File No: LTD/1830

July 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Benzoic Acid, 2-hydroxy, 2-butyloctyl ester (INCI name: Butyloctyl Salicylate)

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:

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

Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1830	Estee Lauder Pty Ltd	Benzoic acid, 2-hydroxy, 2-butyloctyl ester (INCI name: Butyloctyl Salicylate)	No	≤ 1 tonne per annum	Cosmetic ingredient

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).

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.

Based on the available information, when used at ≤ 6% 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

CONTROL MEASURES

Occupational Health and Safety

- 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 suns 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 6% in cosmetic products;
- information becomes available of the potential of the notified chemical to cause increased sun sensitivity;
- the notified chemical is intended to be used as an ultraviolet (UV) filter in a cosmetic to be applied to the skin

or

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

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

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

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Estee Lauder Pty Ltd (ABN: 63 008 444 719)
165 – 175 Mitchell Road
ERSKINEVILLE NSW 2043

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

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for hydrolysis as a function of pH, dissociation constant and oxidising properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
TGA

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Hallbrite BHB
Butyloctyl Salicylate (INCI name)

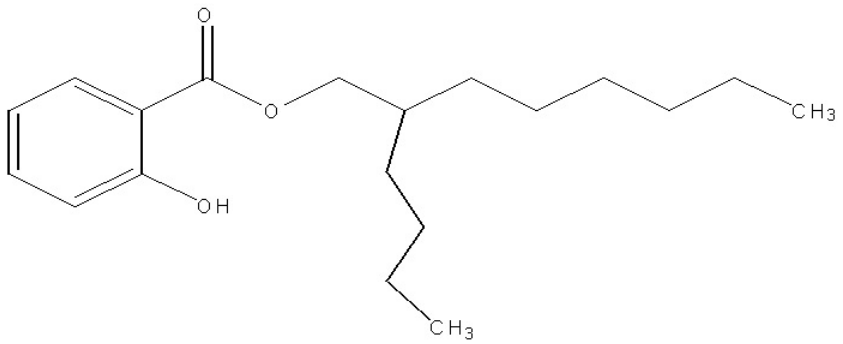
CAS NUMBER
190085-41-7

CHEMICAL NAME
Benzoic acid, 2-hydroxy, 2-butyloctyl ester

OTHER NAME(S)
RX-13643

MOLECULAR FORMULA
$C_{19}H_{30}O_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
306.44 Da

ANALYTICAL DATA
Reference GC and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 95%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: clear to hazy colourless to yellow liquid

Property	Value	Data Source/Justification
Freezing Point	< -25 °C	Measured
Boiling Point	Decomposed from 251-334 °C	Measured
Density	971 kg/m^3 at 20 °C	Measured
Vapour Pressure	0.014 kPa at 25 °C	Measured
Water Solubility	1.1 × 10^{-4} g/L at 25 °C	Calculated (WSKOW v1.42; US EPA, 2011)
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functionality. However, the notified chemical is not expected to be significantly hydrolysed under normal environmental conditions (pH 4 – 9).
Partition Coefficient (n-octanol/water)	log Pow = 6.43	Calculated (KOWIN v1.68, US EPA, 2011)
Adsorption/Desorption	log K_{oc} = 3.6 (MCI method) log K_{oc} = 4.0 (Kow method)	Calculated (KOCWIN v2.00; US EPA, 2011)
Dissociation Constant	Not determined	The notified chemical contains dissociable functionality, with an expected pKa of ~ 6-10.
Flash Point	166 °C at 99.5 kPa	Measured
Flammability	Not flammable	Not expected to be highly flammable based on flash point
Autoignition Temperature	263 °C at 100 kPa	Measured
Explosive Properties	Not explosive	Measured
Oxidising Properties	Not determined	Not expected to be oxidising based on chemical structure

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 be imported into Australia as a component of finished cosmetic products at ≤ 6% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.5	0.6	0.7	0.8	0.995

PORT OF ENTRY
Sydney by sea.

IDENTITY OF MANUFACTURER/RECIPIENTS
Estee Lauder Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported as a component of finished cosmetic products in 50 g containers for retail sale.

