to a naïve site under the same conditions to act as a negative control. Sites were graded at least 30 minutes and about 48 hours after removal of the patches.
Study Group	97 F, 13 M; age range 18-70 years
Vehicle	None
Remarks - Method	Occluded. Patch contact area: 50 mm^2.
RESULTS	
Remarks - Results	106/110 subjects completed the study. Of the subjects that withdrew, 2 withdrew prior to the first reading, 1 withdrew during the induction and 1 withdrew during the rest period. No withdrawals were related to the application of the test substance. Only slight irritation was noted in few subjects at induction and at the first reading of challenge. No adverse responses were noted at the final reading.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	IEC (2008)

B.10. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation (cosmetic product) containing 2% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 mL test substance were applied 3 times per week (Tuesday, Thursday and Saturday) for a total of 9 applications. Patches were removed after 48 ± 4 hours (or 72 ± 4 hours for patches applied on Saturday) and sites were graded 15-30 minutes after removal of the patches. Rest Period: 13 days Challenge Procedure: Patches containing 0.2 mL test substance was applied to the treated site and a naïve site for 48 ± 4 hours. A patch alone was applied to a naïve site under the same conditions to act as a negative control. Sites were graded 30-35 minutes and about 48 ± 4 hours after removal of the patches.
Study Group	92 F, 17 M; age range 20-64 years
Vehicle	None
Remarks - Method	Semi-occluded. Patch contact area: 4 cm^2.
RESULTS	
Remarks - Results	102/109 subjects completed the study. No withdrawals were reported to be related to the application of the test substance. Only slight irritation was noted in few subjects at induction and at the first

reading of challenge. No adverse responses were noted at the final reading.

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

TEST FACILITY IEC (2009)

B.11. Skin sensitisation – human volunteers

TEST SUBSTANCE Formulation (face serum product) containing 0.5% notified chemical

METHOD Repeated insult patch test with challenge

Study Design Induction Procedure: Patches containing 0.02 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed after 48 hours and sites were graded just prior to the application of the next patch.

Rest Period: 10-14 days
Challenge Procedure: Patches containing 0.02 mL test substance was applied to the treated site and a naïve site for 48 hours, followed by site evaluation and scoring. Additional evaluations were conducted at 72 hours and 96 hours post-application.

Study Group 89 F, 23 M; age range 19-70 years

Vehicle None

Remarks - Method Occluded. Patch contact area: 50 mm^2.

RESULTS

Remarks - Results 105/112 subjects completed the study. No withdrawals were related to the application of the test substance.

No adverse responses were noted during the induction phase or at challenge.

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

TEST FACILITY CRL (2010a)

B.12. Skin sensitisation – human volunteers

TEST SUBSTANCE Formulation (face powder product) containing 2% notified chemical

METHOD Repeated insult patch test with challenge

Study Design Induction Procedure: Patches containing 0.02 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed after 48 hours and sites were graded just prior to the application of the next patch.

Rest Period: 10-14 days
Challenge Procedure: Patches containing 0.02 mL test substance was applied to the treated site and a naïve site for 48 hours, followed by site evaluation and scoring. Additional evaluations were conducted at 72 hours and 96 hours post-application.

Study Group 89 F, 23 M; age range 19-70 years

Vehicle None

Remarks - Method Occluded. Patch contact area: 50 mm^2.

RESULTS

Remarks - Results 105/112 subjects completed the study. No withdrawals were related to the application of the test substance.

No adverse responses were noted during the induction phase or at

challenge.

CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2010b)

B.13. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation (cream product) containing 0.5% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	No details were provided in the report. It was stated that the study was performed according to L'Oreal general protocol, reference RSL-SEC-01/E (June 2002) and to the specific dispositions relating to the test products and the study.
Study Group	101 F, 7 M; age range 20-59 years
Vehicle	None
Remarks - Method	Occluded. Patch contact area: 50 mm^2. 0.02 mL applied.
RESULTS	
Remarks - Results	104/108 subjects completed the study. No withdrawals were related to the application of the test substance. No adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	EVIC (2009a)

