File No: LTD/1854

October 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1-Tetradecanol, 1-benzoate

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

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1854	Guthy-Renker Australia Pty Ltd	1-Tetradecanol, 1-Benzoate	ND*	≤ 1 tonne/s per annum	Cosmetic ingredient

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

The environmental hazard classification according to the *Globally Harmonised System 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 Toxicity (Category 3)	H402 - Harmful to aquatic life

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

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable risk to public health.

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced or in the product lauryl/myristyl benzoate (Corum 5014):
  - Enclosed and automated processes
  - Exhaust ventilation

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced, or in the product lauryl/myristyl benzoate (Corum 5014):
  - Avoid contact with eyes

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced, or in the product lauryl/myristyl benzoate (Corum 5014):
  - Coveralls

- Eye protection
- Impervious gloves
- Respiratory protection

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

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

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

Disposal

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

Emergency procedures

- Spills and/or accidental release of the notified chemical should be handled by physical containment, collection and 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;

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Guthy-Renker Australia Pty Ltd (ABN: 20 078 330 180)
Level 2
3 Rider Boulevard
Rhodes, NSW 2138

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: 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: all physico-chemical endpoints

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Corum 5014 (containing the notified chemical at < 70%)
Lauryl/Myristyl Benzoate (containing the notified chemical at < 70%)

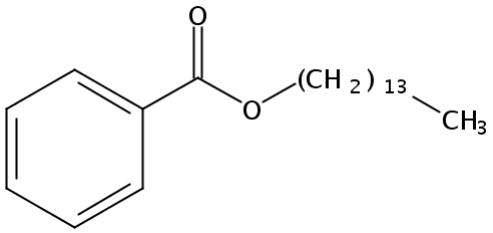
CAS NUMBER
70682-72-3

CHEMICAL NAME
1-Tetradecanol, 1-Benzoate

OTHER NAME(S)
Myristyl Benzoate

MOLECULAR FORMULA
$C_{21}H_{34}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
318.50 Da

ANALYTICAL DATA
A reference IR spectrum was provided.

3. COMPOSITION

DEGREE OF PURITY
> 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Clear liquid (when in the raw material Lauryl/Myristyl Benzoate)

Property	Value	Data Source/Justification
Cloud Point[1]	2 °C	(M)SDS
Boiling Point	386 °C	Calculated (QSAR)
Density	930 kg/m^3 at 20 °C	Analogue data[2]
Vapour Pressure	2.85×10^{-7} kPa at 25 °C	Calculated (QSAR)
Water Solubility	9.3×10^{-7} g/L at 20 °C	Calculated (QSAR)
Hydrolysis as a Function of pH	Not determined	The notified chemical contains hydrolysable functionalities. However, no significant hydrolysis is expected to occur in the environmental pH range of 4 – 9.
Partition Coefficient (n-octanol/water)	log Pow = 8.21	Calculated (QSAR)
Adsorption/Desorption	log K_{oc} = 5.401	Calculated (QSAR)
Dissociation Constant	Not determined	The notified chemical does not contain any functional groups that are expected to dissociate in water
Flash Point[1]	214 °C	(M)SDS
Flammability	Not determined	Introduced as an aqueous solution
Autoignition Temperature	Not determined	Introduced as an aqueous solution
Explosive Properties	Not determined	Not expected to be explosive based on chemical structure.
Oxidising Properties	Not determined	Not expected to be an oxidiser based on chemical structure.

[1]For the imported raw material Lauryl/Myristyl Benzoate containing the notified chemical at < 70% concentration in aqueous solution
[2]Based on Benzoic Acid $C_{12\text{-}15}$ Alkyl Esters

DISCUSSION OF PROPERTIES

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 in Australia. It will be imported as the raw material at > 90% concentration, or as a component of the product Corum 5014 (at < 70% concentration in an aqueous solution) for formulation of cosmetic products. The notified chemical will also be imported as a component of finished cosmetic products (at ≤ 10% concentration).

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
Corum Inc. (overseas)

TRANSPORTATION AND PACKAGING
The notified chemical will be transported at > 90% concentration or as a component of the product Corum 5014 (at < 70% concentration) in 190 kg steel drums. The containers will be packed on pallets and transported by sea. The notified chemical may also be imported as a component of finished cosmetic products at ≤ 10% concentration. Finished cosmetic products containing the notified chemical will be packaged in ≤ 500 mL plastic bottles or tubes for retail sale. These containers will be packaged in cartons and pallets for transport by sea.

USE
The notified chemical will be used as an ingredient in cosmetic products, hairspray and deodorant aerosols at concentrations up to 10%.

OPERATION DESCRIPTION
The notified chemical will be imported in its raw form (at > 90% concentration) or as a component of the product Corum 5014 (at < 70% concentration) for formulation of cosmetic products, or as a component of finished cosmetic products (at ≤ 10% concentration) which will be sold to the public in the same form in which they are imported.

Reformulation
When reformulated, the notified chemical (at > 90% concentration), or as a component of the product Corum 5014 (containing the notified chemical at < 70% concentration) will be blended into end-use consumer products at reformulation 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 reformulation process. Automated processes may include mixing and filling of end-use containers with finished products.

End-use
Finished products containing the notified chemical at ≤ 10% 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 (Dispensing and Capping)	8	12
Store persons	4	12
End Users	8	365

EXPOSURE DETAILS
Transport, storage and retail workers may come into contact with the notified chemical at > 90% concentration, as a component of the product Corum 5014 (at < 70% concentration) or at ≤ 10% concentration in cosmetic products only in the event of accidental rupture of packages.

Reformulation
During reformulation into cosmetic products, dermal, ocular and inhalation exposure of workers to the notified chemical at > 90% 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 ≤ 10% concentration may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. workers in beauty salons). The principal route of exposure will be dermal, while ocular exposure is also possible. Such professionals may use some PPE to minimise repeated exposure, but this is not expected to occur in all workplaces. However, good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

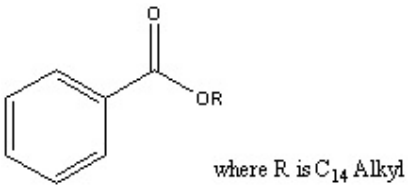
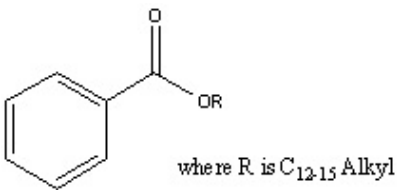
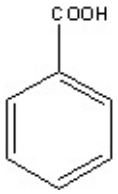
6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical at ≤ 10% concentration through the use of cosmetic products. The principal route of exposure will be dermal. Accidental ocular and oral exposure (from the use of lip products) is also possible. Inhalation exposure is not expected based on the use pattern and low vapour pressure of the notified chemical.

A combined internal dose of 25.05 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

No toxicity data were submitted for the notified chemical. Two analogues of the notified chemical listed below were proposed for the purposes of human health effects assessment. Analogue 1 shares similar structure and physicochemical properties to the notified chemical, and both the notified chemical and analogue 1 share analogue 2 (benzoic acid) as a metabolite. Analogue 1 and Analogue 2 are therefore considered acceptable to be used in the assessment.

