File No: LTD/1829

July 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Benzoic acid, 2,4-dihydroxy-3-methyl-, methyl ester (INCI name: Methyl 3-Methylresorcylate)

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/1829	International Flavours & Fragrances (Australia) Pty Ltd	Benzoic acid, 2,4-dihydroxy-3-methyl-, methyl ester (INCI name: Methyl 3-Methylresorcylate)	Yes	≤ 1 tonne per annum	Fragrance ingredient.

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

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

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:

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.

Based on the available information, when used at ≤ 0.01% in leave-on cosmetic products and ≤ 0.1% in rinse-off cosmetics and household products, the notified chemical is not considered to pose an unreasonable risk to public health.

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

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

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

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

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

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation processes:
  - Enclosed, automated processes, where possible
  - Ventilation system including local exhaust ventilation

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

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during reformulation processes:
  - Coveralls, impervious gloves

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

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

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

Public Health

- The following measures should be taken to minimise public exposure to the notified chemical:
  - The notified chemical should only be used at ≤ 0.01% in leave-on cosmetic products and ≤ 0.1 % in rinse-off cosmetics and household products.

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.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory

obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the notified chemical is intended to be introduced at 100% concentration and/or in powder form;
- the concentration of the notified chemical exceeds or is intended to exceed 0.01% in leave-on cosmetic products and 0.1% in rinse-off cosmetics and household products;
- additional information becomes available on the phototoxicity potential of the notified chemical.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a fragrance ingredient, 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 a 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)
International Flavours and Fragrances (Australia) Pty Ltd. (ABN: 77 004 269 658)
310 Frankston-Dandenong Rd
DANDENONG, VIC 3175

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 as follows: all physico-chemical endpoints (exception: water solubility)

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

NOTIFICATION IN OTHER COUNTRIES
Canada, China, Europe, New Zealand, Philippines, U.S.A

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Oceanol
Seamoss
Methyl 3-Methylresorcylate (INCI name)

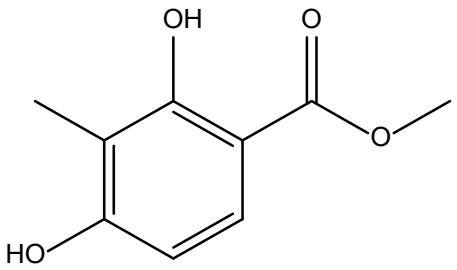
CAS NUMBER
33662-58-7

CHEMICAL NAME
Benzoic acid, 2,4-dihydroxy-3-methyl-, methyl ester

OTHER NAME(S)
Methyl 2,4-dihydroxy-3-methylbenzoate
Methyl 2,4-dihydroxy-m-toluate
TM 10-205
TM 11-206

MOLECULAR FORMULA
$C_9H_{10}O_4$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
182.18 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 99%

IMPURITIES/RESIDUAL MONOMERS
None identified.

ADDITIVES/ADJUVANTS
None.

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: off-white to beige coloured powder.

Property	Value	Data Source/Justification
Melting Point/Freezing Point	130 – 133 °C	(M)SDS
Density	Not determined.	Introduced only in formulated products.
Vapour Pressure	2.06 x 10^{-6} kPa at 25 °C	Estimated – Modified Grain method (US EPA, 2009)
Water Solubility	0.32 +/- 0.02 g/L	Measured
Hydrolysis as a Function of pH	t½ = 4.6 years at pH 7 t½ = 46 years at pH 8	Calculated using HYDROWIN v2.00 (US EPA, 2011)
Partition Coefficient (n-octanol/water)	log Pow = 2.67	Calculated using KOWWIN v1.68 (US EPA, 2011)
Adsorption/Desorption	log K_{oc} = 2.67	Calculated using KOCWIN v2.00 (US EPA, 2011)
Dissociation Constant	Not determined.	No dissociable functionality
Particle Size	Not determined.	Introduced only in formulated products.
Flash Point/Flammability	Not determined.	Introduced only in formulated products. Not expected to be flammable under conditions of use.
Autoignition Temperature	Not determined.	Introduced only in formulated products. Not expected to autoignite under normal conditions.
Explosive Properties	Not determined.	Contains no functional groups that would imply explosive properties.
Oxidising Properties	Not determined.	Contains no functional groups that would imply oxidising properties.

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 limited 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 compounded fragrances.

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.

IDENTITY OF MANUFACTURER/RECIPIENTS
International Flavours & Fragrances (Australia) Pty Ltd.

