File No: LTD/1509

May 2013

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

2-Butenedioic acid (2E)-, di-C12-15-alkyl esters (INCI Name: Di-C12-15 Alkyl Fumarate)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (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 Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of Sustainability, Environment, Water, Population and Communities.

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 SUBSTANCE	INTRODUCTION VOLUME	USE
LTD/1509	Estee Lauder Pty Ltd	2-Butenedioic acid (2E)-, di-C12-15-alkyl esters (INCI Name: Di-C12-15 Alkyl Fumarate)	Yes	≤ 1 tonne per annum	Component of cosmetic products

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Skin Sensitisation (Category 1)	H317 – May cause an allergic skin reaction

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrase(s):
R43: May Cause sensitisation by skin contact

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

When used at ≤ 10% in body lotion, ≤ 6% in other leave-on cosmetic products and ≤ 10% in rinse-off cosmetic products, the notified chemical is not considered to pose an unreasonable risk to public health.

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

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Skin Sensitisation (Category 1): H317 – May cause an allergic skin reaction

- The following should be used for products/mixtures containing the notified chemical:
  - Conc. ≥ 1%: H317

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

CONTROL MEASURES
Occupational Health and Safety

- If beauty care professionals are frequently applying cosmetic products containing the notified chemical to clients, employers should implement the following safe work practices to minimise occupational exposure of workers to the notified chemical:
  - Avoid contact with skin

- If beauty care professionals are frequently applying cosmetic products containing the notified chemical to clients, employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Impervious gloves

  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 *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

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

Public Health

- The following measures should be taken to minimise public exposure to the notified chemical:
  - The notified chemical should only be used at ≤ 10% in body lotion, ≤ 6% in other leave-on cosmetic products and ≤ 10% in rinse-off cosmetic products.

Disposal

- The notified chemical should be disposed of to landfill.

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 notified chemical is introduced in a form other than in finished cosmetic products;
  - the concentration of the notified chemical exceeds or is intended to exceed 10% in body lotion, 6% in other leave-on cosmetic products and 10% in rinse-off cosmetic products;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of cosmetic products, or is likely to change significantly;
  - the chemical has begun to be manufactured in Australia;

- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

(Material) Safety Data Sheet
The (M)SDS of the notified chemical 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)
21 Rosebery Avenue
Rosebery, NSW 2018

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 all physico-chemical endpoints.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Marrix SF

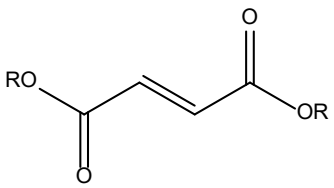
CAS NUMBER
142104-11-8

CHEMICAL NAME
2-Butenedioic acid (2E)-, di-C12-15-alkyl esters

OTHER NAME(S)
Di-C12-15 Alkyl Fumarate (INCI Name)

MOLECULAR FORMULA
Unspecified

STRUCTURAL FORMULA



R = alkyl (C12-15)

MOLECULAR WEIGHT

452-536 Da

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

3. COMPOSITION

DEGREE OF PURITY > 99%

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 ºC AND 101.3 kPa: white solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	32.5-42 ºC	Measured*
Density	912.8 kg/m^3 at 20 ºC	Measured*
Vapour Pressure	0.013 kPa at 25 ºC	Measured*
Water Solubility	$< 7 \times 10^{-10}$ g/L	Calculated using WATERNT Program (v1.01) US EPA (2009)
Hydrolysis as a Function of pH	Not determined	The notified chemical contains hydrolysable functionality, however, based on its low predicted water solubility, hydrolysis is expected to be slow in the environmental pH range (4–9) at ambient temperature
Partition Coefficient (n-octanol/water)	log Kow > 12	Calculated using KOWWIN (v1.67) US EPA (2009)
Adsorption/Desorption	log Koc > 6	Calculated using KOCWIN (v2.00) US EPA (2009)
Dissociation Constant	Not determined	The notified chemical has no dissociable functions
Particle Size	Not determined	Introduced in solution
Flash Point	148 ºC	Measured*
Flammability	Not highly flammable	Measured*
Autoignition Temperature	Not determined	Not expected to autoignite based on the melting point
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties.