Comparison of structural and physicochemical properties of analogue chemicals with the notified chemical:

	Notified Chemical	*Analogue 1*	*Analogue 2*
Chemical Name	1-Tetradecanol, 1-Benzoate	Benzoic acid, C_{12-15} Alkyl Esters	Benzoic acid
INCI Name	None	C_{12-15} Alkyl Benzoate	Benzoic Acid
CAS Number	70682-72-3	68411-27-8	65-85-0
Structural Formula	 where R is C_{14} Alkyl	 where R is C_{12-15} Alkyl	
Molecular Weight	318.5 Da	290.44 - 332.52 Da	122.13 Da
Water Solubility	9.3×10^{-7} g/L at 25 °C (calc.)	9.0×10^{-6} g/L (CIR, 2012)	2.9 g/L (SCCP, 2005)
Partition Coefficient (Log Pow)	8.21 (calc.)	7.23 (CIR 2012)	1.88 (SCCP, 2005)

The results from toxicological investigations conducted on the product lauryl/myristyl benzoate (containing the notified chemical at < 70% concentration) and Analogue 1 are summarised in the following table. Analogue 1 and the notified chemical are considered to be very similar in chemical composition and therefore the endpoints presented below are likely to reflect the toxicity of the notified chemical.

Details of the provided studies of lauryl/myristyl benzoate and analogue 1 can be found in Appendix A.

Endpoint	*Result and Assessment Conclusion*	*Test Substance*
Rat, acute oral toxicity (× 2)	LD50 ≥ 5000 mg/kg bw; low toxicity	Analogue 1
Mouse, acute oral toxicity	LD50 > 5000 mg/kg bw; low toxicity	Analogue 1
Rabbit, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity	Analogue 1
Rat, acute inhalation toxicity	LC50 > 50 mg/L/4 hour; low toxicity	Analogue 1
Skin irritation (human)	non-irritating	Notified chemical (70%)
Skin irritation (*in vitro*)	non-irritating	Analogue 1
Rabbit, skin irritation (× 2)	non-irritating	Analogue 1
Eye irritation (*in vitro*)	non-irritating	Analogue 1
Rabbit, eye irritation (CPT 1978)	non-irritating	Analogue 1
Rabbit, eye irritation (EviC 1994)	slightly irritating	Analogue 1
Guinea pig, skin sensitisation –non-adjuvant test	no evidence of sensitisation	Analogue 1 (10%)
Human, skin sensitisation – RIPT	no evidence of sensitisation	Analogue 1 (20%)
Human, skin sensitisation – RIPT	no evidence of sensitisation	Analogue 1 (16%)
Human, skin sensitisation – RIPT	no evidence of sensitisation	Analogue 1 (16%)
Mutagenicity – bacterial reverse mutation	non mutagenic	Analogue 1

Toxicokinetics, metabolism and distribution
No toxicokinetic data on the notified chemical were submitted.

Alkyl benzoates such as the notified chemical and analogue 1 are expected to share similar structure activity relationships and biological functions as they are all metabolised and excreted via a common pathway ('Becker 2012, OECD 2005). Lauryl/Myristyl Benzoate (containing the notified chemical at < 70%) and analogue 1 (Benzoic acid, C_{12-15} Alkyl Esters) are metabolised to benzoic acid and the corresponding alcohols, before being further metabolised to benzyl glucuronide and benzoyl CoA (intermediate in the formation of hippuric acid). The notified chemical may similarly undergo metabolism by the oral and dermal route.

Dermal absorption
Dermal absorption of the notified chemical is expected to be limited given the estimated high lipophilicity (Log P_{OW} = 8.21) limiting penetration of the hydrophilic epidermis.

The *in vitro* skin penetration of Analogue 1 using pig skin was tested at a concentration of 100% in compliance with OECD TG 428. The mean total systemically available dose was determined as 3.76% of the applied dose. The *in vitro* skin penetration of analogue 1 using pig skin was also tested in the formulations of a sun lotion containing analogue 1 at ≤ 9% concentration, a baby cream containing analogue 1 at ≤ 6% concentration and a sun-protection spray containing analogue 1 at ≤ 7% concentration. The mean total systemically available dose of analogue 1 was 1.15%, 2.55% and 1.85% of the applied dose with a mean recovery of 89.6%, 87.73% and 95.03% in the sun lotion, baby cream and sun-protection spray respectively. However, the study authors indicated that based on the non-representativeness and small sample sizes, the two studies should be considered as a trend (see Appendix A for details).

In a study on frozen and fresh pig skin (referenced in 'Becker *et al*., 2012), Analogue 1 was not detected in the receptor fluid, with 50.76% recovered in the skin, and 34.04% still on the skin.

The Cosmetic Ingredient Review Panel ('Becker *et al*., 2012) indicated that alkyl benzoates with partition coefficient values > 8 are not expected to leave the stratum corneum and reach the epidermis. The CIR concluded alkyl benzoates such as analogue 1 are poorly absorbed through the skin and are therefore not likely to cause systemic toxicity.

Based on the above considerations, the notified chemical is not expected to significantly penetrate the skin and enter the systemic circulation. Therefore, a conservative dermal absorption value of 10% was applied for

exposure calculation purposes, with the exception of lip products where an absorption value of 100% was applied (see Section 6.1.2).

Acute toxicity
The notified chemical is expected to have a low acute oral, dermal and inhalation toxicity based on studies conducted using analogue 1 and other alkyl benzoates.

Irritation
Corum 5014 (containing the notified chemical at < 70% concentration) is not irritating to the skin based on a study conducted in human volunteers. Analogue 1 is not irritating to the skin based on studies conducted on rabbits and in an *in vitro* study conducted using a reconstituted Human Epidermis model (EpiDerm^{TM}). Alkyl benzoates are not expected to be irritating to the skin ('Becker *et al*., 2012).

A 14 day, repeat-dose dermal study was conducted on 10 rabbits. Two doses of analogue 1 (62% and 100% concentration) were applied to each animal. Well-defined erythema was observed from day 1 of the study (1/10 animals) and this effect was maintained, or increased in severity to severe erythema over the course of the study. Very slight to slight oedema was also observed in all animals over the course of the study. Negative control sites (mineral oil) also exhibited very slight to well-defined erythema and oedema over the course of the study. Skin damage was observed (fissures and scaling) in all animals. However, the presence of these effects did not seem to correlate with the severity of the erythema or oedema. No clear dose-response reaction was observed, although sites exposed to neat analogue 1 (100%) tended to show earlier onset of effects when compared to those sites exposed to 62% concentration.

Analogue 1 is slightly irritating to the eyes based on a study conducted in rabbits. Discharge, slight to diffuse redness and chemosis were recorded in the test animals but all recovered within 6 days. No iridial inflammation or corneal opacity were recorded in any of the animals. In another study on rabbits and in an *in vitro* test using the EpiOcular corneal model, analogue 1 has been observed as non-irritating to the eyes.

Sensitisation
Analogue 1 showed no evidence of being a skin sensitiser when tested up to 10% concentration on guinea pigs. In three human repeat insult patch tests (HRIPT), analogue 1 showed no evidence of sensitisation when tested up to 20% concentration, or for an end-use product (lipstick) containing the analogue at 16% concentration. Other alkyl benzoates and benzoic acid (analogue 2) are not expected to be dermal sensitisers (OECD 2001, 'Becker *et al*., 2012).

Repeated dose toxicity
Information on repeat-dose studies is available for analogue 2. At high doses, an increase in mortality, reduced weight gain, liver and kidney effects were observed. NOAEL values of short- and long-term studies (via oral, dermal and inhalation routes) were generally found to be in agreement. The OECD SIDS report (2001) concluded that benzoic acid (and its salts) exhibits very low repeated dose toxicity. A NOAEL of 800 mg/kg bw/day for the analogue was reported in the conclusion.

Mutagenicity/Genotoxicity
Analogue 1 has been found to be negative in a bacterial reverse mutation assay. In addition, the Cosmetic Ingredient Review Panel ('Becker *et al*., 2012) found that alkyl benzoates are not expected to be genotoxic. The OECD SIDS review (2001) also reported, that based on weight-of-evidence, the data available indicated that benzoic acid (analogue 2) was not expected to mutagenic or clastogenic.

Overall, based on the available information, the notified chemical is not expected to be genotoxic.