USE
The notified chemical will be used as an ingredient in cosmetic products at ≤ 6% concentration.

OPERATION DESCRIPTION
The notified chemical will be imported into Australia as a component of finished cosmetic products at ≤ 6% concentration which will be sold to the public in the same form in which they are imported.

The finished cosmetic products 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

EXPOSURE DETAILS
Transport, storage and retail workers may come into contact with the notified chemical at ≤ 6% concentration, only in the event of accidental rupture of packages.

End-use
Exposure to the notified chemical at ≤ 6% concentration in end-use products 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 oral and ocular exposure is also possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by customers 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 concentrations ≤ 6% through the use of cosmetic products containing it. 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.

Data on typical use patterns of cosmetic products in which the notified chemical is proposed to be used are shown in the following table (SCCS, 2012). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption value of 10% (see Section 6.2 for further information) and an oral absorption value of 100% were assumed for the

notified chemical for calculation purposes. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes.

Cosmetic products (dermal exposure):

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Body lotion	7820	6	1	0.733
Face cream	1540	6	1	0.144
Hand cream	2160	6	1	0.203
Shampoo	10460	6	0.01	0.010
Conditioner	3920	6	0.01	0.004
Shower gel	18670	6	0.01	0.018
Hand soap	20000	6	0.01	0.019
Foundation	510	6	1	0.048
Total				1.178

C = concentration; RF = retention factor.
Daily systemic exposure = Amount × C (%) × RF × dermal absorption (%)/body weight (64 kg)

- Cosmetic products (Oral exposure):

Product type	Amount (mg/day)	C (%)	RF (unitless)	Daily systemic exposure (mg/kg bw/day)
Lipstick	57	6	1	0.053

Daily systemic exposure = (Amount x C x RF x oral absorption)/body weight

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 1.231 mg/kg bw/day.

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 > 5000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	moderately irritating
Rabbit, eye irritation	non-irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Human, skin sensitisation – RIPT	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOEL = 150 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non-mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	inconclusive

Toxicokinetics.
No toxicokinetic data are available for the notified chemical.

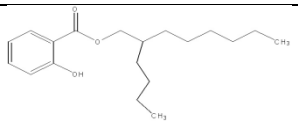
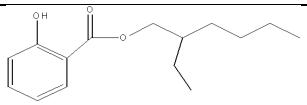
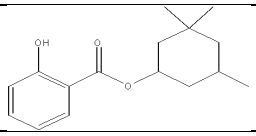
Homosalate, an analogue of the notified chemical (analogue 2), has been suggested to undergo rapid and complete metabolism by esterases in the skin, plasma, liver and other body tissues to salicylic acid and trimethylcyclohexanol (SCCP, 2007). The notified chemical may similarly undergo rapid metabolism by the oral and dermal route to salicylic acid and 2-butyloctanol.

Absorption of salicylates from the stomach is normally quite rapid (CIR, 2003). Therefore the notified chemical is expected to be rapidly absorbed by the oral route.

Dermal absorption is expected to be limited given the high lipophilicity (Log P_{OW} = 6.43) of the notified chemical limiting penetration of the hydrophilic epidermis. This is supported by the low absorption (< 2%)

observed in dermal absorption studies conducted on analogues of the notified chemical. The analogue chemicals have similar structure and physicochemical properties to the notified chemical and are therefore considered acceptable to estimate the dermal absorption potential of the notified chemical.

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

	Notified Chemical	**Analogue 1**	**Analogue 2**
Chemical Name	Benzoic acid, 2-hydroxy, 2-butyloctyl ester	Benzoic acid, 2-hydroxy-, 2-ethylhexyl ester	Benzoic acid, 2-hydroxy-, 3,3,5-trimethylcyclohexyl ester
INCI Name	Butyloctyl Salicylate	Ethylhexyl Salicylate	Homosalate
CAS Number	190085-41-7	118-60-5	118-56-9
Structural Formula			
Molecular Weight	306.44 Da	251 Da	262.02 Da
Water Solubility	1.1×10^{-4} g/L at 25 °C	Insoluble (CIR, 2003)	Immiscible (SCCP, 2007)
Partition Coefficient (Log Pow)	6.43 (calc.)	6.02 (CIR, 2003)	5.82, 6.16 (calc.) (SCCP, 2007)