TRANSPORTATION AND PACKAGING
The notified chemical (at ≤ 0.2% concentration) will be imported as a component of finished fragrance oils in 208.2 L polypropylene-lined steel drums or as a component of finished products. The imported and formulated products containing the notified chemical will be transported within Australia by road. The end-use products (≤ 0.1% concentration of the notified chemical) will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient and incorporated into a variety of cosmetic and household products (at proposed usage concentrations of ≤ 0.01% in leave-on cosmetic products and ≤ 0.1% in rinse-off cosmetics and household products).

OPERATION DESCRIPTION
The notified chemical will not be manufactured within Australia. No reformulating or repackaging of the notified chemical will occur at the notifier facility. The fragrance oils containing the notified chemical will be stored at this facility until they are sold and shipped to customer facilities.

Reformulation
The procedures for incorporating the notified chemical (at ≤ 0.2 % concentration) into end-use products will likely vary depending on the nature of the formulated products and may involve both automated and manual transfer steps. However, in general, it is expected that for the reformulation process, the notified chemical will be weighed and added to the mixing tank where it will be blended with additional additives to form the finished cosmetic and household products. This will be followed by automated filling of the reformulated products into containers of various sizes. The blending operations are expected to be highly automated and use closed systems and/or adequate ventilation. During the formulation process, samples of the notified chemical and the finished cosmetic products will be taken for quality control testing.

Household products
Household products containing the notified chemical (≤ 0.1% concentration) may be used by consumers and professional workers (such as cleaners). The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines, or open processes and manually by rolling, brushing, spraying and dipping.

Cosmetic products
The finished cosmetic products containing the notified chemical at ≤ 0.1% concentration will be used by consumers and professionals (such as beauticians and hairdressers). Depending on the nature of the product, application could be by hand, sprayed or through the use of 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 workers	Unknown	Unknown
Plant operators – mixing/compounding	4	250

Plant operators – drum handling	1	250
Plant operators – drum cleaning/washing	2	250
Plant operators – equipment cleaning/washing	2	250
Plant operators – quality control	1	250
Professional users – (e.g. hair and beauty salon workers, cleaners)	Not specified	Not specified

EXPOSURE DETAILS

Transport and storage
Transport and storage workers may come into contact with the notified chemical as a component of fragrance oils (at ≤ 0.2% concentration) only in the event of accidental rupture of the drum containers.

At the notifier facility, the primary work activity undertaken by transport and warehouse workers will include the handling, loading and off-loading of drums containing fragrance oils formulated with the notified chemical at ≤ 0.2% concentration. Exposure of these workers will be limited to situations involving products sampling for quality control or, in the event of a discharge, clean up from a spill or leaking drum. If such an event occurs, a worker may be exposed through dermal or ocular contact. The notifier states that such exposures will be minimised to the extent possible through the use of personal protective equipment (PPE) including protective overalls, chemical resistant gloves and safety glasses.

Reformulation
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 0.2% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of mechanical ventilation, local exhaust ventilation and/or enclosed systems, and through the use of PPE.

End-use
Exposure to the notified chemical in end-use products (at ≤ 0.1% concentration) may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. hair dressers, workers in beauty salons) or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at ≤ 0.1% concentration) through the use of a wide range of cosmetic and household products. The principal routes of exposure will be dermal, while ocular and inhalation exposures (e.g. through the use of spray products) are also possible.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical or a suitable analogue chemical are summarised in the following table. For full details of the studies, refer to Appendix B. The analogue chemical, Benzoic acid, 2,4-dihydroxy-3,6-dimethyl-, methyl ester (CAS 4707-47-5), was considered to be structurally similar to the notified chemical. The differences in structure/molecular weight between the notified and analogue chemical are not considered significant from a toxicological viewpoint. Where data on the notified chemical were not available, the analogue chemical has been used for read-across purposes for certain endpoints.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity*	LD50 > 5,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity*	LD50 > 5,000 mg/kg bw; low toxicity
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (0.5%)	no evidence of sensitisation
Genotoxicity – *in vitro* BlueScreen HC assay	genotoxic (in absence of metabolic activation)
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vivo* micronucleus assay*	non genotoxic
Phototoxicity – *in vitro* – 3T3 NRU phototoxicity test	predicted to have phototoxic effects

Human, phototoxicity – patch test (0.05, 0.25 & 0.5%)	inadequate evidence of phototoxicity

*Studies conducted on an analogue chemical

Toxicokinetics, metabolism and distribution.
Based on the low molecular weight (182.18 Da), water solubility (0.32 ± 0.02 g/L) and calculated partition coefficient (log P_{ow} = 2.67) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are expected to occur. The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity.
No acute oral, dermal or inhalation toxicity data were provided for the notified chemical. However, a suitable analogue chemical was of low acute toxicity via the oral and dermal routes.