B.14. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation (fluid cream product) containing 0.5% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	No details were provided in the report. It was stated that the study was performed according to L'Oreal general protocol, reference RSL-SEC-01/E (June 2002) and to the specific dispositions relating to the test products and the study.
Study Group	95 F, 13 M; age range 19-56 years
Vehicle	None
Remarks - Method	Occluded. Patch contact area: 50 mm^2. 0.02 mL applied.
RESULTS	
Remarks - Results	106/108 subjects completed the study. No withdrawals were related to the application of the test substance. No adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	EVIC (2009b)

B.15. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation (deodorant aerosol product) containing 2% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.02 mL test substance were

	applied 9 times over 3 consecutive weeks. Patches were removed after 48 hours and sites were graded just prior to the application of the next patch. Rest Period: minimal 2 weeks Challenge Procedure: Patches containing 0.02 mL test substance was applied to the treated site and a naïve site for 48 hours, followed by site evaluation and scoring. A patch alone was applied to a naïve site under the same conditions to act as a negative control. Additional evaluations were conducted at 48 hours and 96 hours post-application.
Study Group	76 F, 32 M; age range 19-65 years
Vehicle	None
Remarks - Method	Occluded. Patch contact area: 50 mm^2.

RESULTS

Remarks - Results	103/108 subjects completed the study. No withdrawals were related to the application of the test substance. No adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	EVIC (2013)

B.16. Ocular Acceptability – human volunteers

TEST SUBSTANCE	Formulation (face product) containing 0.3% notified chemical
METHOD	In-house
Study Design	The test substance was applied to the face and eye contour of subjects twice a day for 4 weeks. Observations were recorded before application and at least 10 minutes after the first application and the last application respectively. Investigations made included functional signs, biomicroscopic examination of ocular and peri-ocular structures, colorimetric examination of the cornea and the conjunctiva, tear film break-up time measurement, contact lenses examination and interrogation about the potential cutaneous signs appeared. The subjects also answered a questionnaire before the last application.
Study Group	54 F, age over 30 years old, presenting all types of skin including 50% of sensitive skin, including at least 20 subjects with sensitive eyes, at least 10 subjects with non-sensitive eyes and at least 20 contact lenses wearers
Vehicle	None

RESULTS

Remarks - Results	49/54 subjects completed the study. 5/54 subjects didn't meet criteria, lost to follow-up or withdrew based on reasons unrelated to the application of the test substance. Functional signs: the test substance induced mechanical ocular signs of moderate intensity for average 2 minutes in 1 subject with sensitive eyes, discomfort palperbral signs of slight intensity for average 0.08 minutes in 1 subject with sensitive eyes and cutaneous signs of slight intensity for average 10.71 minutes in 5 subjects, with low frequencies for the kind of product. Biomicroscopic examination: no appearance of ocular physical signs or palpebral physical signs was noted. Tear film break-up time measurement: the test substance decreased the tear film stability but didn't decrease the ocular surface defense abilities.

	Colorimetric examination revealed a maximal corneal index of 0.50% and a maximal conjunctival index of 0.00%, showing an absence of toxicity to the conjunctiva and a very slight toxicity to the cornea. Contact lenses examination: the test substance did not alter the contact lenses and did not induce any pathology specific to contact lenses wearers. An ocular irritation rate of 0.03% and an ocular comfort rate of 99.83% were revealed at the clinical examinations.
CONCLUSION	The test substance presented good ocular comfort, ocular safety, global ocular tolerance, palpebral tolerance, compatibility with the contact lenses and obtained good appreciation of cosmetic acceptability under the conditions of the test.
TEST FACILITY	Peritesco (2008a)