Reproductive and developmental toxicity
There are no studies available for the notified chemical (or analogue 1) in respect to reproductive and developmental toxicity. A study on isononyl benzoate (structurally similar to the notified chemical) did not exhibit reproductive and developmental toxicity and a NOAEL of 1,000 mg/kg bw/day has been estimated for this chemical ('Becker *et al*., 2012).

Reproductive toxicity information is available for analogue 2 (benzoic acid) which is a potential metabolite of the notified chemical. In an oral teratogenicity study in hamsters, there was an increase in the number of resorptions (≥ 30 mg/kg bw/day) and foetal malformations (> 600 mg/kg bw/day). Two oral studies in rats produced negative results at up to 500 mg/kg bw/day. No effects on reproduction were observed in a 5

generation study on crossbred white mice where animals were administered with 40 mg/kg bw/day benzoic acid for 8 months prior to breeding. The OECD SIDS Panel (2001) concluded that the benzoates studied (including benzoic acid) exhibit no developmental toxicity and established a NOEL of 500 mg/kg bw/day. This NOEL of 500 mg/kg bw/day was used to estimate the margin of exposure (MoE) for the notified chemical.

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

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available information for both the notified chemical and analogues, the notified chemical is expected to be of low hazard presenting only as a slight eye irritant. The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure.

Reformulation
During reformulation workers may be at risk of eye irritation effects when handling the notified chemical at > 90% concentration. This risk should be reduced through the expected use of engineering controls and personal protective equipment (PPE) including eye protection.

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
Workers involved in professions where the services provided involve the application of cosmetic products containing the notified chemical to clients (*e.g.*, hairdressers and beauty salon workers) may be exposed to the notified chemical at concentrations up to 10%. If PPE is used, the risk to these workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical (for details of the public health risk assessment, see Section 6.3.2).

6.3.2. Public Health
Cosmetic products containing the notified chemical at ≤ 10% 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.

Local effects
The notified chemical is not expected to be irritating to the skin or have potential to be a skin sensitiser based on studies on analogue chemicals. The notified chemical may be irritating to the eyes based on an *in vitro* study performed using analogue 1. The greatest risk of eye irritation effects may be through the use of cosmetic products containing the notified chemical. However, based on other *in vitro* studies on analogues, the notified chemical is not expected to have irritating effects at the proposed use concentration in cosmetic and aerosol products (≤ 10%).

Systemic effects
Analogue 2, benzoic acid, is a potential metabolite of the notified chemical. As such, it is reasonable to anticipate the presence of benzoic acid in the system, should exposure to the notified chemical occur. The NOEL of 500 mg/kg bw/day estimated for benzoic acid is therefore considered as appropriate to represent a worst case scenario for the notified chemical. This NOEL of 500 mg/kg bw/day was also applied by the Scientific Committee on Consumer Products to evaluate margin of safety values in their 2005 Opinion paper (SCCP 2005) on benzoic acid and sodium benzoate.

Based on the above consideration, the repeat dose toxicity potential of the notified chemical was estimated by calculation of the MoE using the worst case scenario from use of multiple products resulting in combined internal dose of 2.964 mg/kg bw/day (see Section 6.1.2) and the NOEL of 500 mg/kg bw/day based on the recommendation of the OECD SIDS Panel (2001) for reproductive/developmental effects of analogue 2. A MoE of 168.7 was therefore estimated for the notified chemical. MoE value ≥ 100 is considered acceptable for the notified chemical to account for intra- and inter-species differences.

Overall, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 10% in cosmetics and aerosol 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. It will be imported in neat form for formulation into cosmetic products or as a component of finished cosmetics. There is unlikely to be any significant release to the environment from storage and transport, except in the case of accidental spills. Accidental spills are unlikely, given the imported product will be containerised. If spills do occur, the product containing the notified chemical is expected to be collected with inert material and disposed of in accordance with local regulations.

The reformulation process will involve blending operations that will be highly automated and are expected to occur in a fully enclosed environment. Therefore, a 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. Wastes, which contain the notified chemical, generated during reformulation include equipment washings, empty import containers and spilt materials. The wastes may be collected and released to sewers for the worst case scenario.

RELEASE OF CHEMICAL FROM USE

The notified chemical is a component in rinse-off and leave-on cosmetic products. The formulated product will be applied to body parts 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

Wastes and residue of the notified chemical in empty containers (3%) is likely either to share the fate of the container and be disposed of to landfill, or to be washed to sewer when containers are rinsed before recycling.

7.1.2. Environmental Fate

No environmental fate data was submitted. The products containing the notified chemical are expected to be readily biodegradable based on a biodegradation study provided for an acceptable analogue. Therefore, the notified chemical is expected to rapidly biodegrade and is not expected to persist in the environment. Following its use in cosmetic products, the majority of the notified chemical is expected to enter the sewer before potential release to surface waters on a nationwide basis. Based on its low water solubility, some of the notified chemical is expected to partition to sludge. The notified chemical has low potential to bioaccumulate and it is not expected to be significantly bioavailable in the aquatic environment due to its low water solubility. In surface waters, the notified chemical is expected to disperse and degrade through biotic and abiotic processes to form water and oxides of carbon. A proportion of notified chemical may be applied to land when treated sewage effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill. Notified chemical residues in landfill and soil are not expected to be mobile based on its low water solubility, and are expected to degrade to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated assuming a worst case scenario of 100% release of the notified chemical into sewer systems nationwide and no removal from STPs.

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

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 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 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 20.2 µg/kg and 40.4 µg/kg, respectively.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the analogue chemical of the notified chemical are summarised in the table below.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 46 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 > 100 mg/L	Not harmful to aquatic invertebrates
Inhibition of Bacterial Respiration	3 h EC50 > 1000 mg/L	Not expected to inhibit microbial respiration

Based on the toxicities for the analogue chemical, the notified chemical is considered to be harmful to fish and not harmful to aquatic invertebrates. Under the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS; United Nations, 2009) the notified chemical is harmful to aquatic organisms and is formally classified as Acute Category 3: Harmful to aquatic life. Based on the level of acute toxicity, ready biodegradability and lack of potential for bioaccumulation of the notified chemical, it has not been formally classified under the GHS for long term toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) for the notified chemical has been calculated and is presented in the table below. The PNEC is calculated based on the endpoint for the most sensitive species (fish, LC50) for an analogue chemical. An assessment factor of 1000 has been used as acute toxicity endpoints for analogue chemical has been reported.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Fish).	46	mg/L
Assessment Factor	1,000	
Mitigation Factor	1	
PNEC:	46	µg/L

7.3. Environmental Risk Assessment

The Risk Quotients (Q = PEC/PNEC) for a worst case discharge scenario have been calculated to be < 1 for the river and ocean compartments.

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	0.61	46	0.013
Q - Ocean:	0.06	46	0.001

The risk quotient for discharge containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its reported use pattern and annual introduction quantity. The notified chemical is expected to be readily biodegradable; therefore it is not expected to persist in surface waters, air or soils. In the aquatic environment it is unlikely to bioaccumulate based on its low water solubility. Therefore, on the basis of the PEC/PNEC ratio, maximum annual import volume and the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: TOXICOLOGICAL INVESTIGATIONS

A.1. Acute toxicity – oral (1)

TEST SUBSTANCE: Analogue 1

METHOD: Similar to OECD TG 401 Acute Oral Toxicity.
- Species/Strain: Rat/Albino
- Vehicle: None
- Remarks - Method: Animals were provided with a single dose of test substance at 5,000 mg/kg bw by oral gavage. Animals were observed and recordings made at 1, 3, 6 and 24 hours and then daily to the end of the observation period (14 days). Surviving animals were then necropsied.