Irritation.
No ocular or dermal irritation data were provided for the notified chemical. However, a suitable analogue chemical was slightly irritating to the eyes of rabbits. In addition, while the potential for skin irritation effects cannot be ruled out (due to the absence of an appropriately conducted study), it is noted that irritation effects were not reported in studies where the notified chemical or suitable analogue were applied to the skin of animals (e.g. acute dermal toxicity and LLNA studies).

Sensitisation.
The notified chemical was found to be a skin sensitiser in mice (Local Lymph Node Assay; stimulation indices of 3.28, 4.78 and 3.39 at 10, 25 and 50% concentrations, respectively). Based on the results of this study, an EC_3 value could not be determined.

The sensitising potential of the notified chemical was also tested in a human repeat insult patch test (HRIPT; 100 subjects completing the study). The notified chemical was not a skin sensitiser when tested at 0.5% concentration under the conditions of the study.

Repeated dose toxicity.
No repeated dose toxicity data were provided for the notified chemical.

Mutagenicity/Genotoxicity.
The notified chemical was determined by the study authors to be genotoxic in an *in vitro* BlueScreen HC assay in the absence of metabolic activation (study not validated for regulatory purposes; negative results were reported in the presence of metabolic activation). The notified chemical was not mutagenic in a bacterial reverse mutation study and the analogue chemical was not genotoxic in an *in vivo* micronucleus study. Other fragrance chemicals that are structurally similar to the notified chemical and are reported in the literature to have positive *in vitro* BlueScreen HC assay results, also show negative results in other *in vitro* and *in vivo* tests (Etter *et. al*., 2015).

Phototoxicity.
In an *in vitro* phototoxicity study (BALB/c 3T3 cells), the notified chemical was predicted to be phototoxic.

In a human phototoxicity test, the notified chemical was deemed by the study authors not to be phototoxic, when tested at 0.05, 0.25 and 0.5% concentrations (with 35 subjects completing the study). It is noted, however, that various effects were noted at sites subjected to irradiation. In general the effects were considered by the study authors to be mild, noting that effects were also observed at control sites. However, 1 subject showed moderate erythema at 24, 48 and 72 hours and oedema at 24 and 48 hours at a site treated with 0.25% test substance, indicating phototoxic potential. However, in the absence of a dose-response relationship, this potential was deemed by the study authors to be low.

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

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

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:

R43: May cause sensitisation by skin contact

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Reformulation (and quality control processes)
Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemical (at ≤ 0.2% concentration) during reformulation processes (and during sampling and quality control processes at storage sites). The notified chemical is considered to be a skin sensitiser. Based on the available information, the potential for other effects following exposure to the notified chemical at the proposed concentration (e.g. phototoxicty, repeated dose toxicity) cannot be excluded. Therefore, caution should be exercised when handling the notified chemical during reformulation and quality control processes.

The use of enclosed, automated processes and PPE (e.g. impervious gloves, coveralls) should minimise the potential for exposure. Therefore, provided that adequate control measures are in place to minimise worker exposure, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Cleaners, hair and beauty care professionals will handle the notified chemical at ≤ 0.1% concentration. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. 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 on a regular basis (for details of the public health risk assessment, see Section 6.3.2.).

6.3.2. Public Health
The notified chemical is proposed to be used at ≤ 0.01% concentration in leave-on cosmetic products and ≤ 0.1% concentration in rinse-off cosmetics and household products

Sensitisation, irritation and phototoxicity
Irritation and phototoxic effects are not expected from use of the notified chemical at the proposed concentrations in the relevant product types (noting that the higher proposed usage concentration of 0.1% relates only to rinse-off cosmetic products and household products).

A significant risk associated with use of the notified chemical is its potential to cause sensitisation by skin contact. Proposed methods for the quantitative risk assessment of dermal sensitisation have been the subject of significant discussion (see for example, Api *et al.*, 2008 and RIVM, 2010). Using fine fragrances (containing 0.01% notified chemical) as worst case scenario example of products that may contain the notified chemical, the Consumer Exposure Level (CEL) is estimated to be 0.38 μg/cm^2 (Cadby *et al.*, 2002).

When tested in an HRIPT study at 0.5% concentration, the notified chemical was not a skin sensitiser. Consideration of the study details and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 0.92 μg/cm^2. In this instance, the factors employed included an interspecies factor (1), intraspecies factor (10), a matrix factor (3.16), a use and time factor (3.16), and a database factor (3), giving an overall safety factor of ~300.