B.17. Ocular Acceptability – human volunteers

TEST SUBSTANCE	Formulation (eye contour product) containing 0.3% notified chemical
METHOD	In-house
Study Design	The test substance was applied to the face and the eye contour of the subjects twice a day for 4 weeks. Observations were recorded before application and at least 10 minutes after the first application and the last application respectively. Investigations made included functional signs, biomicroscopic examination of ocular and peri-ocular structures, colorimetric examination of the cornea and the conjunctiva, tear film break-up time measurement, contact lenses examination and interrogation about the potential cutaneous signs appeared. The subjects also answered a questionnaire before the last application.
Study Group	53 F, Asian, age range 30-55 years, presenting all types of skin, including at least 20 subjects with sensitive eyes, at least 10 subjects with non-sensitive eyes and at least 20 contact lenses wearers
Vehicle	None
RESULTS	
Remarks - Results	50/53 subjects completed the study. 1/53 subject lost to follow-up and 2/53 subjects were removed from the study due to wither did not correspond to inclusion criteria anymore or the test substance was not applied in sufficient quantity. Functional signs: the test substance did not induce any palperbral functional signs. The test substance induced ocular burning of moderate intensity for average 3.7 minutes in 1 subject with sensitive eyes and ocular stinging of slight intensity in 1 subject wearing contact lenses, with low frequencies for the kind of product. Biomicroscopic examination: the test substance did not induce any other ocular physical signs but 2 bilateral occcurrences of bulbar conjunctival redness in 2 subjects at the final observation. The test substance did not induce any palpebral physical signs. Tear film break-up time measurement: the test substance did not significantly modify the tear film stability. Colorimetric examination revealed a maximal corneal index of 0.00% and a maximal conjunctival index of 0.00%, showing an absence of toxicity to the conjunctiva and a very slight toxicity to the cornea.

	Contact lenses examination: the test substance did not alter the contact lenses and did not induce any pathology specific to contact lenses wearers. An ocular irritation rate of 0.04% and an ocular comfort rate of 99.88% were revealed at the clinical examinations.
CONCLUSION	The test substance presented good ocular comfort, ocular safety, global ocular tolerance, palpebral tolerance, compatibility with the contact lenses and obtained very good appreciation of cosmetic acceptability under the conditions of the test.
TEST FACILITY	Peritesco (2008b)

B.18. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/CRL:CD(SD)BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 2 weeks
Vehicle	None
Remarks - Method	Minor deviations were not considered to have affected the outcome of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10M, 10F	0	0/20
low dose	5M, 5F	10	0/10
mid dose 1	5M, 5F	30	0/10
mid dose 2	5M, 5F	100	0/10
high dose	10M, 10F	300/200*	5/20
control recovery	5M, 5F	0	0/10
high dose recovery	5M, 5F	0	0/10

* Dose level reduced from 300 mg/kg to 200 mg/kg from Day 13 due to deaths and adverse clinical signs.

Mortality and Time to Death

All (5) deaths occurred in the high dose group. At the dose level of 300 mg/kg, 2 male animals were found dead on Day 2 and Day 9 respectively and 1 male animal was killed in extremis on Day 12. After the dose level was reduced to 200 mg/kg on Day 13, 2 female animals were skill in extremis on Day 15 and Day 16 respectively.

Clinical Observations

No treatment-related clinical signs or adverse effects on body weight gains were noted in the low dose and mid dose 2 groups.

Treatment-related clinical signs including rough coat, piloerection and post-dose salivation were noted in all animals of the high dose group mainly during the first half of the treatment period. Rough coat and piloerection were also noted in animals of mid dose 2 on Day 2 and Day 3 of the treatment period. Noisy respiration was noted in decedent animals prior to death and in 1 mal animal and 1 female animal of the high dose group on Day 15 and Day 16 respectively.

A slight reduction in body weight gain was noted in male animals of the high dose group and in female animals of the mid dose 2 group, correlating with a slight reduction in food consumption. A reduction in body weight gain was also noted in male animals of the high dose recovery group (correlating with a slight reduction in food

consumption) and a slight increase was noted in female animals of the same group.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No treatment-related effects in blood chemistry and haematology were recorded.

Effects in Organs
No significant changes in organ weights for all animals. No treatment related macroscopic or microscopic findings were noted in the low dose and mid dose 2 groups.

A dose-related increase in abnormalities of the stomach (abnormal shape, colour and consistency) was noted in both male and female animals of the mid dose 2 and high dose groups, which was still present in some animals following the recovery period.

Hyperplasia of the non-glandular stomach was noted in both male and female animals of the high dose group, accompanied by chronic inflammation and ulceration. Similar but less severe hyperplastic lesions were noted in 1 male animal of the mid dose 2 and in all animals of the high dose recovery group.