Dermal absorption studies of analogue chemicals

The human skin penetration of analogue 1 has been determined in two representative sunscreen formulations *in vitro* (Walters et al., 1997). When analogue 1 was applied in an oil-in-water emulsion (representative of a typical sunscreen formulation) at a 5% concentration, the average total permeation over 48 hours was 0.65% of the applied dose. When applied in a hydroalcoholic formulation (representative of a stick-type sunscreen product) at a 5% concentration, the average total permeation over 48 hours was 0.59% of the applied dose.

The *in vitro* skin penetration of analogue 2 using human skin was tested as a 10% standard sunscreen formulation in compliance with OECD TG 428 (SCCP, 2007). The mean total absorption was determined as 1.1% of the applied dose with a mean recovery of 92.4%. The highest absorption found was 1.4%.

Based on the studies conducted on the analogue chemicals, a dermal absorption of 10% was considered a reasonable worst case scenario for exposure calculation purposes (see Section 6.1.2).

Acute toxicity.

The notified chemical is expected to have a low acute oral and dermal toxicity based on studies conducted in rats.

Irritation.

The notified chemical is not irritating to the eye, but is irritating to the skin of rabbits. When tested on unabraded skin in a study similar to OECD TG404, the notified chemical produced very slight to well-defined erythema and very slight oedema in all animals. At the end of the observation period of 72 h, all animals exhibited very slight erythema and flaking skin was observed in 2/6 animals. However, these effects were not at a level to warrant hazard classification.

Sensitisation.

The notified chemical was not found to be skin sensitiser when tested up to 100% concentration in two guinea pig maximisation studies or in two human repeat insult patch tests (HRIPT). In addition, a skin sensitisation response was not observed in a further HRIPT for an end-use product (facial cream) containing the notified chemical at 4% concentration.

Repeated dose toxicity.

A NOEL of 150 mg/kg bw/day was established for the notified chemical in a 28-day repeated dose oral gavage toxicity test in rats based on increases in prothrombin and activated partial thromboplastin times at the highest exposure dose (1000 mg/kg bw/day).

Mutagenicity/Genotoxicity.
The notified chemical was negative in a bacterial reverse mutation assay. In an *in vitro* chromosomal aberration study in human lymphocytes the results of the study were inconclusive. In cultures treated with 2500 µg/mL (highest exposure dose) in the presence of metabolic activation a statistically significant increase in chromosomal aberrations was observed. However, there was a lack of reproducibility between the two cultures as the aberration frequency value exceeded the historical negative control range (0-6%) in only one of the two cultures (7%), although the value observed for the other culture (3.3%) was slightly outside the 95% confidence limit of 3%. Therefore under the conditions of this study the clastogenic potential of the notified chemical is inconclusive.

Analogue 1 has been found to be negative in a bacterial reverse mutation assay and negative in an *in vivo* mouse micronucleus assay (CIR, 2003). Analogue 2 has been found to be negative in a bacterial reverse mutation assay and negative in an *in vitro* chromosomal aberration study in Chinese hamster V79 cells (SCCP, 2007).

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

Reproductive and developmental toxicity.
There are no studies available for the notified chemical in respect to reproductive and developmental toxicity.

The notified chemical may be rapidly metabolised to salicylic acid and 2-butyloctanol. Salicylic acid has been reported to cause developmental toxicity (NICNAS). The NOAEL is considered to be 75 mg/kg bw/day based on foetal malformations (skeletal malformations, cleft lip, and growth retardation). There is no reproductive and developmental toxicity data available for 2-butyloctanol. 2-Octyldodecanol, a structurally similar chemical to 2-butyloctanol, revealed no adverse effects when investigated for reproductive and developmental toxicity (REACH).

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

6.3.2. Public Health
Cosmetic products containing the notified chemical at ≤ 6% 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 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.

