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February 2010

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

1,3-Butanediol, 3-methyl- (Isoprene Glycol)

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 the Environment, Water, Heritage and the Arts.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full Public Report is also available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

TABLE OF CONTENTS

FULL PUBLIC REPORT

1,3-Butanediol, 3-methyl- (Isoprene Glycol)

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Unilever Australia Ltd (ABN 66 004 050 828)
20 Cambridge St
EPPING NSW 2121

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne 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:
Water solubility, Hydrolysis as a function of pH, Partition Coefficient (n-octanol/water), Adsorption/Desorption, Dissociation Constant, Autoignition Temperature, Explosive Properties, Reactivity, Bioaccumulation, Acute Toxicity to Fish, Acute/Chronic Toxicity to Aquatic Invertebrates, Algal Growth Inhibition Test.

NOTIFICATION IN OTHER COUNTRIES
EU, Japan, China, Korea, The Philippines

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Isoprene glycol
Isopentyldiol

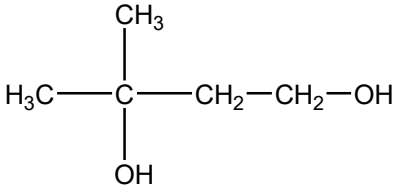
CAS NUMBER
2568-33-4

CHEMICAL NAME
1,3-Butanediol, 3-methyl-

OTHER NAME(S)
Isopentyldiol
Isoprene Glycol

MOLECULAR FORMULA
$C_5H_{12}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
104.05 Da.

ANALYTICAL DATA
Reference IR and GC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
97%

IMPURITIES/RESIDUAL MONOMERS (>1% by weight)

Chemical Name	unknown		
CAS No.	unknown	*Weight %*	3%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Transparent, colourless liquid.

Property	Value	Data Source/Justification
Glass Transition Temperature	<-50°C	Estimated
Boiling Point	203°C at 101.3 kPa	Measured
Density	974-982 kg/m^3	Measured
Vapour Pressure	1.3 kPa at 92°C	Measured
Water Solubility	Expected to be readily soluble in water.	Low molecular weight diols can be expected to have good water solubility, as exemplified by 1,3-butanediol.
Hydrolysis as a Function of pH	Expected to be hydrolytically stable under ambient abiotic conditions in the environmental pH range of 4–9	Hydrolytic stability is expected from the structure. The lower homologue 1,3-butanediol is considered stable to hydrolysis in water (Celanese, 2002).
Partition Coefficient (n-octanol/water)	log Pow = 0.16 at 20°C	Estimated (EPISuite). The estimated value for 1,3-butanediol is -0.29 (Celanese, 2002)
Adsorption/Desorption	log Koc expected to be low	High mobility in soil can be expected from the structure and water solubility, and by analogy to 1,3-butanediol, for which Koc is estimated to be 0.21 (Celanese, 2002)
Dissociation Constant	Not determined	Dissociation is unlikely to occur under normal environmental conditions (pH 4–9) as the notified chemical contains no readily dissociable functions
Dynamic viscosity	~0.3 Pa.s at 20°C	Measured
Flash Point	105°C	Measured
Refractive Index	1.440 – 1.446	Measured

DISCUSSION OF PROPERTIES
The notified chemical is a low molecular weight liquid that is freely soluble in water.
For full details of tests on physical and chemical properties, refer to Appendix A.

Reactivity
The notified chemical is considered to be stable, with no degradation or decomposition expected under normal conditions of use. It may contribute to a fire based on its likely combustible properties. Contact with strong oxidisers and organic peroxides should be avoided.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported in finished cosmetic products at a concentration of <10%. In future, the notified chemical may be imported as a raw material at >90% concentration.

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

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

PORT OF ENTRY
Sydney, NSW

IDENTITY OF MANUFACTURER/RECIPIENTS
Unilever Australia Ltd

TRANSPORTATION AND PACKAGING
Cosmetic products containing the notified chemical at <10% will be imported in containers (<200 mL) and transported to a warehouse for storage and then distributed to end users by road.

USE
The notified chemical will be used as a component of cosmetic products (<10%) such as cleansers and washes, for use by beauticians and hair salons as well as by the general public.

OPERATION DESCRIPTION
The notified chemical will be imported at <10% concentration in finished cosmetic products. Cosmetic products containing the notified chemical will be used by consumers or applied to consumers by hairdressers and beauty therapists.