Remarks – Results
Statistically significant changes in blood chemistry were within the normal range found in the testing facility and were not considered by the study authors to be treatment-related. Other macroscopic or microscopic abnormalities were within the normal range of background alterations. The cause of mortality was not established.

CONCLUSION
The No Observed Effect Level (NOEL) was established as 30 mg/kg bw/day in this study, based on treatment related effects in the stomach at the higher doses tested (100 mg/kg bw/day and 300/200 mg/kg bw/day).

TEST FACILITY Toxicol (1994a)

B.19. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA1538, TA98, TA100, TA98 *E. coli*: WP2uvrA
Metabolic Activation System	S9 mix from β-naphthoflavone/sodium phenobarbitone induced rat liver
Concentration Range in Main Test	Experiment 1 a) With metabolic activation: 1.6-1000 µg/plate b) Without metabolic activation: 1.6-1000 µg/plate Experiment 2 a) With metabolic activation: 0.16-100 µg/plate b) Without metabolic activation: 0.32-200 µg/plate
Vehicle	Ethanol
Remarks - Method	A dose range-finding study was carried out at 1.6-5000 µg/mL. The dose selection for the main experiments was based on toxicity observed in the range-finding study. Positive controls: With metabolic activation: 2-aminoanthracene Without metabolic activation: sodium azide (TA1535, TA100); 9-aminoacridine (TA1537); 2-nitrofluorene (TA1538, TA98); 4-nitroquinoline-1-oxide (WP2uvrA)

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*

Absent				
Test 1	> 200	> 40	not reported	negative
Test 2		> 20	not reported	negative
Present				
Test 1	> 200	> 40	not reported	negative
Test 2		> 20	not reported	negative

Remarks - Results: In both tests, no increases in the frequency of revertant colonies were obtained in the presence or absence of metabolic activation.

The results from the positive controls confirmed the validity of the test.

CONCLUSION: The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY: Toxicol (1994b)

B.20. Genotoxicity – in vitro

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Chinese hamster
Cell Type/Cell Line: Ovary cells
Metabolic Activation System: S9 mix from β-naphthoflavone/sodium phenobarbitone induced rat liver
Vehicle: Ethanol
Remarks - Method: A dose range-finding study was carried out at 4 – 4000 µg/mL. The dose selection for the main experiments was based on toxicity observed in the range-finding study.

Vehicle and positive controls (mitomycin C and cyclophosphamide) were run concurrently with the notified chemical.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	5*,25*,50*	not reported	not reported
Test 2	4*,20*,40*, 80*	not reported	not reported
Present			
Test 1	5*,25*,50*	not reported	not reported
Test 2	4*,20*,40*, 80*	not reported	not reported

*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	> 4	> 50[1] / > 25[2]	not reported	negative
Test 2		> 40[1] / > 4[2]	not reported	negative
Present				
Test 1	> 40	> 50[1] / > 25[2]	not reported	positive[1]
Test 2		> 80[1] / > 4[2]	not reported	positive[1]

[1] Results of the 1st harvest
[2] Results of the 2nd harvest

Remarks - Results: Exposure and harvest times were not reported.

In Test 1, statistically significant increases in chromosome aberrations were observed at 50 µg/mL in the presence of metabolic activation at the first harvest. However the actual frequency was within the background for this cell line.

As the degree of inhibition of mitotic index was not achieved at the top dose in first test, a higher dose was added to the second test.

In Test 2, statistically significant increases in chromosome aberrations were observed at 80 µg/mL in the presence of metabolic activation at the first harvest. In this case the actual frequency was above the background for this cell line.

No statistically significant increases in chromosome aberrations were observed in the absence of activation system.

The results of the positive controls confirmed the validity of the test system.

CONCLUSION

The notified chemical was clastogenic to Chinese hamster ovary cells treated in vitro under the conditions of the test.

TEST FACILITY

Toxicol (1994c)

B.21. Genotoxicity – in vivo

TEST SUBSTANCE

Notified chemical

METHOD

Similar to OECD TG 474 Mammalian Erythrocyte Micronucleus Test.