Local effects
The notified chemical is moderately irritating to skin. Given the low proposed use concentration (≤ 6%) irritation effects are not expected.

Systemic effects
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 1.231 mg/kg bw/day (see Section 6.1.2). Using a NOEL of 150 mg/kg bw/day derived from a 28-day repeated dose oral toxicity study on the notified chemical, the MoE was estimated to be 121.9. A MoE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences.

The notified chemical may also be metabolised in the skin to salicylic acid and 2-butyloctanol. Salicylic acid has been reported to cause developmental toxicity. Assuming 100% metabolism to salicylic acid and 2-butyloctanol, the estimated systemic exposure for salicylic acid from use of multiple products is 0.554 mg/kg bw/day. Using a NOAEL of 75 mg/kg bw/day for salicylic acid with respect to developmental toxicity, the MoE was estimated to be 135.4. Therefore, when taking into consideration metabolism of the notified chemical, the overall systemic toxicity potential of the notified chemical is not altered as the MoE for the metabolite for salicylic acid is similar to the estimated MoE for the notified chemical itself.

Therefore, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 6% 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 or reformulated in Australia; therefore there is no release of the notified chemical to the environment from these activities. Environmental release during importation, transport and distribution may occur as a result of accidental spills. In the event of a spill, the notified chemical is expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

RELEASE OF CHEMICAL FROM USE
The majority of the notified chemical is expected to be released to sewers across Australia as a result of its use in cosmetic products, which are washed off the skin of and disposed of to the sewer.

RELEASE OF CHEMICAL FROM DISPOSAL
It is expected that some of the product containing the notified chemical will remain in end-use containers. The containers are expected to be disposed of through domestic garbage disposal and will enter landfill, or be subjected to recycling processes.

7.1.2. Environmental Fate
Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system before potential release to surface waters on a nationwide basis. Based on its calculated low water solubility and high log Kow value, a significant amount of the notified chemical is expected to partition to sludge. The notified chemical has high potential to bioaccumulate based on its calculated high partition coefficient (log Pow = 6.43). 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 effluent is used for irrigation, or disposed of to landfill as waste. Notified chemical residues in landfill and soils are expected to have low mobility based on its predicted high soil adsorption coefficient and predicted low water solubility. In the aquatic and soil compartments, the notified chemical is expected to slowly degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)
The calculation for the Predicted Environmental Concentration (PEC) is summarised in the table below. Based on the reported use in cosmetics products, it is assumed that 100% of the total import volume of the notified chemical is released to the sewer. The release is assumed to be nationwide over 365 days per year. Based on the Simple Treat model (European Commission, 2003), the notified chemical, with log Kow > 6, has been assumed to have a removal efficiency of 85% during sewage treatment processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment

Total Annual Import/Manufactured Volume	995	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	995	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.73	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	85%	**Mitigation**
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.09	µg/L
PEC - Ocean:	0.01	µg/L

Partitioning to biosolids in STPs Australia-wide may result in an average biosolids concentration of 5.124 mg/kg (dry wt). Biosolids are applied to agricultural soils, with an assumed average rate of 10 t/ha/year. Assuming a soil bulk density of 1500 kg/m^3 and a soil-mixing zone of 10 cm, the concentration of the notified chemical may approximate 0.034 mg/kg in applied soil. This assumes that degradation of the notified chemical occurs in the soil within 1 year from application. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated biosolids application, the concentration of notified chemical in the applied soil in 5 and 10 years may approximate 0.17 mg/kg and 0.34 mg/kg, respectively.

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 0.09 µg/L may potentially result in a soil concentration of approximately 0.6 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 3.01 µg/kg and 6.02 µg/kg, respectively.

7.2. Environmental Effects Assessment

No ecotoxicity data for the notified chemical were submitted. The ecotoxicity effects of the notified chemical were predicted using Ecological Structure Activity relationship (ECOSAR v1.11, US EPA 2012). The conservative toxicity results are summarised in the table below.