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of fine fragrances (a worst case example) at ≤ 0.01% concentration is not considered to be unreasonable. Based on the generally lower expected exposure level from other leave-on cosmetic products (also containing ≤ 0.01% notified chemical), rinse-off cosmetics and household products (both containing ≤ 0.1% notified chemical), by inference, the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Repeat dose toxicity
The repeated dose toxicity effects of the notified chemical have not been determined. However, exposure is expected to be limited by the low concentrations of the notified chemical in end use products.

Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.01% in leave-on cosmetic products and ≤ 0.1% in rinse-off cosmetics and household products, is not considered to be unreasonable. In the absence of data on the repeated dose toxicity potential of the notified chemical, use of the notified chemical is supported only under limited exposure conditions, which are reflected in the low concentration of the notified chemical in end-use products.

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 fragrance ingredient for local reformulation into a variety of consumer products or as a component of finished products. Release during reformulation in Australia is expected to be limited to accidental spills or leaks of drums and residues in import containers. Waste water from reformulation equipment cleaning is expected to be discharged to an on-site and/or local wastewater treatment plant for recycling (no release estimate).

RELEASE OF CHEMICAL FROM USE

The notified chemical is expected to be released to the aquatic compartment through sewers during its use in various cosmetic and household products.

RELEASE OF CHEMICAL FROM DISPOSAL

Any product residues remaining in the end use containers are expected to be disposed of or land filled through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system through its use as a component of cosmetics and household products, before potential release to surface waters nationwide. Based on a modelled fate study (EPI Suite, US EPA, 2011), the notified chemical is considered readily biodegradable. Based on its calculated adsorption coefficient (log K_{OC} = 2.67), release to surface waters may occur as only partial partitioning to sludge is expected. The notified chemical is not expected to bioaccumulate due to its calculated n-octanol/water partition coefficient (log P_{OW} = 2.67) and ready biodegradability. Therefore, in surface waters the notified chemical is expected to disperse and degrade through abiotic and biotic processes to form water and oxides of carbon.

The notified chemical is highly volatile from water (log H = -3.46 Pa/m^3/mol; European Commission, 2003) and will volatilise to air during sewage treatment. The half-life of the notified chemical in air is calculated to be 0.64 hours, based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, the notified chemical is not expected to persist in the air compartment.

The majority of the notified chemical will be released to sewer after use. A small proportion of the notified chemical may be applied to land when effluent is used for irrigation, or when sewage sludge is used for soil remediation, or disposed to landfill as collected spills and empty containers. The notified chemical residues in landfill, soil and sludge are expected to have low mobility based on the reported adsorption coefficient (log K_{OC} = 2.67), and is expected to eventually degrade to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

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 1,000 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

No ecotoxicity data were submitted. By using ECOSAR (US EPA, 2011), the following acute toxicity data have been predicted for the notified chemical:

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC_{50} = 9.88 mg/L	Toxic to fish
Daphnia Toxicity	48 h EC_{50} = 19.12 mg/L	Harmful to *Daphnia*
Algal Toxicity	72 h EC_{50} = 7.31 mg/L	Toxic to algae

The notified chemical is considered to be toxic based on the above predicted endpoints. These data are for risk assessment purposes only. Modelled data are not used for the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009). Therefore, the notified chemical has not been formally classified under GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) was calculated using the predicted endpoint for algae which is considered to be the most sensitive species. A safety factor of 100 was used as acute toxicity values from three trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC_{50} (Algal)	7.31	mg/L
Assessment Factor	100	
PNEC:	73.1	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River:	0.61	73.1	0.008
Q - Ocean:	0.06	73.1	0.0008

The risk quotient (Q = PEC/PNEC) for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity. Therefore, on the basis of the PEC/PNEC ratio and the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Water Solubility 0.32 +/- 0.02 g/L at 22 °C

Method	OECD TG 105 Water Solubility.
Remarks	Flask Method
Test Facility	IFF (2015)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Analogue chemical

METHOD: Study method supplied by the Notifier (Protocol OLD (7/25/79))
Similar to OECD TG 401 Acute Oral Toxicity – Limit Test.

Species/Strain	Rat/TacN(SD)fBR
Vehicle	Unspecified diluent
Remarks - Method	GLP Compliance.

A range-finding test was conducted using 2 animals (1 per sex; 5,000 mg/kg bw) with a 72 hour observation period.