Species/Strain: Mouse/CD1 outbred

Route of Administration: Oral – gavage

Vehicle: 0.5% aqueous carboxymethylcellulose

Remarks - Method: A dose range-finding study was carried out at 50 – 1000 mg/kg bw. The dose selection for the main experiments was based on toxicity observed in the range-finding study.

Toxicity was indicated by the ratio of polychromatic erythrocytes (PCEs) and normochromatic erythrocytes (NCEs) and clastogenic response was indicated by the relevant increase of micronucleated PCEs.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
vehicle control 1	5M/5F	0	24 h
vehicle control 2	5M/5F	0	48 h
vehicle control 3	5M/5F	0	72 h
low dose 1	5M/5F	250	24 h
low dose 2	5M/5F	250	48 h
low dose 3	5M/5F	250	72 h
mid dose 1	5M/5F	500	24 h
mid dose 2	5M/5F	500	48 h
mid dose 3	5M/5F	500	72 h
high dose 1	5M/5F	1000	24 h
high dose 2	5M/5F	1000	48 h
high dose 2	5M/5F	1000	72 h
positive control, MC	5M/5F	A single intraperitoneal injection of 0.4 mg/kg	24 h

MC = mitomycin C

RESULTS

Doses Producing Toxicity: No mortality or clinical signs were reported in the range-finding and main

	tests. Analysis of the PCE/NCE ratio for the treatment group and control group revealed evidence of toxicity to the erythroid stem cells of bone marrow 24 hours after dosing at 1000 mg/kg.
Genotoxic Effects	There were no statistically significant increases in the frequency of micronucleated PCEs.
Remarks - Results	The positive and negative controls gave a satisfactory response confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo mammalian erythrocyte micronucleus test.
TEST FACILITY	Toxicol (1994d)

B.22. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test (1997).
Species/Strain	Mouse/Swiss CD1
Route of Administration	Oral – gavage
Vehicle	0.5% aqueous carboxymethylcellulose
Remarks - Method	Toxicity was indicated by the ratio of polychromatic erythrocytes (PCEs) and normochromatic erythrocytes (NCEs) and clinical observations and clastogenic response was indicated by the relevant increase of micronucleated PCEs. A preliminary toxicity study was carried out in which 2 male and 2 female animals were dosed once at 2000 mg/kg bw and observed for 48 hours. Following treatment one animal died and all animals showed reduced activity. An increase in the ratio of NCE/PCE was observed in the females only. The dose selection for the main experiment was based on these results.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
vehicle control 1	5M/5F	0	24 h
vehicle control 2	5M/5F	0	48 h
low dose	5M/5F	500	24 h
mid dose	5M/5F	1000	24 h
high dose 1	5M/5F	2000	24 h
high dose 2	5M/5F	2000	48 h
positive control, MC	5M/5F	3	24 h

MC = mitomycin C

RESULTS	
Doses Producing Toxicity	Two female animals and 1 male animal were found dead 24 hours after treatment in the high dose group. These 3 animals were substituted with reserve animals. Piloerection was noted in all animals on the day of treatment in the mid-dose group. Piloerection and swollen abdomen and dirty urogenital region in one male animal were noted in the high-dose group. A slight increase in the PCE/NCE ratio was observed in the high-dose male group only at the 24 hour sampling time, indicating inhibitory effect on erythropoietic cell division. This accompanied by the observation of clinical signs was taken to indicate that the test substance had reached the bone marrow.
Genotoxic Effects	There were no statistically significant increases in the frequency of micronucleated PCEs.
Remarks - Results	The positive and negative controls gave a satisfactory response confirming the validity of the test system.

CONCLUSION The notified chemical was not clastogenic under the conditions of this in vivo mammalian erythrocyte micronucleus test.