*Studies were conducted by Chemtest Laboratories Inc. (Chemtest, 1994). Full study reports were not available.

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

Reactivity
Expected to be stable under normal conditions of use. The notified chemical is incompatible with strong acids, alkalis and oxidising agents.

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported into Australia as a component (≤ 10%) of finished cosmetic products.

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

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

PORT OF ENTRY
Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Estee Lauder Pty Ltd

TRANSPORTATION AND PACKAGING
The products containing the notified chemical (at ≤ 10% concentration) will be imported in containers suitable for retail sale. These will be packaged in cardboard cartons. The cartons will be distributed to retail outlets within Australia by road.

USE
The notified chemical is intended to be used as a skin conditioning agent/emollient in cosmetic products (proposed usage concentration: 10% concentration, e.g. in topical creams).

OPERATION DESCRIPTION
The notified chemical will be imported as a component of finished cosmetic products. Reformulation will not take-place in Australia.

The finished products containing the notified chemical will be used by consumers and professionals (such as workers in beauty salons). Depending on the nature of the product, application could be by hand or through the use of an applicator.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	12	4	12
Store persons	5	4	12
Salon workers	unspecified	unspecified	unspecified

EXPOSURE DETAILS
Transport and storage workers may come into contact with the notified chemical as a component of end-use products (at ≤ 10%) only in the event of accidental rupture of containers.

Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hair dressers, workers in beauty salons). Such professionals may use some personal protective equipment (PPE) to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public exposure
There will be widespread and repeated exposure of the public to the notified chemical through the use of the rinse-off and leave-on cosmetic and personal care products. The principal route of exposure will be dermal.

6.2. Human health effects assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity[1]	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute oral toxicity[2]	LD50 > 5,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity[2,3]	LD50 > 2,000 mg/kg bw; low toxicity
Rabbit, skin irritation[1]	non-irritating
Rabbit, eye irritation[2,3]	non-irritating
Guinea pig, skin sensitisation – adjuvant test[1] (at 100%)	evidence of sensitisation
Guinea pig, skin sensitisation – adjuvant test[1] (at 75%)	no evidence of sensitisation
Human, skin sensitisation – RIPT[1] (at 2.4-4%)	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation[2,3]	non mutagenic

[1]Details of study can be found in Appendix B;
[2]Full study report not provided;
[3]Date source: CIR (2009).

Toxicokinetics, metabolism and distribution.
While passive diffusion of the notified chemical across the gastrointestinal (GI) tract and dermal absorption may occur, it is expected to be limited by the low water solubility ($< 7 \times 10^{-10}$ g/L calculated), high partition coefficient (log Kow > 12 calculated) and relatively high molecular weight (452-536 Da) of the notified chemical.

Acute toxicity.
The notified chemical was of low acute oral and dermal toxicity in rats.

Irritation and Sensitisation.
The notified chemical was non-irritating to the skin and eyes of rabbits.

The notified chemical (at 100% induction concentration; 100% challenge concentration) was found to be a sensitiser in guinea pigs (Magnusson-Kligman method), with scattered mild redness noted in 10/20 and 8/20 animals at 24 and 48 hours after patch removal, respectively. In a second study in guinea pigs (Magnusson-Kligman method; 75% induction concentration; 75% challenge concentration), there was no evidence of reactions indicative of skin sensitisation to the notified chemical. The notified chemical (at 2.4%-15% concentration) was not a skin sensitiser in human repeat insult patch studies.

Based on the above studies, and given the structural similarities between the notified chemical and chemicals that have also been shown to be skin sensitisers (e.g. dimethyl fumarate; CIR, 2009), there is insufficient evidence to indicate that the notified chemical is not a potential skin sensitiser. Therefore, for risk assessment purposes, the notified chemical is considered to be a sensitiser.

Repeated Dose Toxicity.
No repeat dose toxicity data were provided for the notified chemical. However, several repeat dose toxicity studies conducted using formulations containing fumaric acid (~1%) in rats are reported (CIR, 2009), with no notable effects.

Mutagenicity.
The notified chemical was not mutagenic in a bacterial reverse mutation study.