In future, the notified chemical may be imported at >90% notified chemical for reformulation into cosmetic products. The notified chemical will be transported to a reformulation site where it will be tested by a chemist for quality assurance. It will be stored then an appropriate quantity will be weighed by a compounder into a container for addition to a mixing tank with other ingredients for reformulation into finished cosmetic products (containing <10% notified chemical). The finished cosmetic formulation will be tested for quality assurance purposes before being packaged and distributed for retail sale.

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	10	4	12
Professional Compounder	1	8	12
Chemist	1	3	12
Packers (Dispensing and Capping)	2	8	12
Store Persons	2	4	12
End Users	>300,000	8	365

EXPOSURE DETAILS
Formulation
Workers involved in transporting either the notified chemical (>90%) or finished cosmetic products containing the notified chemical (<10%) are not expected to experience exposure except in the case of accidental breaching of the packaging.

Dermal and ocular exposure to drips, spills and splashes of the notified chemical (>90%) may occur during quality assurance testing, charging of mixing vessels, mixing and filling of product packaging. Exposure is expected to be limited given the anticipated use of closed mixing systems and workers wearing personal protective equipment (PPE), such as safety goggles, impervious gloves and coveralls.

Inhalation exposure to aerosols is also possible during these processes. However, it is expected that exhaust ventilation will be in use to minimise exposure via this route.

End-use in cosmetic products
Occupational exposure is possible for workers in hair and beauty salons applying products containing the notified chemical (<10%) by hand or spray. Dermal exposure is expected to be extensive given that moisturiser products containing the notified chemical will be applied directly to the skin. Accidental ocular exposure and inhalation of aerosols could occur where application is by spray. There is also potential for accidental ingestion via the oral route.

Although the level and route of exposure will vary depending on the method of application and work practices employed, extensive dermal exposure is expected in some occupational settings. This exposure is likely to be greater than that expected for the public (see below).

6.1.2. Public exposure

Public exposure to the notified chemical is expected to be widespread and frequent through daily use of cosmetic products containing the notified chemical at concentrations up to 10%. Exposure to the notified chemical will vary depending on individual use patterns. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible during the use of products applied by spray. Oral exposure from the use of these types of products is also possible from accidental ingestion during facial use.

Public exposure to the notified chemical in Australia has been estimated using the Scientific Committee on Consumer Products' (SCCP's) Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation and applying the following assumptions:

- Bodyweight of 60 kg for females (SCCNFP, 2006);
- The concentration of the notified chemical in cosmetic products does not exceed 10%;
- 100% dermal absorption (SCCNFP, 2006);
- An individual uses all product types containing the notified chemical.
- A retention factor to take into account rinsing off and dilution of finished products by application on wet skin or hair (e.g. shower gels, shampoos, etc) (SCCNFP, 2006)

Product(s) used	*Use level for each product*	*Retention factor*	*Systemic Exposure (mg/kg bw/day)*
Make-up remover	2.5 g per use x 2 applications/day	0.1	0.833
Face washes, gels, scrubs[1]	0.8 g per use x 2 applications/day	0.01	2.6×10^{-2}
Facial cleanser	0.8 g x 0.5 applications/day	1	6.67×10^{-3}
Total			**0.86**

[1] Api et al., 2007

This exposure estimate was produced using highly conservative assumptions and is expected to reflect a worst-case scenario. In reality, the level of exposure is expected to be lower than 0.86 mg/kg bw/day as it is assumed that consumers would not wear all these products at the same time.

6.2. Human health effects assessment

The following table contains results of toxicological tests conducted on the notified chemical. Information on 3 analogous chemicals 1,3-butanediol, 2-methyl-2,4-pentanediol and 3-methyl-1-butanol was also considered to estimate the effects on toxicological endpoints where data for the notified chemical were not available.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	oral LD50 >5000 mg/kg bw low toxicity
Rat, acute dermal toxicity	LD50>200mg/kg bw
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	non-irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rabbit, Dermal Irritancy – 28 day repeat application	non-irritating
Mutagenicity – bacterial reverse mutation	non-mutagenic
Genotoxicity – bacterial DNA repair assay	non-mutagenic
Photoirritation	non-irritating
Photosensitisation	not sensitising
Skin irritation – human volunteers	slightly irritating

Toxicokinetics, metabolism and distribution

Limited data is available to describe the likely toxicokinetic properties of the notified chemical. Given its relatively high water solubility, log P_{ow} of ~0 and molecular weight of <500 Da., absorption might be expected following ingestion, dermal or inhalation exposure (EC, 2003). 1,3-Butanediol and 2-Methyl-2,4-pentanediol are expected to have similar potential for absorption based on their molecular weight, vapour pressure and solubility in water and alcohol, whereas 3-methyl-1-butanol may be less readily absorbed given its lower water solubility.