TEST FACILITY RTC (2001)

B.23. Genotoxicity – in vivo

TEST SUBSTANCE Notified chemical

METHOD OECD TG 486 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo.
Species/Strain Rats/Sprague Dawley
Route of Administration Oral – gavage
Vehicle 0.5% aqueous carboxymethylcellulose
Remarks - Method Doses were selected on the results of a preliminary toxicity test that showed no signs of toxicity up to 2000 mg/kg bw.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
Test 1			
vehicle control	4 M	0	14
low dose	4 M	500	14
mid dose	4 M	1000*	14
high dose	4 M	2000*	14
positive control (2-AAF)	4 M	100*	14
Test 2			
vehicle control	4 M	0	2
low dose	4 M	500	2
mid dose	4 M	1000*	2
high dose	4 M	2000*	2
positive control (MNU)	4 M	80*	2

2-AAF = 2-acetamidofluorene; MNU = methylnitrosourea
* Doses selected for scoring

RESULTS
Doses Producing Toxicity No mortality or clinical signs were seen.
Genotoxic Effects Treatment with the test substance did no produce a group mean net grain value greater than -0.88 and no more than 6% of the cells were found in repair.
Remarks - Results The positive and negative controls gave a satisfactory response confirming the validity of the test system.

CONCLUSION The notified chemical was not clastogenic under the conditions of this in vivo mammalian erythrocyte micronucleus test.

TEST FACILITY RTC (2000)

B.24. Developmental toxicity

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 414 Prenatal Development Toxicity Study.
Species/Strain Rat/Sprague-Dawley
Route of Administration Dermal
Exposure Information Exposure days: day 6 through to day 15 of gestation
Duration of exposure: 6 hours/day
Post-exposure observation period: day 16 through to day 20 of gestation
Vehicle PEG 300
Remarks - Method No significant protocol deviations. The dose selection was based on the results from a preliminary study (not provided).

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
Control	24F	0	0/24
Low dose	24F	40	0/24
High dose	24F	100	0/24

Effects on Dams

Daily clinical observations during the gestation period did not reveal any treatment-related clinical signs of systemic toxicity.

In the low-dose group, slight to moderate erythema was noted during the dosing and immediate post-dosing period. Eschar formation and/or desquamation at the application site was noted in 9/24 animals towards the end of the post-dosing period. For the majority of animals irritation effects were noted from day 6 of the treatment period to day 18 of pregnancy (3 days post-dose). Also slight oedema was noted in 2/24 animals for 4-6 days during the late dosing and immediate post-dosing periods.

In the high-dose group, slight to severe erythema with slight eschar formation and very slight oedema was noted during the dosing and post-dosing period.

Statistically significant reductions in mean body weight gain were noted in both treatment groups. No effect was seen on the mean maternal body weight and mean maternal food consumption.

There were no treatment-related abnormalities at necropsy with exception for scabbing and/or reddening at the application site for all animals in the high-dose group.

No treatment-related effects on the pregnancy data.

Effects on Foetus

No treatment-related effects were seen on the mean foetal weight, incidences of major abnormalities and number of foetuses with one or more minor external and visceral abnormalities.

A high overall incidence of minor abnormalities was noted in the high dose group, which was considered by the study authors to be mainly due to the high incidence of incomplete ossification of the sacral neural arch. Although the abnormality was noted at a high incidence in all groups including the control group without statistically significant differences, treatment attribution to the abnormality was not completely ruled out.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) for developmental toxicity was established as 40 mg/kg bw/day, based on an increase in the incidence of foetuses with incomplete ossification of the sacral neural arch at 100 mg/kg bw/day.

The NOAEL was not established for maternal toxicity as treatment related effects (local reaction at the site of administration and reductions in bodyweight gain) were observed at both doses tested.

TEST FACILITY Quintiles (1996)

B.25. Toxicity to reproduction – one generation study

TEST SUBSTANCE Notified chemical

METHOD OECD TG 412 Reproduction/Developmental Toxicity Screening Test

Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Exposure period - female: 2 weeks before mating until 4 days after lactation Exposure period - male: 2 weeks before mating until 22-35 days after last day of mating

Vehicle	PEG 300
Remarks – Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
Control	10M/10F	0	0/20
Low dose	10M/10F	10	0/20
Mid dose	10M/10F	30	0/20
High dose	10M/10F	100	0/20

Effects on Parental (P) animals:
No treatment-related adverse effects were seen.