No GLP statement provided.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 M, 5 F	5,000	0/10

- LD50: > 5,000 mg/kg bw
- Signs of Toxicity: No mortalities were recorded. All animals gained the expected amount of body weight.
- Effects in Organs: The spleen appeared enlarged in 9/10 animals (4/5 M and 5/5 F).
- Remarks - Results: No other adverse effects were recorded.

CONCLUSION: The test substance is of low toxicity via the oral route.

TEST FACILITY: CPT (1978)

A.2. Acute toxicity – oral (2)

TEST SUBSTANCE: Analogue 1

METHOD: Similar to OECD TG 420 Acute Oral Toxicity
- Species/Strain: Rat/Wistar
- Vehicle: None
- Remarks - Method: Animals were dosed with the test substance by oral gavage at the doses described in the sighting study and main study below. Animals were observed and recordings made at 1, 3, 6 and 24 hours post-dose and then daily to the end of the observation period (14 days). Animals in the sighting study were dosed at the same time. Surviving animals were then necropsied.

No GLP statement provided

RESULTS

Sighting Study

Dose mg/kg bw	*Administered*	*Evident Toxicity*	*Mortality*
40,000	Oral gavage	Slight depression, matted hair	0/1
25,000	Oral gavage	Slight depression, matted hair	0/1
10,000	Oral gavage	Slight depression, matted hair	0/1
5,000	Oral gavage	None	0/1
3,000	Oral gavage	None	0/1
1,000	Oral gavage	None	1/1
500	Oral gavage	None	0/1

Signs of Toxicity

All animals made satisfactory weight gains. One animal treated at 1,000 mg/kg bw died at day 13. However, no signs of toxicity were recorded prior to death.

Animals dosed with the three highest amounts exhibited non-continuous observations of slight depression from 1 to 3 hours post-exposure (with recovery by day 7) as well as moist, matted hair at all post-exposure observations from 1 to 4 days (with recovery by day 5).

The authors did not consider the animal death at dose 1,000 mg/kg bw to be treatment related.

Effects in Organs

The animal that died on day 13 (M; 1000 mg/kg bw dose) had fibrous tissue encasing the heart and lungs.

Main Study

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	3 M, 3 F	30,000	0/6
2	3 M, 3 F	33,000	4/6
3	3 M, 3 F	37,000	5/6
4	3 M, 3 F	40,000	4/6

Discriminating Dose

5,000 mg/kg bw

Signs of Toxicity

All animals exhibited slight to severe depression from 1 hour post-exposure through to the end of the observation period, except for 3/6 in Group 1 and surviving 2 animals in Group 2 which showed recovery on day 14.

Loss in body weight was recorded for 13/24 animals (1/6, Group 1; 4/6 Group 2; 5/6, Group 3; 3/6, Group 4).

Moist and/or matted hair was observed in all animals at various times commencing between 1 and 24 hours, with full recovery in all animals by days 7 - 8. Matted, unkempt hair was also observed in Groups 2 and 3 (3/6 and 5/6 respectively). Marked to significant hair loss was observed in 6/24 animals but a dose-response relationship was not evident. Near complete hair loss was observed in 1/6 animals in each of Groups 2 and 3.

Effects in Organs

One animal in Group 1 exhibited consolidated lung tissue, and this was also observed in 1/6 animals in Group 2 where the lung tissue was also enlarged. One animal in Group 3 exhibited firm spherical lesions (0.5 - 2 cm diameter), some containing yellow white pus in the lobes of the lung. No lung effects were recorded in Group 4 animals

A crust-like substance covering the skin was recorded in 2/6 animals in Group 2 and small scabs covering the dorsum (1/6; Group 2) and on the ventrum (1/6; Group 3) were also observed. No skin effects were recorded in Group 4 animals.

Some animals in Groups 2, 3 and 4 exhibited slight to severely reddened pyloric and intestinal mucosa (1/6, 3/6 and 2/6 respectively), with one animals in Group 2 exhibiting distended and gas filled pyloric and intestinal mucosa.

No gross changes or gross internal changes were observed in 3/24 animals (Group 4) or 11/24 animals (5/6 Group 1; 4/6 Group 2; 1/6 Group 3; 1/6 Group 4) respectively.

Remarks - Results

Of the 11 animals that survived to the end of the observation period, 6 showed recovery from the effects of the treatment (3 from Group 1; 2 from

Group 2 and 1 from Group 3). Of the 13 animals that died, the earliest mortality was recorded on day 2 in Groups 3 and 4 (1 M, 1 F and 1 F respectively) and day 4 in Group 2 (1 F). The latest recorded death was on day 12 (1 M, Group 3).

No clear dose-response relationships were observed for the effects observed.

The authors did not indicate if the effects observed were due to the treatment regime or the test substance.

CONCLUSION The test substance is of low toxicity via the oral route; however, high dose above 10,000 mg/kg bw may cause adverse effects.

TEST FACILITY CPT (1979a)

A.3. Acute toxicity – oral (3)

TEST SUBSTANCE Analogue 1

METHOD Similar to OECD TG 401 Acute Oral Toxicity.
Species/Strain Mice/NMRI EOPS
Vehicle None
Remarks - Method 5 female mice were provided with a single dose of test substance at 5,000 mg/kg bw. Animals were observed for 6 days post-exposure.

No GLP statement provided.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Mortality*
1	5 M, 5 F	5,000	0/10

LD50 > 5,000 mg/kg bw
Signs of Toxicity No mortalities were recorded. All animals gained a satisfactory amount of body weight.
Effects in Organs No description provided
Remarks - Results No clinical or behavioural anomalies observed.

CONCLUSION The test substance is of low toxicity via the oral route.

TEST FACILITY EViC (1991)

A.4. Acute toxicity – dermal

TEST SUBSTANCE Analogue 1

METHOD Similar to OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain Rabbit/Albino
Vehicle None
Type of dressing Occlusive
Remarks - Method Test substance was applied to abraded (Group 1) or non-abraded (Group 2) skin (trunk) of each animal and then encased in a sleeve of plasticized material for 24 hours. Skin was washed after the exposure period.

No GLP statement provided.

RESULTS

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

LD50	2,000 mg/kg bw
Signs of Toxicity - Local	Very slight to well-defined erythema and oedema was observed 24 hours after exposure (plastic sleeve removed). No other adverse or gross changes were observed
Signs of Toxicity - Systemic	One animal died (1 M, Group 1) on day 13. Body weight losses were recorded in the animal that died and the 2 females in Group 2. However, the loss was significant in only one of these females. The remaining three animals made satisfactory body weight gains.
Effects in Organs	None recorded
Remarks - Results	Test summary did not include a description or explanation regarding the death of one animal.

CONCLUSION The test substance is of low toxicity via the dermal route.

TEST FACILITY CPT (1979a)

A.5. Acute toxicity – inhalation

TEST SUBSTANCE Analogue 1

METHOD Similar to OECD TG 403 Acute Inhalation Toxicity.

Species/Strain	Rat/Wistar
Vehicle	None
Method of Exposure	Whole-body exposure
Exposure Period	1 hour
Physical Form	Liquid aerosol
Remarks - Method	Animals were placed in a three-cub-foot plastic chamber for a single, 1 hour dynamic exposure period. The chamber was initially charged with 200 mg/L of test substance. The nominal chamber concentration was continued over the exposure period using preconditioned supportive air supplied at 5 L/min with the test substance presented from a compressor activated generator or timer operated solenoid. Animals were observed daily for 14 days post-exposure. No GLP statement provided.