For the main test, observations were made at 1, 3, 5 and 24 hours post dosing (day zero), and twice daily until the end of the 14 day study period.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	10 per sex	5,000	0/20

LD_{50}	> 5,000 mg/kg bw
Signs of Toxicity	There were no treatment related signs of systemic toxicity noted in any of the animals over the study period.
Effects in Organs	No macroscopic abnormalities were observed at necropsy.
Remarks - Results	All animals survived until the scheduled termination and showed gains in bodyweight over the study period.

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

TEST FACILITY: CSE (1980a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Analogue chemical

METHOD: Study method supplied by the Notifier (Protocol DLD (9/7/79))
Similar to OECD TG 402 Acute Dermal Toxicity.

Species/Strain	Rat/albino (Charles River)
Vehicle	Unspecified alcohol-based diluent.
Type of dressing	No dressing was specified.
Remarks - Method	GLP Compliance.

The test article was allowed to remain in contact with the skin and open to air for 24 hours, after which any excess material was removed.

A range-finding test was conducted using 2 animals (1 per sex; 5,000 mg/kg bw) with a 72 hour observation period.

For the main test, observations were made at 1, 3, 5 and 24 hours post dosing (day zero), and twice daily until the end of the 14 day study period.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*

2	8 per sex	5,000	0/16

LD_{50}	> 5,000 mg/kg bw
Signs of Toxicity - Local	There were no signs of local irritation reported in any of the animals over the study period
Signs of Toxicity - Systemic	There were no treatment related signs of systemic toxicity noted in any of the animals over the study period.
Effects in Organs	No macroscopic abnormalities were observed at necropsy.
Remarks - Results	All animals survived until the scheduled termination and showed gains in bodyweight over the study period.

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

TEST FACILITY CSE (1980b)

B.3. Irritation – eye

TEST SUBSTANCE Analogue chemical

METHOD Study method supplied by the Notifier (Protocol #RE (7/23/79))
Similar to OECD TG 405 Acute Eye Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	6 (sex not specified)
Observation Period	7 days
Remarks - Method	GLP Compliance.

Prior to dosing (24 hours) and post-dosing (at 24 hours and 7 days), the eyes were examined using fluorescein.

RESULTS

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Conjunctiva: redness	0	0	0.33	0.33	0	0	1	< 48 hours	0
Conjunctiva: chemosis	0	0	0	0	0	0	0	-	0
Conjunctiva: discharge	0	0	0	0	0	0	0	-	0
Corneal opacity	0	0	0	0	0	0	0	-	0
Iridial inflammation	0	0	0	0	0	0	0	-	0

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

Remarks - Results	2 animals presented with conjunctival redness (vessels definitely injected above normal) at the 24 hour observations only. No other signs of irritation were seen during the study period

CONCLUSION The test substance is slightly irritating to the eye.

TEST FACILITY CSE (1980c)

B.4. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay.

Species/Strain	Mouse/ CBA/Ca (CBA/CaOlaHsd).
Vehicle	Acetone/olive oil (4:1 v/v; AOO).
Remarks - Method	No significant protocol deviations.

GLP Compliance.

A preliminary toxicity study (using 1 mouse) was performed with the test substance at 50% w/w and was used to select the concentrations for the main test. No signs of systemic toxicity were noted. Off white coloured residual test substance was noted on the ear of the animal post-dosing on days 1 to 3.

A concurrent positive control study was not conducted, but had been conducted previously in the test laboratory (α-Hexylcinnamaldehyde Tech, 85%, as a 15% v/v dilution in 4:1 v/v AOO).

RESULTS

Concentration (% w/w)	*Mean Disintegrations (DPM/animal))*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	795.78 (± 312.94)	N/A
10	2,606.88 (± 976.84)	3.28
25	3,800.42 (± 1,358.40)*	4.78
50	2,697.56 (± 737.27)	3.39

*Significantly different from the control group $p < 0.05$

Remarks - Results

No signs of systemic toxicity were noted in the test or control animals during the study. Off white coloured residual test substance was noted on the ears of animals treated at 50% w/w on days 1 to 3 post-dosing, and in animals treated at 25% w/w on day 3 post-dosing.

The results show that the test substance elicited stimulation indices > 3 for all concentration levels tested. A statistically significant difference was noted between the control group and the 25% w/w dose group.

The EC3 value could not be determined.

All control and test animals maintained or gained body weight over the course of the study, except 1 animal of the 50% w/w group (1 g loss).

CONCLUSION

There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY

Safepharm (2008a)

B.5. Skin sensitisation – human volunteers

TEST SUBSTANCE

Notified chemical (0.5% w/w 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 hours and graded after an additional 24 hours (or 48 hours for patches applied on Friday).

Rest Period: approximately 2 weeks.