Endpoint	Result	Assessment Conclusion
Fish	LC50 (96 h) = 0.108 mg/L	Expected to be very toxic to fish
Daphnia	LC50 (48 h) = 0.139 mg/L	Not expected to be harmful to aquatic invertebrates at its saturation
Algae	EC50 (96 h) = 0.029 mg/L	Expected to be very toxic to algae

The ECOSAR estimation endpoints indicate that the notified chemical is potentially very toxic to the freshwater fish and green algae and potentially not harmful to aquatic vertebrates at its saturation. However, the actual toxicity of the notified chemical to aquatic life may be overestimated by ECOSAR estimation used here as surface water tend to have higher total organic content (TOC) and dissolved organic content (DOC) than what is used in standard aquatic toxicity testing media. Since the log Kow value of the notified chemical is > 6, a significant amount of the notified chemical is expected to be removed from water columns by means of partition to suspended sediment and dissolved organic matter in the natural water. As a result, the environmentally relevant concentrations of the notified chemical may not exhibit aquatic ecotoxicity to aquatic organisms in the natural aquatic system. Consequently, ECOSAR estimations of the notified chemical may not reflect the actual toxicity of the notified chemical. For this reason, the notified chemical has not been formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) was calculated using the most sensitive toxicity endpoint (Algae, EC50) of the notified chemical. An assessment factor of 250 was used as measured ecotoxicological endpoints

were not available for the notified chemical. It has been determined that the assessment factor used is appropriate as the toxicity endpoints predicted by ECOSAR, which is a conservative approach as the toxicity data is generated from toxicity tests using surface water, may have overestimated the ecotoxicity of the notified chemical.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Algae)	0.029	mg/L
Assessment Factor	250	
PNEC:	0.116	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient values (PEC/PNEC) have been calculated as follows:

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	0.09	0.116	0.776
Q - Ocean:	0.01	0.116	0.086

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 importation quantity. The notified chemical has potential to be bioaccumulative. However, the notified chemical has predicted low water solubility. Therefore, on the basis of the PEC/PNEC ratio, maximum annual import volume and assessed use pattern in cosmetic products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < -25 °C

Method	OECD TG 102 Melting Point/Melting Range. EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks	Crystallisation point apparatus
Test Facility	Huntingdon (1998a)

Boiling Point > 200 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	Ebulliometric method. Notified chemical decomposed from 251 °C to 334 °C in replicate tests. Maximum boiling temperature was 334 ^{0}C before settling to a constant reflux at 310 °C
Test Facility	Huntingdon (1998a)

Density 971 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids. EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks	Pycnometer method.
Test Facility	Huntingdon (1998a)

Vapour Pressure 0.014 kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Isoteniscope method.
Test Facility	Huntingdon (1998a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 401 Acute Oral Toxicity – Limit Test.
Species/Strain	Rat/Sprague Dawley
Vehicle	None
Remarks - Method	Animals were dosed using oral gavage. No significant deviation from OECD TG 401.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 M, 5 F	5000	0/10

LD50	> 5000 mg/kg bw
Signs of Toxicity	All animals showed yellow anogenital staining on days 1 and 2 of the observation period which persisted in one animal through days 3 and 4. No other clinical observations.
Effects in Organs	No gross abnormalities observed.
Remarks - Results	None
CONCLUSION	The notified chemical of low toxicity via the oral route.
TEST FACILITY	Celsis (1996a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/Sprague Dawley
Vehicle	None
Type of dressing	Occlusive.
Remarks - Method	No significant deviation from OECD TG 402.
RESULTS	Huntingdon (1998a)

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

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	Slight red staining was observed on the snouts of 6/10 animals on the day of dosing. Staining was absent in all animals by Day 2. Dermal irritation not observed in any of the animals.
Signs of Toxicity - Systemic	No effect on body weight observed.
Effects in Organs	At necropsy, no macroscopic abnormalities were observed in 9/10 animals, while one animal exhibited slightly firm, slightly white discoloured lungs.
Remarks - Results	There were no unscheduled deaths and no systemic response to treatment was observed.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Huntingdon (1998a)

B.3. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	Federal Hazardous Substances Act. 16 CFR 1500.41 Similar to OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Vehicle	None
Observation Period	72 hr
Type of Dressing	Occlusive.
Remarks - Method	Test was performed on abraded and intact skin.