RESULTS

Group	*Number and Sex of Animals*	*Concentration mg/L Nominal*	*Mortality*
1	5 M, 5 F	200	1/10

LC50	> 200 mg/L/1 hour
Signs of Toxicity	Slight depression was observed in all animals 1 hour post-exposure, with full recovery at 3 hours post-exposure.
Effects in Organs	All lobes of the right lung were enlarged and consolidated in the 1 animal that died. No gross changes were observed in the surviving 9 animals.
Remarks - Results	One animal died on Day 9 of the post-exposure period. All surviving animals gained the expected body weight over the observation period. No other adverse effects were recorded. To determine a GHS classification, the LC50 value for 1 hr exposure was converted to that expected for a 4 hr exposure, by dividing by a factor of 4. This gave an LC50 value of 50 mg/L/4 hour.

CONCLUSION	The test substance is of low toxicity via inhalation.
TEST FACILITY	CPT (1979b)

A.6. Skin irritation – human volunteers

TEST SUBSTANCE	Corum 5014 (containing the notified chemical at < 70%)
METHOD	Single Patch Test
Study Design	Internal test. No equivalent OECD Test Guideline available
Study Group	22 F; age range 22 - 60 years
Vehicle	None
Remarks - Method	Semi-occluded patch test. The test substance was spread on a 4 cm^2 patch and applied to the external face of the arm. Patches were applied once for 48 hours. The tested skin areas were examined 30 min, 24 and 48 hours after patch removal and scored based on the extent of erythema and/or oedema using a system similar to that for the Draize test. An acute irritation index (M.I.I.) was calculated by summing the scores for each test subject and dividing the total score by the number of test subjects. Negative controls (patch applied without product) were run concurrently. Test is a qualitative assessment only. No GLP statement provided.
RESULTS	
Remarks - Results	No evidence of erythema or oedema was recorded in any of the test subjects. No other evidence of irritation was observed
CONCLUSION	The test substance (containing the notified chemical at < 70% concentration) was non-irritating to the skin under the conditions of the test.
TEST FACILITY	Dermascan (2010)

A.7. Irritation – skin (*in vitro*)

TEST SUBSTANCE	Analogue 1
METHOD	Similar to OECD TG 439 *In Vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method: EpiDerm™ Skin irritation Test Model
Vehicle	Not described
Remarks - Method	MatTek EpiDerm™ Skin Model used. The test substance (100 µL) at 100% and 10% concentrations were applied to the tissues in triplicate. Following 2, 4 and 18 hour exposure periods (at 37 °C, 5% carbon dioxide, ≥ 90% humidity), the tissues were rinsed twice with phosphate buffered saline (PBS) and then incubated with MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) for 3 hours at 37 °C (5% carbon dioxide, ≥ 90% humidity). Following overnight extraction at room temperature, the optical densities were determined (570 nm). Positive control samples (1% Triton X-100) were applied to the tissues in triplicate and exposed for the same periods as those used for the test substance. Six replicates of the negative control (corn oil) were applied to tissues and exposed for 4 hours only.

The test substance was considered by the study authors to be an irritant if the ET_{50} value (exposure time required to reduce cell viability by 50%) was < 24 hours.

Quality Assurance statement included

RESULTS

Test material	*Exposure period (hours)*	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*ET_{50} Value (hours)*
Negative control	4	1.331	100	-
Test substance (100%)	2	1.586	119	> 24
	4	1.459	110	
	18	1.291	97	
Test substance (10%)	2	1.551	117	> 24
	4	1.369	103	
	18	1.200	90	
Positive control	2	0.986	74	6
	4	1.016	76	
	18	0.152	11	

OD = optical density; SD = standard deviation

Remarks - Results: Tissue viability after exposure to the test substance at neat or 10% concentration was not reduced to ≤ 50% in any of the exposure periods.

The negative control performed within the acceptability range described in TG 439 for EpiDerm™ skin irritation test method.

The positive control performed as expected.

CONCLUSION: The test substance was non-irritating to the skin at 100% concentration under the conditions of the test.

TEST FACILITY: CPT (1998a)

A.8. Irritation – skin (1)

TEST SUBSTANCE: Analogue 1

METHOD: Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain: Rabbit/New Zealand White
Number of Animals: 6 (males and females)
Vehicle: None
Observation Period: 72 hour
Type of Dressing: Occlusive.
Remarks - Method: Test substance was applied to abraded and non-abraded skin of trunk of each animal. Test substance (0.5 mL) was applied to skin under a 2 $inch^2$ gauze patch covered by adhesive tape. Entire trunk of animal was covered with impermeable occlusive wrapping. Exposure period was 24 hours. Erythema and oedema scores were made at 24 and 72 hours. Scoring was based on the Draize method (1944).

No GLP statement provided.

RESULTS
Remarks - Results: None of the animals exhibited erythema or oedema in the presence of the test substance on non-abraded skin. One animal exhibited very slight erythema on an abraded test site at the 24 hour observation and recovered during the 72 hour observation. No other adverse effects were recorded in any of the animals (including controls).

CONCLUSION	The test substance is non-irritating to the skin.
TEST FACILITY	CPT (1978)

A.9. Irritation – skin (2)

TEST SUBSTANCE	Analogue 1
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Vehicle	Unknown
Observation Period	72 hr
Type of Dressing	Not provided
Remarks - Method	No GLP statement provided. Summary report only provided.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0	0.3	1	< 48 hr	0
Oedema	0	0	0	0	-	-

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

Remarks - Results	Very slight to slight erythema was observed in all animals 1 hr post exposure, persisting in one animal at 24 hr. Very slight oedema was observed in 2/3 animals 1 hr post exposure with none observed at 24 hr. All adverse effects were reversed within 48 hr.
CONCLUSION	The test substance is non-irritating to the skin.
TEST FACILITY	EviC (1991)

A.17. Repeat dermal irritation study

TEST SUBSTANCE	Analogue 1
METHOD	Not specified
Species/Strain	Rabbit/New Zealand
Route of Administration	Dermal –non-occluded
Exposure Information	Total exposure days: 14 days Dose regimen: 7 days per week Duration of exposure (dermal): Not described Post-exposure observation period: 1 day
Vehicle	Corn oil
Remarks - Method	Each animal had 4 application sites, two test sites (application of 0.5 ml of 62% and 100% solution of test substance) and two control sites (application of 0.5 mL of mineral oil and isopropyl myristate). Test sites were scored prior to each application and 24 hours after the last application. Quality Assurance statement provided.

RESULTS

Group	*Number and Sex of Animals*	*Dose (% test substance)*	*Mortality*
low dose	5 M, 5 F (4 test sites for each animal)	62	0/10
high dose		100	
Mineral oil		-	
Isopropyl myristate		-	

Mortality and Time to Death
No animals died during the study period.

Clinical Observations
All sites exposed to the test substance exhibited well defined erythema on Day 1 which was either maintained for the duration of the study period (1/10 animals), or increased to severe erythema (9/10 animals). The increase in severity occurred at different times with the earliest development being on Day 5 (one animal, both test substance sites). Very slight to slight oedema was recorded at test substance sites with the earliest recording on Day 1 (1/10 animals, both test sites exhibiting very slight oedema with all animals exhibiting very slight to slight oedema by Day 4.

All animals exhibited fissures and scales at the test substance sites during the treatment period. The presence of these effects did not correlate with the severity or erythema or oedema. However, sites exposed to neat test substance tended to exhibit earlier onset of these effects (Days 4-6) than those sites tested with 62% test substance (Days 9-13). Two animals exhibited early onset of fissures and/or scale at both sites (Day 5).

Four of the animals exhibited diarrhoea with the longest period being 5 days. Four animals exhibited weight loss, but not at significant levels.

Sites exposed to mineral oil exhibited very slight to well-defined erythema and oedema with effects observed from Day 1. No fissures or scaling were observed. Sites exposed to isopropyl myristate exhibited erythema and oedema effects which increased from very slight to severe over the course of the test period. Fissures and scaling was also observed on those sites exposed to isopropyl myristate.