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

Hazard classification	***Hazard statement***
Skin Sensitisation (Category 1)	H317 – May cause an allergic skin reaction

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

R43: May Cause sensitisation by skin contact

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

It is intended that beauty care professionals will handle the notified chemical at ≤ 10% concentration, similar to public use. Therefore, the risk for beauty care professionals who regularly use products containing the notified chemical is expected to be of a similar or lesser extent than that experienced by members of the public who use such products on a regular basis. For details of the public health risk assessment see section 6.3.2.

6.3.2. Public health

Repeat dose toxicity data are not available for the notified chemical. However, the main risk associated with use of the notified chemical at ≤ 10% concentration in cosmetic products, is its potential to cause sensitisation by skin contact.

Methods for the quantitative risk assessment for dermal sensitisation have been proposed and been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). As is shown in the table below, the Consumer Exposure Level (CEL) from use of the notified chemical in a number of possible cosmetic products may be estimated (SCCS, 2010). When tested at 15% concentration (and below) in human repeat insult patch studies, the notified chemical was not a skin sensitiser. Consideration of the details of the studies and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of ~163 µg/cm^2 (derived from the study conducted at 7.5-15% concentration). In this instance, the factors employed included an intraspecies factor (10), a matrix factor (1), a use and time factor (3.16) and a database factor (3.16), giving an overall safety factor of ~100.

Product type	Proposed usage concentration (%)	CEL (µg/cm^2)	AEL (µg/cm^2)	Recommended usage concentration (%)
Body lotion	10	50	163	≤ 10
Other leave-on cosmetics (assumed: face cream)	10	273	163	≤ 6
Rinse-off cosmetics (assumed: conditioner)	10	2.7	163	≤ 10

As the AEL>CEL, the risk to the public of the induction of sensitisation that is associated with the use of the notified chemical at ≤ 10% concentration in body lotion and rinse-off cosmetic products (using conditioner as a typical example) is not considered to be unreasonable. With regards to other leave-on cosmetic products (using face cream as a worst case example), as the CEL>AEL, the risk to the public of the induction of sensitisation that is associated with use of the notified chemical at ≤ 10% concentration is considered to be unreasonable. Reducing the concentration of the notified chemical in other leave-on cosmetic products to ≤ 6% allows recalculation of the consumer exposure to acceptable levels. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 10% in body lotion, ≤ 6% in other leave-on cosmetic products and ≤ 10% in rinse-off cosmetic products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of finished cosmetic products. In the unlikely event of an accidental spill during transport or storage, the notified chemical is expected to be collected and disposed of to landfill.

RELEASE OF CHEMICAL FROM USE
The majority of the notified chemical is expected to be washed to sewer as a result of its use pattern in rinse-off and leave-on cosmetic products.

RELEASE OF CHEMICAL FROM DISPOSAL
Residue of the notified chemical in empty containers will share the fate of the container and will either be disposed of to landfill, or washed to sewer when containers are rinsed before recycling. Waste and expired material is expected to be disposed of to landfill.

7.1.2 Environmental fate
No environmental fate data were submitted. However, the notified chemical is predicted to be readily biodegradable by modules of the estimation program BIOWIN (v4.10) (US EPA, 2009). The majority of the notified chemical is expected to be released to the sewerage system. In waste water treatment processes in sewage treatment plants (STPs), a high proportion of the notified chemical is expected to be removed from influent due to a combination of biodegradation and partitioning of the notified chemical to sludge and suspended solids. The notified chemical that partitions to sludge will be removed for disposal to landfill or used on land for soil remediation where it is not expected to be mobile, based on the estimated high log Koc (> 6). In soil, the notified chemical is expected to be degraded by abiotic and biotic processes to form water and oxides of carbon. If released to surface waters, the notified chemical will partition to suspended solids and organic matter and is expected disperse and degrade. The notified chemical is not expected to bioaccumulate as calculations with BCFBAF (v3.00) (US EPA, 2009) indicate a very low bioconcentration potential (BCF < 46.3 L/kg wet-wt).

7.1.3 Predicted Environmental Concentration (PEC)
The predicted environmental concentration (PEC) is estimated as outlined below based on a worst case scenario of complete discharge of the total annual import of the notified chemical to receiving waters via sewage treatment works nationwide.