RESULTS

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Intact skin									
Erythema/Eschar	1.5	1	1.5	1.5	1.5	1.5	2	> 72 h	1
Oedema	0.5	0	0.5	0.5	0.5	0.5	1	> 24 h	0
Abraded skin									
Erythema/Eschar	1.5	1.5	2	2	1.5	1.5	2	> 72 h	2
Oedema	0.5	0.5	1	1.5	0.5	0.5	1	> 72 h	1

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

Remarks - Results	When tested on intact skin, the notified chemical produced very slight to well-defined erythema and very slight oedema in all animals. At the end of the observation period, all animals exhibited very slight erythema and flaking skin was observed in 2/6 animals. When tested on abraded skin, the notified produced very slight to well-defined erythema and very slight to well-defined oedema. At the end of the observation period, all animals exhibited very slight to well-defined erythema and 2/6 animals exhibited very slight oedema. In addition, blanched skin was observed in 1/6 animals and flaking skin was observed in 2/6 animals.
CONCLUSION	The notified chemical is moderately irritating to the skin.
TEST FACILITY	Celsis (1996b)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	Federal Hazardous Substances Act.. 16 CFR 1500.42 which is similar to OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/Albino
Number of Animals	6
Observation Period	72 hr
Remarks - Method	None

RESULTS

Remarks - Results	A study summary was only supplied. Details of results for each animal were not provided.

	Minimal conjunctival irritation was observed in 3/6 animals. No irritation was recorded in the remaining animals. All irritation was reversed by 72 hr observation.
CONCLUSION	The notified chemical is non-irritating to the eye.
TEST FACILITY	Celsis (1996c)

B.5. Skin sensitisation

TEST SUBSTANCE	Notified Chemical
METHOD	Similar to OECD TG 406 Skin Sensitisation – Magnusson and Kligman Guinea Pig Maximisation Test – adjuvant test
Species/Strain	Guinea pig/ Dunkin Hartley
PRELIMINARY STUDY	No preliminary study
MAIN STUDY	
Number of Animals	Test Group: 10 M Control Group: 5 M
INDUCTION PHASE	Induction Concentration: intradermal: 5% (vehicle: propylene glycol) topical: 100%
Signs of Irritation	No details about severity were provided. However, any irritation observed was attributed to Freund's Complete Adjuvant.
CHALLENGE PHASE	
1st challenge	Topical application to two sites/animal Site 1: 100% Site 2: 50%
Remarks - Method	Procedure used is based on method described by Magnusson and Kligman (1970). Challenge with the notified chemical at 50% and 100% were performed at the same time, on different sites on each animal.
RESULTS	
Remarks - Results	There were no mortalities. No evidence of sensitisation reactions were observed in test animals challenged with 100% notified chemical. Of the animals challenged with 50% of the notified chemical, 1/10 exhibited a dermal response ≥ 1 (discrete or patchy erythema). No animals in the control group exhibited a significant dermal response.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Huntingdon (1998c)

B.6. Skin sensitisation

TEST SUBSTANCE	Notified chemical (95%)
METHOD	Similar to OECD TG 406 Skin Sensitisation – Guinea Pig Maximisation Test – adjuvant study
Species/Strain	Guinea pig/Dunkin Hartley
PRELIMINARY STUDY	No preliminary study
MAIN STUDY	
Number of Animals	Test Group: 10 M Control Group: 5 M