1,3-Butanediol is metabolised through normal physiological pathways. Firstly, undergoing β-oxidation followed by further oxidation to eventually form carbon dioxide in the tricarboxylic acid cycle (Cosmetic Ingredient Review Expert Panel, 1985). Little is known about the metabolism of 2-methyl-2,4-pentanediol. A study in humans showed that daily doses of 600 mg or less were not detected in urine but daily doses of up to 5 g resulted in urinary excretion of substantial amounts of 2-methyl-2,4-pentanediol and its conjugate, persisting up to 10 days after cessation of dosing (p.4697, Patty's Industrial Hygiene and Toxicology Vol.2, Part F, 4th Ed., 1994). 3-Methyl-1-butanol is metabolised to a carboxylic acid and excreted (p.2656, Patty's Industrial Hygiene and Toxicology Vol.2, Part D, 4th Ed., 1994).

It is unknown to what extent the differences in structure between these chemicals and the notified chemical have on its toxicokinetics. Oxidation to form a carboxylic acid is likely to be a common mechanism for 1,3-butanediol. However, given the notified chemical has a methyl and a hydroxyl group in the position β to the primary alcohol, it will not be metabolised in the same way. Oxidation of the primary alcohol of the notified chemical is considered likely but it is unlikely to continue to undergo oxidation via the tricarboxylic acid cycle. The tertiary hydroxyl group of the notified chemical may be conjugated like 2-methyl-2,4-pentanediol but this is considered less likely than the oxidation of the primary alcohol. Therefore, its elimination is likely to be slower than 1,3-butanediol but possibly faster than 3-methyl-1-butanediol and 2-methyl-2,4-pentanediol. It is possible that elimination may resemble 2-methyl-2,4-pentanediol more closely than the other two analogues.

Acute toxicity

In an acute oral toxicity study in rats, the notified chemical was found to have an LD50 >5000 mg/kg bw. No mortality occurred, and no systemic signs of toxicity were observed.

In an acute dermal irritation study in rabbits, the notified chemical did not cause irritation or systemic toxicity following dermal application of 200 mg/kg bw. The method used was an in-house method, equivalent to OECD TG 404. No mortality occurred, and no signs of irritation or systemic toxicity were observed.

No acute inhalation toxicity study was conducted using the notified chemical. Rats exposed to saturated vapours of 1,3-butanediol for 8 hrs did not show any signs of adverse effects. However, the low vapour pressure of the chemical may have resulted in a low level of exposure accounting for the absence of adverse effects. Inhalation studies using 2-methyl-2,4-pentanediol (vapour pressure not determined) in rats and rabbits also elicited no adverse effects (p. 4691, 4697 Patty's Industrial Hygiene and Toxicology Vol.2, Part F, 4th Ed., 1994). Analogous chemicals did not exhibit acute inhalation toxicity in rats or rabbits. Given the other similarities in acute toxic effects, the acute inhalation toxicity of the notified chemical is also expected to be low.

Irritation and Sensitisation

Skin irritation

No signs of irritation were observed during an acute dermal irritation study in rabbits (see above).

In a 28-day repeated application skin irritation study in rabbits, application of 15 µL of the notified chemical elicited only minor signs of irritation. The dose level tested was not provided and therefore a No Observed Adverse Effect Level (NOAEL) was not able to be established.

In a skin irritation study in humans, an unspecified quantity of the notified chemical at 100% concentration was soaked onto filter paper and administered to 30 volunteers for 48 hrs. Thirty minutes after removal of the notified chemical, slight erythema was observed in two volunteers but there was no evidence of irritation 24 hrs later.

Based on the available data on the notified chemical, the notified chemical is considered to have the potential to be slightly irritating to the skin. However, the available data were insufficient for the notified chemical to be classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

In a photoirritation study in guinea pigs, the notified chemical was applied to guinea pigs exposed to UVA radiation. No signs of irritation were observed following treatment (see Appendix B for details). Based on these tests, the notified chemical is not anticipated to cause photoirritation or photosensitisation in humans, following exposure to sunlight after dermal application.

Eye irritation
In a rabbit acute eye irritation study, the notified chemical was found to be non-irritating to eyes.

Skin sensitisation
The notified chemical does not contain any structural alerts for skin sensitisation (Barratt *et al*, 1994). Supporting this prediction, it was found to be not sensitising in a guinea pig skin sensitisation (Magnusson & Kligman) test. In addition, it was found not to be sensitising in a photosensitisation test in guinea pigs (see Appendix B for details).