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)	21.161	million
Removal within STP	0%	
Daily effluent production:	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.65	µg/L
PEC - Ocean:	0.06	µg/L

The notified chemical is predicted to partition to sludge and to be readily biodegradable, hence the removal of 97% of the notified chemical from influent by sewage treatment plant (STP) processes is expected (Simple Treat; European Commission, 2003). However, in this worst case model, the majority of the notified chemical is assumed to be released in effluent. 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 0.647 µg/L may potentially result in a soil concentration of approximately 4.316 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 21.58 µg/kg and 43.16 µg/kg, respectively. However, due to the absorptive characteristics of the notified chemical, and its likely biodegradability, these calculated values represent maximum concentrations only.

7.2. Environmental effects assessment
No experimental ecotoxicity data were submitted. The notified chemical is not expected to be bioavailable

based on its high predicted log Kow and, in general, no adverse effects to aquatic organisms are expected for chemicals with log Kow exceeding 8. The notified chemical is therefore not likely to have adverse effects at its water saturation concentration. This conclusion is supported by ECOSAR calculations (US EPA, 2009) where no effects at saturation are predicted for log Kow > 5 (for acute fish and daphnia toxicity endpoints) and log Kow > 6.4 (for green algae toxicity endpoint).

7.2.1 Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) was not calculated since no adverse effects at saturation are predicted for the notified chemical.

7.3. Environmental risk assessment

A risk quotient (PEC/PNEC) for the notified chemical was not calculated as a PNEC was not derived. However, the notified chemical is likely to have very limited aquatic exposure based on the expected efficient removal of the chemical from waste water by sorption to sewage sludge and biodegradation. The notified chemical is also not expected to be bioavailable to aquatic organisms in surface waters based on its estimated hydrophobicity. Therefore, when used as proposed the notified chemical is not expected to pose a risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Water Solubility $< 7 \times 10^{-10}$ g/L (WATERNT Program v1.10, US EPA,2009)

Method OECD TG 105 Water Solubility

Remarks A full test report was not available and only a brief summary of the test report was submitted. The water solubility was reported as 2 g/L based on a gravimetric determination. However a 'severe emulsion problem' was reported. As it cannot be discounted that the emulsion did not affect the test results, these results should be treated with caution.

The water solubility was estimated by the WATERNT Program v1.10 (US EPA, 2009). The notified chemical is expected to have low water solubility based on its predominantly hydrophobic structure.

Test Facility Chemtest (1994)

Partition Coefficient (n-octanol/water) log Kow > 12 (KOWWIN v1.67, US EPA 2009)

Method Modification of OECD TG 107 Partition Coefficient (n-octanol/water): Shake Flask Method

Remarks A full test report was not available and only a brief summary of the test report was submitted. The test substance was added to a 1:1 mixture of water and n-octanol (25 mL : 25 mL) and mechanically stirred for 30 min. The mixture was left overnight so that the aqueous and octanol layers could separate. Each layer was evaporated and the recovered solids were weighed on an analytical balance. The partition coefficient was reported as being 36.1 (log Kow = 1.56). However 'emulsion problems' were reported and the recovered solid (7.4767 g) was significantly less than the initial amount dissolved (9.1280 g). As it cannot be discounted that the emulsion did not affect the test results, these results should be treated with caution.

The partition coefficient for the notified chemical was estimated using the QSAR estimations program KOWWIN (v1.67) (US EPA 2009). The notified chemical is expected to partition from water to octanol based on its predominantly hydrophobic structure.

Test Facility Chemtest (1994)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/HanBrl: Wist (SPF)
Vehicle	Corn oil
Remarks - Method	The test substance was applied as a single dose (2,000 mg/kg bw) to 3 male and 3 female animals. The study report is unsigned and therefore not in accordance with GLP.
RESULTS	
Remarks - Results	There were no mortalities observed.
LD50	> 2,000 mg/kg bw
Signs of Toxicity	None
Effects in Organs	None
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	RCC (2001)