Effects in Organs
No gross changes observed in any of the animals.

Remarks – Results
All animals exhibited adverse dermal reactions when in contact with the test substance.

CONCLUSION
A No Observed (Adverse) Effect Level (NO(A)EL) cannot be established based on the limitations of the data presented.

TEST FACILITY CPT (1988)

A.10. Irritation – eye (*in vitro*)

TEST SUBSTANCE Analogue 1

METHOD Determination of Ocular Irritation Potential Using the EpiOcular *in vitro* toxicity testing system.

Vehicle Corn oil

Remarks - Method MatTek EpiOcular Corneal Model used. Consists of normal, human-derived epidermal keratinocytes cultured to form a stratified, squamous epithelium similar to that found in the cornea. The test substance (100 µL) at 20% and 2% concentrations [dilutions based on the specific gravity of the test substance (> 0.95 g/mL)] was applied to the tissues in triplicate.

Following 20 min, 1 and 3 hour exposure periods (at 37 °C, 5% carbon dioxide, ≥ 90% humidity), the tissues were rinsed with phosphate buffered

saline (PBS) and then incubated with MTT [3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) for 3 hours at 37 °C (5% carbon dioxide, ≥ 90% humidity). Following overnight extraction at room temperature, the optical densities were determined (570 nm).

Positive control samples (0.3% Triton X-100) were applied to the tissues in triplicate and exposed for 5 min, 15 min and 1 hr. Six replicates of the negative control (corn oil) were applied to tissues and exposed for 1 hour only. Samples were then treated the same as the test substance.

The test substance was considered by the study authors to be an irritant if the ET_{50} value (exposure time required to reduce cell viability by 50%) was < 2 hour.

Quality Assurance statement included.

RESULTS

Test material	*Exposure period*	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*ET_{50} Value*
Negative control	1	1.709	100	-
Test substance (20%)	20 min	1.866	109	> 2 hr
	1 hr	1.849	108	
	3 hr	1.849	108	
Test substance (2%)	20 min	1.631	95	> 2 hr
	1 hr	1.786	105	
	3 hr	1.706	100	
Positive control	5 min	1.474	86	21 min
	15 min	1.123	66	
	1 hr	0.263	15	

OD = optical density

Remarks - Results: Tissue viability after exposure to the test substance at 20% or 2% concentration was not reduced to ≤ 50% in any of the exposure periods.

The positive control performed as expected.

CONCLUSION: The test substance was considered to be non-irritating to the eye under the conditions of the test.

TEST FACILITY: CPT (1998b)

A.11. Irritation – eye (1)

TEST SUBSTANCE: Analogue 1

METHOD: Similar to OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain: Rabbit/New Zealand White
Number of Animals: 6 (Males and Females)
Observation Period: 72 hours
Remarks - Method: Test substance (0.1 mL) was instilled in the right eye (left eye remained untreated and acted as a control) and the eye remained unwashed. Eyes were examined 24 hours after exposure. Scoring was based on the Draize method (1944).

No GLP statement provided.

RESULTS
Remarks - Results: None of the animals exhibited an adverse effect to the test substance.

CONCLUSION The test substance is non-irritating to the eye.

TEST FACILITY CPT (1978)

A.12. Irritation – eye (2)

TEST SUBSTANCE Analogue 1

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain Rabbit/New Zealand White
Number of Animals 3
Observation Period 6 days
Remarks - Method No GLP statement provided.

Summary report only provided.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	1.7	0.7	1.3	2	5 days	0
Conjunctiva: chemosis	0.7	0	1	1	< 5 days	0
Conjunctiva: discharge	0	0	0	0	-	0
Corneal opacity	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	-	0

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

Remarks - Results No iridial inflammation or corneal opacity were recorded in any of the animals. Slight to diffuse redness was recorded in 1/3 and 2/3 animals respectively with signs of recovery at 48 hr (2/3) and 72 hr. Recovery was observed in 2/3 animals at Day 5, while all animals had recovered by Day 6. Chemosis was recorded in 2/3 animals persisting for up to at least 72 hr (1/3 animals). All animals had recovered by Day 5. Discharge was observed 1 hr after exposure but the effect had been reversed by the next observation (at 24 hr).

No adverse effects were recorded at the end of the observation period.

CONCLUSION The test substance is slightly irritating to the eye.

TEST FACILITY EviC (1994)

A.13. Skin sensitisation

TEST SUBSTANCE Analogue 1

METHOD Similar to OECD TG 406 Skin Sensitisation – Buehler Test.
Species/Strain Guinea pig
PRELIMINARY STUDY Maximum Non-irritating Concentration:
topical: 10%
MAIN STUDY
Number of Animals Test Group: 12 (M) Control Group: 0
Vehicle Water
Positive control None
INDUCTION PHASE Induction Concentration:
topical: 10%
Signs of Irritation None
CHALLENGE PHASE
Dorsal challenge topical: 10%

Ventral challenge	topical: 10%
Remarks - Method	A preliminary study was conducted to determine a concentration of test substance for sensitisation which caused the least irritation response. Four concentrations were tested, 5%, 10%, 25% and 50% (v/v aqueous) and scored at 16 and 40 hours post exposure. Animals exposed to a 25% concentration of the test substance exhibited very slight oedema. No other signs of irritation were recorded. A 3" × 3" gauze pad was wetted with 0.5 mL of a 10% solution of the test substance and applied to the 3-4 cm^2 shaved dorsal midline of the back of the animals under occlusive conditions for 6 hours. A total of 9 applications were made (3 per week). Retest applications were made in the dorsal and ventral areas of the back 14 days after the 9^{th} application. Irritation was scored based on the Draize system. No GLP statement provided.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		dorsal challenge		*ventral challenge*	
		6 h	*24 h*	*6 h*	*24 h*
Test Group	10%	0/12	0/12	0/12	0/12

Remarks - Results	No irritation was observed in any of the animals. All animals were autopsied at the end of the study period and no gross changes were recorded Four animals were replaced during the study due to premature death. At autopsy, 1 animal exhibited a consolidated inferior portion of the left lung (died on day 9 of induction phase), 1 animal exhibited a whitish, yellow fibrous-filled sac encasing the heart and right lung (died on day 8 of induction phase), 1 animal exhibited fibrous tissue throughout the abdominal cavity (died on day 2 of induction phase) and 1 animal exhibited fibrous tissue encasing the heart and lung (died on day 8 of induction phase). These effects do not appear related to the application site or the test substance.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the test substance at the concentration of 10% under the conditions of the test.
TEST FACILITY	CPT (1979b)

A.14. Skin sensitisation – human volunteers (1)

TEST SUBSTANCE	Analogue 1
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 mL test substance (20% dilution) were applied 3 times per week (Monday, Wednesday and Friday) for a total of 10 applications. Patches were removed by the applicants after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: 14 days Challenge Procedure: A patch was applied to the original site and a naïve site. Sites were graded 24 and 48 h after exposure. Two batches of the test substance were tested.
Study Group	47 F, 6 M; age range 18 - 70 years
Vehicle	Corn oil

Remarks - Method	Semi-occluded. The test substance was spread on a 2.5 cm × 2.5 cm patch.
RESULTS	
Remarks - Results	48/53 subjects completed the study. Four subjects withdrew voluntarily (1 discontinued the study prior to recording the first induction observation; 2 discontinued the study after 1 induction observation; 1 discontinued the study after 4 induction observations) and 1 subject was lost to follow up (failed to present for grading of the rechallenge sites 24 hr after exposure). No adverse responses were noted during the induction phase or at challenge for either test substance batch.
CONCLUSION	The test substance was non-sensitising at 20% concentration under the conditions of the test.
TEST FACILITY	CPT (1994)