Challenge Procedure: A patch was applied to a naïve site. Patches were removed by technicians after 24 hours. Sites were graded 24 and 48 hours post-patch removal. Subjects exhibiting reactions during the Challenge Phase of the study underwent re-evaluation 72 hours after patch removal.

Study Group

76 F, 36 M; age range 18 – 69 years

Vehicle	EtOH:DEP (1:3)
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm^2 patch, and allowed to evaporate for 30 – 90 minutes prior to patch application. Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. A parallel study using the same cohort was run using the vehicle control EtOH:DEP (1:3).
RESULTS	
Remarks - Results	100/112 subjects completed the study, with 12/112 subjects reported to have discontinued for reasons unrelated to the test material (0 – 9 induction observations recorded). 1 male subject presented with barely perceptible erythema at the 4th induction observation. No responses were evident in subjects in the challenge phase.
CONCLUSION	The test substance was considered by the study authors to be non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2008)

B.6. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	BlueScreen HC Assay
Cell Type/Cell Line	Genetically modified strain of cultured human lymphoblastoid TK6 cells (GLuc-T01; GLuc reporter system is reported to exploit the proper regulation of the GADD45a gene, which mediates the adaptive response to genotoxic stress)
Metabolic Activation System	S9 fraction from Aroclor-1254 induced rat liver.
Concentration Range in Test	a) With metabolic activation: 4.88, 9.77, 19.5, 39.1, 78.1, 156, 313, 625 µM (~ 0.89 – 114 µg/mL) b) Without metabolic activation: 4.88, 9.77, 19.5, 39.1, 78.1, 156, 313, 625 µM (~ 0.89 – 114 µg/mL)
Vehicle	DMSO and water
Remarks - Method	Full study report not provided. Utilised a 96-well microplate format, testing the test substance with the vehicle and positive controls, over 8 dilutions. - BlueScreen HC assay (without metabolic activation): microplate wells containing the test substance and medium were covered with a breathable membrane and incubated at 37 °C (5% CO_2 and 95% humidity) for 48 hours. The plates are then assessed using fluorescence measurements to determine cell density, then using flash luminescence to determine genotoxicity. - BlueScreen HC S9 assay (with metabolic activation): wells containing the test substance, S9 fraction and medium were incubated (as above) for 3 hours, then washed, harvested and allowed to recover in medium for 45 hours at 37 °C. The plates were then assessed similar to that above. Reduced (≤ 80%) cell density compared to untreated cells (vehicle control) was used to provide a measure of cytotoxicity of the test substance. Increased (1.8 fold without metabolic activation; 1.5 fold with metabolic activation) induction of GLuc expression relative to the vehicle control was used to provide a measure of genotoxicity of the test substance. Where a positive result was obtained, the Lowest Effective Concentration (LEC; µM) was determined.

Vehicle and positive (without metabolic activation: 4-nitroquinoline-1-oxide at 0.125 and 0.5 µg/mL; with metabolic activation: cyclophosphamide at 5 and 25 µg/mL) controls were used in parallel with the test substance.

RESULTS

Metabolic Activation	*Cytotoxicity*	*LEC (µM)*	*Genotoxic Effect*	*LEC (µM)*
Absent	positive	≥ 39.1	positive	≥ 156
Present	positive	≥ 625	negative	-

*LEC = Lowest Effective Concentration for a positive result

Remarks - Results

In the absence of metabolic activation, the test substance significantly reduced the relative cell density (at ≥ 39.1 µM concentration) and induced GLuc expression (at ≥ 156 µM concentration), compared to the vehicle control groups.

In the presence of metabolic activation, the test substance significantly reduced the relative cell density (at ≥ 625 µM concentration), compared to the vehicle control groups, but was not considered to have had a genotoxic effect (the maximum luminescence induction was ~1.4 fold at the highest tested concentration).

CONCLUSION

The notified chemical was considered by the study authors to be genotoxic in the absence of metabolic activation, under the conditions of the test.

TEST FACILITY

Gentronix Limited (2014)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure

Species/Strain

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

Metabolic Activation System

S9 fraction from phenobarbitone/β-naphthoflavone induced rat liver.

Concentration Range in Main Test

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

Vehicle

Dimethyl formamide

Remarks - Method

No significant protocol deviations.
GLP Compliance.

A preliminary test was conducted using TA100 and WP2uvrA in the presence and absence of metabolic activation between 0.15 – 5,000 µg/plate.

The dose ranges for Test 2 (15 – 5,000 µg/plate) were selected based on the results of Test 1 (5 – 5,000 µg/plate).