B.2. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	FHSLA, 16 CFR 1500.41
Species/Strain	Rabbit/New Zealand White
Number of Animals	6
Vehicle	None reported
Observation Period	72 hours
Type of Dressing	Occlusive
Remarks - Method	Six healthy rabbits were each uniquely identified and then prepared by clipping the trunk free of hair. Two 2.5 cm square patches were placed over intact skin and abraded skin on each rabbit. 0.5 g of the test substance was placed under each patch. The entire trunk of the animal was wrapped with a rubberised elastic cloth to retard evaporation and as an aid in maintaining test patch position. Rabbits were placed in neck collars and returned to their individual cages. Collars were removed after 24 hours. All test sites were wiped with a cloth to prevent further exposure. Skin lesions were evaluated at 24 and 72 hours and scored in accordance with FHSLA 16 CFR 1500.41. The test substance was applied at 36 ºC.
RESULTS	
Remarks - Results	No reactions to the test substance were noted on either intact or abraded skin, therefore, the test substance was considered by the study authors to be a non-primary irritant to the skin.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	AMA (1991)

B.3. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 406 Skin Sensitisation - Magnusson and Kligman

guinea pig maximisation test.

Species/Strain: Albino guinea pig/Hartley derived

PRELIMINARY STUDY: Minimum Irritant Concentration:
intradermal: 3%
topical: 100%

MAIN STUDY

Number of Animals: Test Group: 10M/10F Vehicle Control Group: 5M/5F

INDUCTION PHASE: Induction Concentration:
intradermal: 3%
topical: 100%

Signs of Irritation: It is noted that prior to the topical induction phase, the animals were pre-treated with 10% sodium lauryl sulfate (SLS) to create a local irritation.

CHALLENGE PHASE

1st challenge: topical: 100%

Remarks - Method: The vehicle for the test substance was ethyl alcohol. Two patches saturated with the relevant substance (approx. 0.5 mL) were applied to i) the left flank (100%) and ii) the right flank (vehicle only). A positive control study (using phenylacetaldehyde) was also conducted.

24 hours post-challenge patch application, the patches were removed and the site wiped clean of excess substance.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	100%	10/20	8/20
	0%	0/20	0/20
Vehicle Control Group	100%	1/10	0/10
	0%	0/10	0/10

Remarks - Results: Scattered mild redness was noted in 10/20 and 8/20 animals at 24 and 48 hours after patch removal, respectively. Based on these results, the study authors concluded that the notified chemical has the potential to be a moderate sensitizer.

In the vehicle control group, 1/10 animals exhibited scattered mild redness at 24 hours, while in the positive control group skin reactions were noted for 10/10 and 9/10 animals at 24 and 48 hours, respectively.

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

TEST FACILITY: Laberco-Celsis (1996)

B.4. Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 406 Skin Sensitisation - Magnusson and Kligman guinea pig maximisation test.

Species/Strain: guinea pig/lbm: GOHI (Himalayan spotted)

PRELIMINARY STUDY: Maximum Non-irritating Concentration:
intradermal: 50%
topical: 75%

MAIN STUDY

Number of Animals: Test Group: 10M Vehicle Control Group: 5M

INDUCTION PHASE	Induction Concentration: intradermal: 50% topical: 75%
Signs of Irritation	Following the intradermal induction phase, skin reactions (unspecified) were noted for both the control and test group. Discrete/patchy erythema was noted in all animals 24 and 48 hours following the topical induction phase. The animals were pre-treated with 10% sodium lauryl sulfate (SLS).
CHALLENGE PHASE	
1st challenge	topical: 75% and 15%,
Remarks - Method	The vehicle for the test substance was corn oil. Three patches saturated with the relevant substance (approx. 0.2 mL) were applied to i) left caudal flank (75%), ii) left cranial flank (15%) and iii) right flank (vehicle only). 24 hours post-challenge patch application, the patches were removed. 21 hours after removal of the dressing, the test sites were depiliated with a depilatory cream.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: 1st challenge*	
		24 h	*48 h*
Test Group	75%	0/10	0/10
	15%	0/10	0/10
	0%	0/10	0/10
Control Group	75%	0/5	0/5
	15%	0/5	0/5
	0%	0/5	0/5

Remarks - Results	Following the challenge phase, no signs of skin reaction were noted for animals in both the test and control groups. A positive control study (using 2-mercaptobenzothiazole) had been previously conducted in the laboratory.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	RCC (2002)

B.5. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation containing 3.5% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches infused with 200 µL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: 9 days Challenge Procedure: Identical patches were applied to original sites and naïve sites. Patches remained in place for 24 h. Sites were graded at patch removal and 24 h post-patch removal.
Study Group	68 F, 42 M; age range 18-76 years
Vehicle	None
Remarks - Method	Semi-occluded. The test substance was spread on a 2 cm x 2 cm patch.