A.15. Skin sensitisation – human volunteers (2)

TEST SUBSTANCE	Lipstick (containing Analogue 1 at 16% concentration)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 mL test substance were applied over nine 24 hr induction applications (following standard RIPT methodology). Rest Period: 10-15 days Challenge Procedure: Single 24 hr challenge application.
Study Group	82 F, 34 M; age range 20-70 years
Vehicle	None
Remarks - Method	Occluded.
RESULTS	
Remarks - Results	104/116 subjects completed the study. Twelve subjects withdrew voluntarily (6 discontinued the study prior to the first induction reading, 3 discontinued the study after the second induction reading; 1 discontinued the study after 4 induction readings; 1 discontinued the study after 5 induction readings and 1 subject discontinued the study after 6 induction readings). One subject exhibited erythema (no oedema) 48 hr after exposure to the challenge dose. However, this response was described as minimal or doubtful and slightly different from the surrounding normal skin when recorded 72 hr after the challenge dose. No other adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The test substance (containing Analogue 1 at 16% concentration) was non-sensitising under the conditions of the test.
TEST FACILITY	TKL (2005a)

A.16. Skin sensitisation – human volunteers (3)

TEST SUBSTANCE	Lipstick (containing Analogue 1 at 16% concentration)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 g test substance were applied over nine 24 hr induction applications (following standard RIPT methodology).

	Rest Period: 10-15 days Challenge Procedure: Single 24 hr challenge application.
Study Group	97 F, 25 M; age range 18-66 years
Vehicle	None
Remarks - Method	Occluded.

RESULTS

Remarks - Results	107/122 subjects completed the study. Fifteen subjects withdrew voluntarily (3 discontinued the study prior to the first induction reading, 4 discontinued the study after the first 1 induction reading; 1 discontinued the study after 3 induction readings; 1 discontinued the study after 7 induction readings; 1 missed one induction (third) reading and discontinued the study after the sixth induction reading, 1 missed one induction reading (fourth) and discontinued the study after the fifth induction reading, 1 missed one induction reading (sixth) and discontinued the study after the seventh induction reading and 3 did not present for the challenge phase readings). One subject exhibited a response described as minimal or doubtful and slightly different from the surrounding normal skin at the sixth induction reading. No seventh induction reading was taken and no other adverse effects were recorded for this subject. No other adverse responses were noted during the induction phase or at challenge. One subject exhibited a topical infection which did not affect their participation in the study (no missed induction readings). This study was repeated (study reference DS107305-6) under the same conditions with the same panel of test subjects

CONCLUSION	The test substance (containing Analogue 1 at 16% concentration) was non-sensitising under the conditions of the test.
TEST FACILITY	TKL (2005b)

A.18. Genotoxicity – bacteria

TEST SUBSTANCE	Analogue 1
METHOD	Similar to OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100
Metabolic Activation System	S9 fraction from Aroclor 1254 induced male rat liver.
Concentration Range in Main Test	Only one concentration of test substance tested in the presence and absence of metabolic activation.
Vehicle	None
Remarks - Method	Positive controls (presence and absence of metabolic activation): - Dexon (paradimethyl aminobenzene diazosulfonic acid sodium salt) - TA98, TA100, TA1537; - Sodium azide - TA1535; - 2-nitrofluorene - TA1538; - 2-aminofluorene – TA100, TA1538. Negative control: 0.85% saline (with and without metabolic activation). Controls run concurrently with the test substance. A preliminary toxicity screen was performed using a spot plate technique (as per standard plate incorporation method except test substance was

added to a filter disc and placed on the agar-bacterial mix instead of being directly added to the agar mix). No cytotoxicity was observed.

RESULTS

Metabolic Activation	*Cytotoxicity in Preliminary Test*	*Test Substance Concentration Resulting in: Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	> 100%	> 100%	negative
Present				
Test 1	-	> 100%	> 100%	negative

Remarks - Results: No significant increase in the frequency of revertant colonies in the presence or absence of metabolic activation was recorded.

All positive and negative controls performed as expected confirming the validity of the system.

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

TEST FACILITY: NamSA (1994)

A.19. Dermal penetration – *in vitro* (1)

TEST SUBSTANCE: Analogue 1

METHOD: OECD TG 428 Skin Absorption: *in vitro* Method

Species/strain	Pig skin (dermatomed)
Membrane integrity	Not provided
Group size	3 skin membranes from 1 pig donor
Purity	100%
Dose(s) applied	3860 µg/ cm^2 of test substance in 5 mg/cm^2 of the test formulation
Dose volume/amount	4 mg/cm^2
Receptor Fluid	Sodium chloride (0.9%), Bovine Serum Albumin (1%), Gentamycin sulphate (0.02%)
Method of Analysis	HPLC

Remarks - Method: The authors state that based on the partition coefficient values for C_{12}-, C_{13}-, C_{14}- and C_{15}-Benzoic acid-alkyl ester (log P_{OW} of 8.0, 8.6, 9.1 and 9.6 at pH 3 respectively) indicate that a percutaneous penetration of the test substance is not expected.

The penetration of the test substance through pig skin over 24 hr (un-occluded) was then determined *in vitro* using static glass diffusion cells. Mean dose applied was 1316 µg ± 54.2 µg. Application surface was 4.9 cm^2.

The receptor fluid, skin surface (prepared by gentle scraping with a spatula), the stratum corneum (prepared by tape stripping), dermis (cut into small pieces) and epidermis (separated from dermis with forceps) were analysed by HPLC to determine the distribution of test substance within the test system.

RESULTS

Test compartment	*Recovery (mean ± SD, n =3)*	
	[µg/cm^2]	*[% of applied dose]*
Donor chamber	21.5 ± 18.6	0.591 ± 0.512
Skin surface	2231.4 ± 428.6	57.4 ± 5.5
Stratum corneum	788.6 ± 210	20.3 ± 4.11

Test compartment	*Recovery (mean ± SD, n =3)*	
	[µg/cm²]	*[% of applied dose]*
Remaining epidermis	45.1 ± 12.8	1.2 ± 0.434
Dermis	100.1 ± 25.1	2.57 ± 0.452
Receptor fluid	0	0
Total non-absorbed[1]	3041.5 ± 550.15	78.3 ± 5.62
Systemically available[2]	145.2 ± 18.5	3.76 ± 0.426
Total recovered	3186.7 ± 559.13	82.02 ± 5.46

SD – standard deviation; n: number of samples
[1] Sum of the applied dose retrieved in the donor chamber, skin surface and stratum corneum
[2] Sum of the applied dose retrieved in the remaining epidermis, dermis and the receptor fluid

Remarks - Results

Mean recovery of the applied test item was 82.02 ± 5.46% (n=3), with individual cell values ranging from 77.4 to 88%. The mean amount of remaining notified chemical on the skin surface 24 hr after application was 57.4 ± 5.5% (2231.4 ± 428.6 µg/cm²). The mean amount of the dose present in the outer layers of the *stratum corneum* was 20.3 ± 4.11% of the applied dose (788.6 ± 210 µg/cm²) with 1.2 ± 0.434% of the dose (45.1 ± 12.8 µg/cm²) present in the remaining epidermis. The mean amount recovered for the dermis was 2.57 ± 0.452% of the applied dose (100.1 ± 25.1 µg/cm²).

No test substance was recorded in the receptor fluid after the 24 hr exposure. The mean total non-absorbed dose (donor chamber, skin surface, and *stratum corneum*) represented 78.3 ± 5.62% (14903 ± 2695 µg/cm²) of the applied dose.

The mean total systemically available dose (remaining epidermis plus dermis and receptor fluid) of the notified chemical was 3.76 ± 0.426% of the applied dose (corresponding to 711 ± 90 µg/cm²).

The authors indicate that based on the non-representativeness and small sample size, the study should be considered as a trend.