Based on the skin sensitisation tests conducted on the notified chemical, it is not expected to be sensitising or photosensitising to human skin.

Mutagenicity
The notified chemical contains no structural alerts for mutagenicity and was negative in a bacterial reverse mutation assay (Ames test), conducted both with and without metabolic activation using a method equivalent to OECD TG 471. The notified chemical was also found to be negative in a *rec* assay, conducted both with and without metabolic activation at concentrations up to 100 mg/plate (see Appendix B for details). No data on the ability of the notified chemical to induce chromosomal damage is available.

1,3-Butanediol was also found to be negative in a chromosome aberration test (p. 4691, Patty's Industrial Hygiene and Toxicology Vol.2, Part F, 4th Ed., 1994). On the basis of the available information, the notified chemical is not expected to be mutagenic.

Repeat Dose/Chronic toxicity
The 28-day dermal toxicity study for the notified chemical had many limitations (dose used was not specified to derive a NOAEL) and no repeat dose chronic toxicity studies were conducted on the notified chemical. Various repeat dose and chronic studies have been conducted on 1,3-butanediol and 2-methyl-2,4-pentanediol revealing low toxicity of both chemicals in various species. For example, a NOAEL of 5,600 mg/kg bw/day was established in a 90 day repeat dose oral toxicity study in rats using 1,3-butanediol (p. 4690, Patty's Industrial Hygiene and Toxicology Vol.2, Part F, 4th Ed., 1994). Tobin et al. found no adverse effects in human volunteers fed a diet containing up to 10% of 1,3-butanediol for 5 to 7 days, except for a slight decrease in blood glucose levels (Cosmetic Ingredient Review Expert Panel, 1985). A NOAEL >590 mg/kg bw/day was established in an 8 month repeat dose oral toxicity study in rats using 2-methyl-2,4-pentanediol (p. 4696, Patty's Industrial Hygiene and Toxicology Vol.2, Part F, 4th Ed., 1994). In a 90 day repeat dose oral toxicity study in rats using 3-methyl-1-butanol, a NOAEL of 340 mg/kg bw/day was established for males. Schilling, K. et al., (1997) reported changes in red blood cells, mean corpuscular volume and hemoglobin at the highest dose (1250 mg/kg bw/day) in males but not in females.

However, as discussed previously, the metabolic pathways of these structurally similar chemicals are considered to differ markedly from the notified chemical, as the notified chemical cannot undergo β-oxidation, because of its substitution. Assuming similar mechanisms of toxicity between the notified chemical and analogues, the likely NOAEL of the notified chemical would be based on its ability to be excreted. Therefore the NOAEL for the notified chemical would be expected to fall between the lowest NOAEL of 340 mg/kg bw/day for 3-methyl-1-butanol and the highest NOAEL of 5,600 mg/kg bw/day for 1,3-butanediol.

Summary of expected human health effects
Based on studies on the notified chemical and chemicals with structural similarities in animals and humans, the notified chemical is not expected to cause systemic toxicity in humans. Based on the slight, isolated instances of skin irritation observed following repeated dermal exposure of the notified chemical in humans and animals, it is considered to have the potential to cause minor skin irritation. It is not expected to cause eye irritation based on studies in rabbits.

Health hazard classification
Based on the available data the notified chemical is not classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Formulation

Studies on the notified chemical indicate it has the potential to cause slight skin irritation. However, dermal exposure to workers wearing impervious gloves and coveralls during reformulation of the notified chemical at > 90% concentration is not expected to present an unreasonable risk of skin irritation.

End-use in cosmetic products

Employees in hair and beauty salons will experience extensive dermal exposure during application of products containing the notified chemical (<10%) by hand or spray. If these employees use products containing the notified chemical for personal use as well as in a work setting their level of exposure would be higher than that of consumers. However, exposure to the notified chemical at low concentrations (<10%) is not expected to cause skin or eye irritation. The risk of toxicity following repeated exposure is not anticipated to be unacceptable based on the NOAELs reported in repeat dose studies on analogous chemicals.

6.3.2. Public health

Members of the public will experience widespread and frequent exposure to the notified chemical through daily use of cosmetic products (<10%) which will be applied directly to the skin and hair. At this concentration, the notified chemical is not expected to cause skin or eye irritation.