RESULTS	
Remarks - Results	99/110 subjects completed the study. Of the subjects that did not complete the study, 0-9 induction observations were recorded. No adverse responses were noted during induction or at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	PI (2010)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation containing 2.4% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches infused with 150 µL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications (Exception: application 9 was applied on Thursday and removed Friday). Patches were removed after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: 10 days Challenge Procedure: Identical patches were applied to original sites and naïve sites. Patches remained in place for 24 h. Sites were graded at patch removal and 24 h post-patch removal.
Study Group	74 F, 37 M; age range 18-70 years
Vehicle	None
Remarks - Method	Semi-occluded. The test substance was spread on a 2 cm x 2 cm patch.
RESULTS	
Remarks - Results	99/110 subjects completed the study. Of the subjects that did not complete the study, 1-9 induction observations were recorded. No adverse responses were noted during induction or at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	PI (2008a)

B.7. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation containing 2.5% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches infused with 150 µL test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: 9 days Challenge Procedure: Identical patches were applied to original sites and naïve sites. Patches remained in place for 24 h. Sites were graded at patch removal and 24 h post-patch removal.
Study Group	76 F, 35 M; age range 18-70 years
Vehicle	None
Remarks - Method	Semi-occluded. The test substance was spread on a 2 cm x 2 cm patch and then the patch was exposed to ambient air for at least 30 minutes prior to application.
RESULTS	
Remarks - Results	100/111 subjects completed the study. Of the subjects that did not complete the study, 0-9 induction observations were recorded.

	No adverse responses were noted during induction or at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	PI (2008b)

B.8. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulation containing 4% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 g 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). The first patch removal was supervised. Rest Period: ~14 days Challenge Procedure: A patch was applied to a naïve site. Patches remained in place for 24 h. Sites were graded at patch removal and 48 h post-patch removal.
Study Group	85 F, 29 M; age range 18-70 years
Vehicle	None
Remarks - Method	Semi-occluded. The test substance was spread on a 2.54 cm (1 inch) x 2.54 cm (1 inch) patch.
RESULTS	
Remarks - Results	108/114 subjects completed the study. It is reported that the remaining subjects discontinued participation for reasons unrelated to the application of the test material. Of the subjects that did not complete the study, 0-9 induction observations were recorded. No adverse responses were noted during induction or at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	CPT (2009)

B.9. Skin sensitisation – human volunteers

TEST SUBSTANCE	Formulations containing 0-15% notified chemical
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: Patches containing 0.2 g test substances (bands 1-4 on the left back of the subjects were assigned for formulations containing 0, 7.5, 10 and 15%, respectively) were applied 3 times per week (in general, Monday, Wednesday and Friday) for a total of 9 applications. In-general, patches were removed by a technician after 24 h (except for patches applied on Friday, which were removed by the applicants) and graded after an additional 24 h (or 48 h for patches applied on Friday). However, in week 1, patches were applied on Monday, Tuesday and Wednesday, with the first 2 patches removed by a technician and the site graded prior to application of a new patch. Rest Period: 9 days Challenge Procedure: Identical patches were applied to original sites and naïve sites. Patches remained in place for 24 h. Sites were graded at patch removal and 24 h post-patch removal.
Study Group	123 F, 97 M; age range 18-86 years; grouped in two panels
Vehicle	None
Remarks - Method	Semi-occluded. The test substance was spread on four 2 cm x 2 cm

	patches, each containing 0, 7.5, 10 and 15% concentration, respectively.
RESULTS	
Remarks - Results	213/220 subjects completed the study. Of the subjects that did not complete the study, 1-7 induction observations were recorded. No adverse responses were noted during induction or at challenge.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	PI (2012)

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