INDUCTION PHASE	Induction Concentration: intradermal: 5% (vehicle: propylene glycol) topical: 100%
Signs of Irritation	All animals exhibited severe dermal reactions at the intradermal injection sites. This reaction was attributed to the FCA.
CHALLENGE PHASE	
1st challenge	
	Site 1: topical: 100% Site 2: topical: 50% (vehicle: 70% ethanol)
Remarks - Method	On the day prior to the topical induction phase, animals were pre-treated with 0.5 mL of 10% sodium lauryl sulfate in petrolatum. Adjuvant: Freund's complete adjuvant (FCA) Positive Control: Hexylcinnamic aldehyde (HCA) Challenge with the notified chemical at 50% and 100% were performed at the same time, on different sites on each animal.
RESULTS	
Remarks - Results	There were no mortalities or clinical abnormalities. All animals gained weight during the study. No signs of irritation were observed at the 100% challenge test sites. At the 50% challenge test sites, 2/10 animals exhibited a very slight erythema response (Grade 0.5) which was not considered to be a positive response by the authors. No other dermal responses were observed in the test or control animals. Negative and positive control performed as expected.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Huntingdon (1999)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (25% in vehicle)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 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 a naïve site. Patches were removed by the applicants after 24 h. Sites were graded 24 and 72 h post-application.
Study Group	37 F, 24 M; age range 17-73 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	53/61 subjects completed the study. Of the subjects that withdrew, 5 withdrew prior to the first induction patch being read, 2 withdrew during the first week of induction and 1 withdrew prior to the challenge dose. No withdrawals were related to the application of the test material. No adverse reactions were noted in those 3 subjects who withdrew after commencing or completing the induction phase.

	No adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	Consumer Product Testing (2009)

B.8. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical (100%)
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 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 a naïve site. Patches were removed by the applicants after 24 h. Sites were graded 24 and 72 h post-application.
Study Group	157 F, 72 M; age range 16 - 74 years
Vehicle	Notified chemical applied undiluted
Remarks - Method	Occluded. The test substance was spread on a 2 cm × 2 cm patch.
RESULTS	
Remarks - Results	208/229 subjects completed the study. Of the subjects that withdrew, 9 withdrew prior to the first induction patch being read, 7 withdrew during the first week of induction, 3 withdrew during the second week of induction, 1 withdrew during the last week of induction and 1 withdrew prior to the challenge dose. No withdrawals were related to the application of the test material. No adverse reactions were noted in the 12 subjects who withdrew after commencing or completing the induction phase. No adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	Consumer Product Testing (2013)

B.9. Skin sensitisation – human volunteers

TEST SUBSTANCE	End-use product (face cream) containing the notified chemical at 4% concentration
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.15 mL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by study technicians after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday where applicants would remove the patches). Rest Period: ~ 7 days Challenge Procedure: A patch was applied to a naïve site. Patches were removed by study technicians after 24 h and evaluated. Sites were re-evaluated 24 h and 48 h post-application.
Study Group	89 F, 23 M; age range 17 - 69 years
Vehicle	Notified chemical applied in end-use product (face cream)
Remarks - Method	Occluded. The test substance was spread on a 2 cm × 2 cm patch.
RESULTS	

Remarks - Results	106/112 subjects completed the study. No withdrawals were related to the application of the test material. No adverse reactions were noted in the 6 subjects who withdrew after commencing or completing the induction phase. No adverse responses were noted during the induction phase or at challenge.
CONCLUSION	The notified chemical was non-sensitising under the conditions of the test.
TEST FACILITY	Clinical Research Laboratories (2009)

B.10. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Sprague Dawley
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	Corn Oil
Remarks - Method	None

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 M, 5 F	0	0/10
low dose	5 M, 5 F	15	0/10
mid dose	5 M, 5 F	150	0/10
high dose	5 M, 5 F	1000	0/10

Mortality and Time to Death

No animals died prior to scheduled euthanasia.

Clinical Observations

No test substance related clinical observations or effects in food consumption were observed in the low- and mid-dose groups. Excessive salivation was observed in the high-dose group (one female, week 2; two males and two females, week 3). One of the females exhibiting excessive salivation in week 3 also exhibited slight red staining on the snout. Lacrimation was also observed in a third female during week 3. All effects reversed and were not observed during Week 4.

Females in all dose groups showed appropriate weight gains. Males in the mid- and high-dose groups showed smaller weight gains (when compared to controls). A dose-relationship was not observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No significant haematological effects were recorded for animals in the low-and mid-dose groups.

In the high-dose group, animals exhibited increased mean prothrombin and activated partial thromboplastin times which were attributed to the nature of the notified chemical. In addition, an increased albumin/globulin ratio (male and females) and triglyceride levels (females only), were observed in the high-dose group; however, these effects were not considered biologically significant as there were no accompanying microscopic changes in the organs/tissues examined.