Effects on 1st Filial Generation (F1)
No treatment-related adverse effects were seen.

CONCLUSION
The No Observed Effect Level (NOEL) was established as 100 mg/kg bw for reproductive/developmental toxicity in this screening study, based on an absence of treatment-related adverse effects.

TEST FACILITY Bioagri (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 D Ready Biodegradability: Closed Bottle Test.
Inoculum	River water sampled 3 km downstream of a local domestic wastewater treatment plant (Heveadorp, The Netherlands)
Exposure Period	28 days
Auxiliary Solvent	Dichloromethane
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	Ammonium chloride was omitted from the test medium to prevent oxygen consumption due to nitrification. The deviation from protocol was not deemed to have had a significant impact on the validity or integrity of the study. All other validity criteria were met and satisfied.

RESULTS

Test substance		*Sodium acetate*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0
7	6	7	81
14	43	14	87
21	50		
28	64		

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium acetate, surpassed the threshold level of 60% by 7 days (81%) and reached 87% degradation by 14 days. Therefore, the test indicates the suitability of the inoculums. The notified chemical attained 64% degradation by 28 days, but failed the 10-day window (< 50%). A degradation plateau was not achieved by 28 days. Therefore, the notified chemical cannot be classified as readily biodegradable according to the OECD (301D) guideline. However, the notified chemical exhibited inherent, primary biodegradability.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Akzo Nobel (2012)

C.1.2. Inherent biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 302 B Inherent Biodegradability: Zahn-Wellens/EMPA Test.
Inoculum	Activated sludge from a municipal domestic sewage treatment plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Chemical Oxygen Demand (COD)
Remarks – Method	No significant deviation in protocol.

RESULTS

Test substance		*Diethylene glycol*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0

10	58	10	100
21	100	21	100
24	100	24	100
28	90	28	100

Remarks – Results

During the test period, the lowest temperature recorded was 19.5 °C, which fell below the minimum 20 °C stated in the protocol. The lowest pH of the test solutions recorded were 6.31 for the control group, and 6.38 for the reference group, which fell outside of the pH 6.5-8.0 range stated in the protocol. The pH was readjusted with 1N NaOH. Neither deviation in protocol was deemed to have had a significant impact on the validity or integrity of the study. All other validity criteria for the test were met and satisfied.

The percentage degradation of the reference compound, diethylene glycol, surpassed the threshold level of 70% by 10 days and reached complete degradation (100%). Therefore, the test indicates the suitability of the inoculums.

The notified chemical attained 90% degradation by 28 days. Therefore, the notified chemical is classified as inherently biodegradable according to the OECD (302B) guideline.

CONCLUSION

The notified chemical is inherently biodegradable.

TEST FACILITY

SEPC (1995)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 203 Fish, Acute Toxicity Test – Static.
EC Council Regulation No 440/2008 C.1 Acute Toxicity for Fish – Static.

Species	*Brachydanio rerio* (zebra fish)
Exposure Period	96 hours
Auxiliary Solvent	Ethanol
Water Hardness	90 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	Following the range finding test (conducted at nominal concentrations of 1, 5, 10, 50, and 100 mg/L of the notified chemical), the definitive test was conducted at nominal concentrations of 3.9, 6.3, 10.0, 16.0, 25.6, and 41.0 mg/L of the notified chemical due to its low water solubility. No significant deviation in protocol.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*3.5 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	10	0	0	0	0	0
3.9	3.444	10	0	0	0	0	0
6.3	5.430	10	0	0	0	0	0
10.0	7.613	10	0	0	0	0	0
16.0	14.12	10	0	60	100	100	100
25.6	19.78	10	50	100	100	100	100
41.0	42.14	10	100	100	100	100	100

LC50	10-16 mg/L at 96 hours.
NOEC (or LOEC)	Not determined

Remarks – Results	Two fish were measured to be larger than the 3.5 cm stated in the protocol (3.7 cm for both). The 41.0 mg/L test medium showed 100% mortality after 3 h 30 min, and was not sampled prior to elimination from the study. Neither deviation in protocol was deemed to have had a significant impact on the validity or integrity of the study. All other validity criteria for the test were met and satisfied. The test solutions were not renewed during the 96 h test period. The actual concentrations of the test substance were measured by Pharmakon Europe at 96 hours (or when the sample was eliminated from the study following 100% mortality). The 96 h LC50 for fish was determined to be 10-16 mg/L, based on measured concentrations.
CONCLUSION	Under the study conditions, the notified chemical is considered to be toxic to fish on an acute basis.
TEST FACILITY	SEPC (1994b)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE

METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static. EC Council Regulation No 440/2008 C.2 Acute Toxicity for Daphnia – Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	180 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	Following the range finding test (conducted at nominal concentrations of 1, 10, 50, 100, and 250 mg/L of the notified chemical), the definitive test was conducted at nominal concentrations of 10, 15, 22, 33, and 50 mg/L of the notified chemical due to its low water solubility. No significant deviation in protocol.

RESULTS

Concentration mg/L			*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*			*24 h*	*48 h*
	0 h	*48 h*			
Control	Control	Control	20	0	0
10	9.779	9.113	20	0	0
15	14.76	14.54	20	0	0
22	21.54	19.46	20	5	35
33	31.63	32.15	20	5	70
50	43.48	39.61	20	80	100

EC50	43.4 mg/L at 24 hours 26.1 mg/L at 48 hours
NOEC (or LOEC)	Not determined
Remarks - Results	One litre of dilution water contained 200 mL deionised water instead of distilled water. The highest pH value was recorded as 8.4, which fell outside of the pH 7.6-8.2 range stated in the protocol. Neither deviation in protocol was deemed to have had a significant impact on the validity or the integrity of the study. All other validity criteria for the test were met and satisfied. The actual concentrations of the notified chemical were measured by

Pharmakon Europe at 0 and 48 hours within the 48 h test period. The test solutions were not renewed during the 48 h test period. The 48 h EC50 for daphnids was determined to be 21.6 mg/L, based on measured concentrations.

CONCLUSION Under the study conditions, the notified chemical is considered to be harmful to daphnids on an acute basis.

TEST FACILITY SEPC (1994c)

C.2.3. 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	
Exposure Period	72 hours
Concentration Range	Nominal: 25-262 mg/L Actual: 21.44-244.4 mg/L
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	HPLC
Remarks - Method	Following the range finding test (conducted at nominal concentrations of 1, 10, 50, 100, and 250 mg/L of the notified chemical), the definitive test was conducted at nominal concentrations of 25, 45, 81, 146, and 262 mg/L of the notified chemical. No significant deviation in protocol.

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 72 h	*NOE_bC*	*E_rC50 mg/L at 72h*	*NOE_rC*
Not determined	Not determined	75 (95% CL 62-91)	45

Remarks - Results All validity criteria for the test were satisfied. The actual concentrations of the notified chemical were measured by Pharmakon Europe at 0 and 72 hours within the 72 h test period. The test solutions were not renewed during the 72 h test period. The 72 h E_rC50 and NOE_rC were determined to be 75 (95% CL 62-91 mg/L) and 45 mg/L, respectively, based on measured concentrations.

CONCLUSION Under the study conditions, the notified chemical is considered to be harmful to algae on an acute basis.

TEST FACILITY SEPC (1994d)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.
EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test

Inoculum	Aerated activated sludge from a synthetic sewage feed.
Exposure Period	3 hours
Concentration Range	Nominal: 10-1000 mg/L Actual: Not determined
Remarks – Method	No significant deviation in protocol.

RESULTS	
IC50	413 mg/L (95% CL 394-434 mg/L) at 3 hours
NOEC	179 mg/L (95% CL 161-195 mg/L) at 3 hours
Remarks – Results	All validity criteria for the test were satisfied. No inhibitory effects were observed at concentrations up to 100 mg/L, however 35 and 91% inhibition were observed at 320 and 1000 mg/L of the notified chemical, respectively. The 3 h EC50 was determined to be 413 mg/L, based on nominal concentrations. The notified chemical is not considered to be inhibitory to sludge microbial activity.
CONCLUSION	The notified chemical is not inhibitory to microbial activity.
TEST FACILITY	Harlan (2010)

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