Vehicle and positive controls were used in parallel with the test material.
Positive controls: i) without S9: N-ethyl-N'-nitro-N-nitrosoguanidine (used as the positive control for the tester strains: WP2uvrA$^-$, TA100, TA1535), 9-aminoacridine (TA1537) and 4-nitroquinoline-1-oxide (TA98); ii) with S9: 2-aminoanthracene (TA100, TA1535, TA1537, WP2uvrA$^-$) and benzo(a)pyrene (TA98).

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 5,000	≥ 1,500	> 5,000	negative
Test 2		≥ 5,000	> 5,000	negative
Present				
Test 1	≥ 5,000	≥ 5,000	> 5,000	negative
Test 2		≥ 5,000	> 5,000	negative

Remarks - Results

The test material caused a visible reduction in the growth of the bacterial background lawn and/or a substantial reduction in the frequency of revertant colonies at ≥ 1,500 µg/plate both in the presence and absence of metabolic activation

No significant increases in the frequency of revertant colonies were recorded for any of the strains of bacteria, at any dose level either with or without metabolic activation.

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

CONCLUSION

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

TEST FACILITY

Safepharm (2008b)

B.8. Genotoxicity – in vivo

TEST SUBSTANCE

Analogue chemical

METHOD

OECD TG 474 Mammalian Erythrocyte Micronucleus Test.

Species/Strain: Mouse/ICR

Route of Administration: Intraperitoneal injection (20 mL/kg bw)

Vehicle: Corn oil

Remarks - Method: GLP Compliance.

A preliminary toxicity study was conducted, in which mice were treated with the test substance at ≤ 1,000 mg/kg bw (see details in the below table). Mortality following dose administration and/or clinical signs of toxicity (lethargy and piloerection) in the 3 days following administration, were noted in animals of all treatment groups.

In the main study, animals were given a single injection of the test substance and samples of bone marrow were taken at 24 hours (low and mid-dose groups) or 24 and 48 hours (vehicle control and high dose groups). While 15 animals/sex were treated with the test substance in the high dose group, only 5 animals/sex were used for bone marrow collection at the 24 and 48 hour intervals following test substance administration.

A positive control (cyclophosphamide) study was conducted in parallel with the test substance.

The proportion of polychromatic erythrocytes to total erythrocytes (per 1000 erythrocytes) was recorded. The incidence of micronucleated polychromatic erythrocytes per 2000 polychromatic erythrocytes was determined.

Toxicity Assay

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*

1	5 per sex	300	0/10
2	5 per sex	500	6/10 (2 M/4 F)
3	5 per sex	700	10/10
4	5 per sex	1,000	10/10

Micronucleus Assay

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	10 per sex	-	24 & 48 hours
II (low dose)	5 per sex	95	24 hours
III (mid dose)	5 per sex	190	24 hours
IV (high dose)	15 per sex	380	24 & 48 hours
V (positive control, CP)	5 per sex	50	24 hours

CP=cyclophosphamide.

RESULTS

Doses Producing Toxicity	≥ 380 mg/kg bw (clinical signs of toxicity; a significant decrease in the proportion of polychromatic erythrocytes among total erythrocytes was not observed; ≤ 17%).
Genotoxic Effects	None.
Remarks - Results	All test animals survived till scheduled termination. Clinical signs of lethargy and piloerection were seen in all animals of the 380 mg/kg bw group. No other clinical signs were noted. No significant increases in the frequency of micronucleated polychromatic erythrocytes were recorded for both sexes at any dose level 24 hours after dose administration and in males at 48 hours after dose administration (compared to control groups). A statistically significant increase was observed in high dose females 48 hours after dose administration. However, this increase was deemed by the study authors to not be biologically significant, based on the lack of dose response at the 24 hour harvest time and the maximum number of micronuclei observed per animal (within the historical control range). The controls produced satisfactory responses, thus confirming the validity of the test.

CONCLUSION The test substance was not genotoxic under the conditions of this *in vivo* mammalian erythrocyte test.

TEST FACILITY BioReliance (2000)

B.9. Phototoxicity (in vitro)

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 432 In vitro – 3T3 NRU Phototoxicity Test

Vehicle	1% v/v ethanol in HBSS.
Remarks - Method	GLP Compliance. Irradiation was performed with a solar simulator (produced wavelength of simulator with filter was > 320 nm). Negative and positive (chlorpromazine) controls, with and without irradiation with artificial sunlight, were used in parallel with the test substance. A preliminary experiment was conducted with the notified chemical at 0.291 – 1,000 µg/mL. For solubility reasons, the concentrated dosing

solutions were sonicated (5 minutes) and heated (37 °C, 5 minutes) prior to treatment.