Effects in Organs

No significant changes in organ weights were observed. There were no treatment related macroscopic or microscopic findings.

Remarks – Results

Exposure to 1000 mg/kg bw/day of the notified chemical produced occasional increases in salivation and increased in prothrombin and activated partial thromboplastin times. Any other effects observed could not be attributed solely to the presence of the notified chemical.

CONCLUSION

The No Observed Effect Level (NOEL) was established as 150 mg/kg bw/day in this study, based on increases in prothrombin and activated partial thromboplastin times at the high exposure dose.

TEST FACILITY Huntingdon (1998d)

B.11. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Test 1: Plate incorporation procedure
Test 2: Pre incubation procedure

Species/Strain *S. typhimurium*: TA1535, TA1537, TA98, TA100
E. coli: WP2uvrA (pKM101)

Metabolic Activation System S9 mix from Aroclor 1254 induced rat liver

Concentration Range in Test 1
a) With metabolic activation: 5 – 5000 µg/plate
b) Without metabolic activation: 5 – 5000 µg/plate

Concentration Range in Test 2
a) With metabolic activation: 50 – 5000 µg/plate
b) Without metabolic activation: 50 – 5000 µg/plate

Vehicle Dimethyl sulphoxide

Remarks - Method
Positive controls:
With metabolic activation: 2-aminoanthracene; benzo(a)pyrene
Without metabolic activation *N*-Ethyl-*N'*-nitro-*N*-nitrosoguanidine [TA1535, TA100, WP2uvrA(pKM101)]; 9-Aminoacridine (TA1537); 2-Nitrofluorene (TA98).

The Test 2 results for WP2uvrA(pKM101) were not provided.

RESULTS

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

Remarks - Results
In both tests, no biologically relevant increases in the frequency of revertant colonies were obtained in the presence or absence of metabolic activation. No visible thinning of the background lawn of non-revertant cells was observed.

Positive controls performed as expected.

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

TEST FACILITY Huntingdon (1998e)

B.12. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical (95%)

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

Species/Strain	Human
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	S-9 fraction from Aroclor 1254 induced rat liver
Vehicle	Dimethyl sulphoxide
Remarks - Method	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	50, 75, 100, 150, 200*, 300, 400*, 500*	3 h	20 h
Test 2	10, 20*, 40*, 60*, 80, 100, 200, 400	20 h	20 h
Present			
Test 1	50, 100, 150, 200, 350, 500*, 750*, 1000*	3 h	20 h
Test 2	200, 350, 500, 750, 1000*, 1500*, 2000, 2500*	3 h	20 h

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	> 500	> 500	negative
Test 2	-	≥ 60	> 400	negative
Present				
Test 1	-	> 1000	> 1000	negative
Test 2	-	> 2500	> 2500	equivocal

Remarks - Results

In Test 1, no statistically significant increases in the proportion of cells with chromosomal aberrations (including or excluding gap-type aberrations) were observed in the presence or absence of metabolic activation.

In Test 2, no statistically significant increases in the proportion of cells with chromosomal aberrations (including gap-type aberrations) were observed in the presence or absence of metabolic activation.

Gaps are generally not included in the total aberration frequency. When gaps were excluded, no statistically significant increase in the proportion of chromosomal aberrations were observed in the absence of metabolic activation or in cultures treated with 1000 µg/mL and 1500 µg/mL in the presence of metabolic activation, but there was a statistically significant increase in chromosomal aberrations observed in cultures treated with 2500 µg/mL. However, there is a lack of reproducibility between the two cultures as the aberration frequency value exceeded the historical negative control range (0-6%) in only one of the two cultures (7%), although the value observed for the other culture (3.3%) was slightly outside the 95% confidence limit of 3%.

The positive and negative controls gave a satisfactory response confirming

	the validity of the test system.
CONCLUSION	Under the conditions of the study, the clastogenic potential of the notified chemical was inconclusive.
TEST FACILITY	Huntingdon (1998f)

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