CONCLUSION

The mean total systemically available dose (remaining epidermis plus dermis and receptor fluid) of the test substance was 3.76 ± 0.426% of the applied dose (corresponding to 711 ± 90 µg/cm²).

TEST FACILITY

BDF (2010a)

A.20. Dermal penetration – *in vitro* (2)

TEST SUBSTANCES

1. Sun-Lotion (containing analogue 1 at ≤ 9%)
2. Baby cream (containing analogue 1 at ≤ 6%)
3. Sun-protection spray (containing analogue 1 at ≤ 7%)

METHOD

OECD TG 428 Skin Absorption: *in vitro* Method

Species/strain	Pig skin (dermatomed)
Membrane integrity	Not provided
Group size	3 skin membranes from 1 pig donor per test substance
Concentration	1. Sun-Lotion: 7.5 ± 0.5% 2. Baby cream: 5.4 ± 0.3% 3. Sun-protection spray: 6.6 ± 0.3%
Dose(s) applied	233 µg/ cm² of test substance in 5 mg/cm² of the test formulation
Dose volume/amount	4 mg/cm²
Receptor Fluid	Sodium chloride (0.9%), Bovine Serum Albumin (1%), Gentamycin sulphate (0.02%)
Method of Analysis	HPLC
Remarks - Method	The authors state that based on the partition coefficient values for C_{12}-Benzoic acid-alkyl ester, C_{13}-Benzoic acid-alkyl ester, C_{14}-Benzoic acid-alkyl ester and

C_{15}-Benzoic acid-alkyl ester ($logP_{OW}$ of 8.0, 8.6, 9.1 and 9.6 (pH 3) respectively) indicate that a percutaneous penetration of the test substance is not expected.

The penetration of the test substance through pig skin over 24 hr (un-occluded) was then determined *in vitro* using static glass diffusion cells. Mean dose applied was as follows for each test substance:
1. Sun-Lotion: 1600 µg ± 80.2 µg. Application surface was 4.9 cm^2
2. Baby cream: 983 µg ± 91.5 µg. Application surface was 4.9 cm^2
3. Sun-protection spray: 1315 µg ± 54.2 µg. Application surface was 4.9 cm^2

The receptor fluid, skin surface (prepared by gentle scraping with a spatula), the stratum corneum (prepared by tape stripping), dermis (cut into small pieces) and epidermis (separated from dermis with forceps) were analysed by HPLC to determine the distribution of test substance within the test system.

RESULTS

1. Sun-Lotion (containing analogue 1 at ≤ 9%)

Test compartment	*Recovery (mean ± SD, n =3)*	
	[µg/cm²]	*[% of applied dose]*
Donor chamber	0	0
Skin surface	232.9 ± 32.03	71.2 ± 6.4
Stratum corneum	56.48 ± 18.95	17.3 ± 5.8
Remaining epidermis	3.741 ± 0.312	1.15 ± 0.09
Dermis	0	0
Receptor fluid	0	0
Total non-absorbed[1]	289.4 ± 31.3	88.5 ± 5.6
Systemically available[2]	3.74 ± 0.31	1.15 ± 0.09
Total recovered	293.2 ± 31.5	89.6 ± 5.6

2. Baby micropigmentcreme (containing analogue 1 at ≤ 6%)

Test compartment	*Recovery (mean ± SD, n =3)*	
	[µg/cm²]	*[% of applied dose]*
Donor chamber	0	0
Skin surface	116.3 ± 33.14	57.4 ± 11.5
Stratum corneum	55.59 ± 16.7	27.79 ± 8.46
Remaining epidermis	5.17 ± 1.36	2.55 ± 0.472
Dermis	0	0
Receptor fluid	0	0
Total non-absorbed[1]	171.84 ± 30.4	85.2 ± 7.2
Systemically available[2]	5.17 ± 1.36	2.55 ± 0.472
Total recovered	177.01 ± 31.67	87.73 ± 7.64

3. Protection spray (containing analogue 1 at ≤ 7%)

Test compartment	*Recovery (mean ± SD, n =3)*	
	[µg/cm²]	*[% of applied dose]*
Donor chamber	0	0
Skin surface	188.23 ± 12.48	70.19 ± 5.12
Stratum corneum	62.2 ± 22.43	23 ± 7.7
Remaining epidermis	4.97 ± 0.62	1.85 ± 0.174
Dermis	0	0
Receptor fluid	0	0
Total non-absorbed[1]	250.4 ± 21.2	93.18 ± 4.13
Systemically available[2]	5 ± 0.62	1.85 ± 0.174
Total recovered	255.4 ± 21.7	95.03 ± 4.24

SD – standard deviation; n: number of samples
[1] Sum of the applied dose retrieved in the donor chamber, skin surface and stratum corneum
[2] Sum of the applied dose retrieved in the remaining epidermis, dermis and the receptor fluid

Remarks - Results	Mean recovery of the analogue 1 was 89.6 ± 5.6%, 87.73 ± 7.64% and, 95.03 ± 4.24% (n=3) when formulated in sun-lotion, baby cream and sun-protection spray respectively. Individual cell values ranging from 79.8% to 98.5%. The mean amount of remaining analogue 1 on the skin surface 24 hr after application was 71.2 ± 6.4% (232.9 ± 32.03 µg/cm^2), 57.4 ± 11.5% (116.3 ± 33.14 µg/cm^2) and 70.19 ± 5.12% (188.23 ± 12.48 µg/cm^2) when formulated in sun-lotion, baby micropigmentcreme and protection spray respectively. The mean amount of the dose present in the outer layers of the *stratum corneum* was 17.3 ± 5.8% (56.48 ± 18.95 µg/cm^2), 27.79 ± 8.46% (55.59 ± 16.7 µg/cm^2) , 23 ± 7.7% (62.2 ± 22.43 µg/cm^2) of the applied dose when formulated in sun-lotion, baby cream and sun-protection spray respectively, with 1.15 ± 0.09% (3.741 ± 0.312 µg/cm^2), 2.55 ± 0.472% (5.17 ± 1.36 µg/cm^2), 1.85 ± 0.174% (4.97 ± 0.62 µg/cm^2) of the dose present in the remaining epidermis (respectively). Analogue 1 was not recovered from the dermis or recorded in the receptor fluid for any of the formulations. The mean total non-absorbed dose (donor chamber, skin surface, and *stratum corneum*) represented 88.5 ± 5.6% (289.4 ± 31.3 µg/cm^2), 85.2 ± 7.2% (171.8 ± 30.4 µg/cm^2) and 93.18 ± 4.13% (250.4 ± 21.2 µg/cm^2) of the applied dose of analogue 1 when formulated in sun-lotion, baby cream and sun-protection spray respectively. The mean total systemically available dose (remaining epidermis plus dermis and receptor fluid) of the test substance was 1.15 ± 0.09%, 2.55 ± 0.472% and 1.85 ± 0.174% of the applied dose when formulated in sun-lotion, baby cream and sun-protection spray respectively (corresponding to 3.74 ± 0.31 µg/cm^2, 5.17 ± 1.36 µg/cm^2 and 5 ± 0.62 µg/cm^2 respectively). The authors indicate that based on the non-representativeness and small sample size, the study should be considered as a trend.
CONCLUSION	The mean total systemically available dose (remaining epidermis plus dermis and receptor fluid) of the test substance was 1.15 ± 0.09%, 2.55 ± 0.472% and 1.85 ± 0.174% of the applied dose when formulated in sun-lotion, baby cream and sun-protection spray (corresponding to 3.74 ± 0.31 µg/cm^2, 5.17 ± 1.36 µg/cm^2 and 5 ± 0.62 µg/cm^2 respectively).
TEST FACILITY	BDF (2010b)

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