The main experiment (3 trials) was conducted at 1.51 – 92.6 µg/mL (with irradiation) and 4.90 – 300 µg/mL (without irradiation). It is noted that microbial contaminants were observed in the stock cell cultures after plate seeding for one of these trials (no contamination was observed in the plates).

The absorbance was determined at 550 nm.

RESULTS

Test material	*IC_{50} Value (+ UV) [µg/mL]**	*IC_{50} Value (- UV) [µg/mL]**	*PIF**	*MPE**
Positive control	1.09	19.57	17.97	0.57
Test substance	31.2	197.67	6.99	0.41

IC_{50} = half maximal Inhibitory Concentration the concentration of the test chemical by which the cell viability is reduced by 50%
PIF = Photo-Irritation Factor
MPE = Mean Photo Effect
* Calculated on the basis of the results in 3 trials.

Remarks - Results

A cytotoxic response was observed after treatment of cells with the notified chemical in both the presence and absence of irradiation with artificial sunlight. This cytotoxicity was noted in the preliminary experiment and confirmed by the main experiment.

A phototoxic effect was predicted.

The control gave responses within the expected range, confirming the validity of the test system.

CONCLUSION

The notified chemical was predicted to have phototoxic effects on BALB/c 3T3 fibroblast cells, under the test conditions.

TEST FACILITY

Institute for In Vitro Sciences, Inc. (2011)

B.10. Phototoxicity – human volunteers

TEST SUBSTANCE

Notified chemical (0.05, 0.25 and 0.5% w/w in vehicle).

METHOD

Phototoxicity evaluation in human subjects.

Study Design

The minimum erythema dose (MED) was determined for each subject by exposing naïve skin to a series of 5 UVB/UVA exposures (each 25% greater than the previous dose) An additional 5 exposures of UVA were also done. The sites were then evaluated ~ 22-24 hours later (sites illuminated by a 100 watt incandescent white bulb).

A single 0.2 mL application of test material at each concentration, was applied in duplicate to naïve sites on the paraspinal region of the back (patches applied on either side of the back). Patches on the left of the back were removed by technicians after ~ 24 hours (any excess test substance was removed prior to irradiation) and sites exposed to UVA irradiation (10 J/cm^2 or 0.5 MED, whichever was greater) within 10 minutes of patch removal and then UVB/UVA irradiation (0.75 MED). Patches on the right of the back were then removed. Test and control sites were evaluated at ~ 1, 24, 48 and 72 after patch removal.

Irradiation was performed with a solar simulator with filter (producing

	spectrum of UVB: 290 – 320 nm and UVA: 320 – 400 nm; and UVA only).
Study Group	26 F, 9 M; reported age range 18 – 65 years
Vehicle	EtOH:DEP (1:3)
Remarks - Method	Hill Top Chamber patches. Occluded. 3 negative control groups were run in parallel to the test substance (1 with 100% vehicle (occluded), 1 blank patch (occluded) and 1 blank site (without dressing)).

RESULTS

Remarks - Results	2 subjects showed responses at non-irradiated sites, ranging in severity from slight, confluent patchy erythema (at the blank patch site with occlusive dressing) to mild, pink erythema (at a site treated with 0.25% concentration of test substance), seen at the 1 hour observation only. No other responses were seen at non-irradiated sites over the study period. Various responses were seen at irradiated sites, with only 4 subjects showing no responses over the course of the study. 28/35 subjects exhibited slight to mild erythema at 1 or more sites and at 1 or more observation time points (1, 24, 48 and/or 72 hours), with only 2 of these subjects showing responses only at test-substance treated sites (and 5 showing responses only at control sites). 1 subject showed glazing at the site treated with 0.05% concentration of test substance, at the 1 hour observation only. The study authors deemed these responses as mild and indicated that most subjects also showed similar signs at the control sites. 3 subjects exhibited more severe responses including erythema of mild to moderate severity (3/3), oedema (3/3) and hyperpigmentation (2/3). 2 of these subjects showed the greatest severity erythema effects at control sites, hence were discounted by the study authors and were not indicative of phototoxic potential. The third subject showed moderate erythema at 24, 48 and 72 hours and oedema-swelling at 24 and 48 hours, at a site treated with 0.25% concentration of test substance. These responses were acknowledged by the study authors as indicating phototoxic potential, however, as the effects did not show a dose-response relationship, this potential was deemed by the study authors to be low.
CONCLUSION	The test substance was considered by the study authors to not produce definitive signs of phototoxicity, under the conditions of the test.
TEST FACILITY	HTR (2012)

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