A maximum systemic exposure of 0.86 mg/kg bw/day was estimated (see Section 6.1.2) for a person using various products containing the notified chemical at 10% concentration at the same time. A NOAEL could not be established for the notified chemical itself, but it is estimated to lie between the NOAELs for structurally similar chemicals (340 – 5,600 mg/kg bw/day). Therefore a conservative estimate of the margin of exposure (MoE) for the notified chemical could be estimated as follows:

$$\text{MoE} = \frac{\text{Estimated NOAEL}}{\text{Estimated typical daily exposure}} = \frac{\text{340 to 5,600 mg/kg bw/day}}{\text{0.86 mg/kg bw/day}}$$

$$= \text{395 to 6511}$$

This MoE range indicates the level of risk for products used by the general public (MoE >100) is not considered to be unacceptable.

Overall, based on the available data, the notified chemical is not considered to pose an unreasonable risk to public health at concentrations up to 10% in cosmetic products.

7. ENVIRONMENTAL IMPLICATIONS

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a minor constituent of finished cosmetic products or as a raw material for reformulation into cosmetic products. Accidental spills and leaks during transport are expected to be physically contained and disposed of to landfill. Of the notified chemical imported as raw material, it is estimated 1% will remain in drums as residues and be sent to landfill. Formulation of the notified chemical will occur in closed systems and should therefore experience minimal release to the sewerage system due to cleaning of equipment.

RELEASE OF CHEMICAL FROM USE

It is expected that the majority of the imported quantity of the notified chemical (estimated 99%) will be washed to sewer as the chemical is intended for use in cosmetic products. This release will occur in a diffuse and widespread manner.

RELEASE OF CHEMICAL FROM DISPOSAL

Small amounts as residues in empty containers (estimated 1% of the imported quantity of the notified chemical) are expected to be disposed of to landfill with normal household rubbish.

7.1.2 Environmental fate

A single ready biodegradability test report was submitted for the notified chemical. The test report indicates that the notified chemical is readily biodegradable. For the details of the environmental fate study refer to Appendix C.

The notified chemical is likely to pass through the sewer treatment plant and enter receiving waters as it is water soluble. However, some degradation is assumed as the notified chemical is readily biodegradable and is expected to form water and oxides of carbon. Since the notified chemical is expected to be highly water soluble and is readily biodegradable, it is not expected to bioaccumulate.

7.1.3 Predicted Environmental Concentration (PEC)

Since most of the notified chemical will be released to the sewer, the predicted environmental concentrations (PEC) for release to ocean and inland river are calculated as follows based on the water consumption of the Australian population. The PECs estimated below are an overestimate as the notified chemical is readily biodegradable and will be substantially biodegraded during sewage treatment.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	5,000	kg/year
Proportion expected to be released to sewer	99%	
Annual quantity of chemical released to sewer	4,950	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	13.65	kg/day
Water use	200	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:	3.20	µg/L
PEC - Ocean:	0.32	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 3.2 µg/L may potentially result in a soil concentration of approximately 0.021 mg/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 0.11 mg/kg and 0.21 mg/kg, respectively.

7.2. Environmental effects assessment

The ecotoxicity result from the 'Inhibition of Bacterial Respiration' test conducted on the notified chemical and the results from ecotoxicological investigations in an International Uniform Chemical Information Database (IUCLID) Data Set conducted on acceptable analogues of the notified chemical (IUCLID, 2003) are summarised in the table below. Limited details of the studies on the analogues were available.

Endpoint, Test species, Test	*Result*	*Assessment Conclusion*
Fish Toxicity (*Oryzias latipes*) OECD 203	LC50 (96 h) > 100 mg/L	Not harmful
Daphnia Toxicity (*Daphnia magna*) OECD 202	EC50 (48 h) > 1000 mg/L	Not harmful
Algal Toxicity (*Selenastrum capricornutum*) OECD 201	E_rC_{50} (72 h) > 1070 mg/L	Not harmful
Inhibition of Bacterial Respiration OECD 209	IC50 (3h) > 1000 mg/L	Not harmful

The results of the ecotoxicity studies submitted indicated that the notified chemical is not expected to be harmful to aquatic organisms.

7.2.1 Predicted No-Effect Concentration

The lowest endpoint from ecotoxicological studies of an acceptable analogue to the notified chemical was used to calculate the PNEC. A conservative assessment factor of 1000 was used as we have not assessed the study reports.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish)	>100	mg/L
Assessment Factor	1,000	
PNEC:	>100	µg/L

7.3. Environmental risk assessment

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

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	3.20	>100	<0.032
Q - Ocean	0.32	>100	<0.003

The risk quotient for aquatic exposure is calculated to be <<1 based on the above calculated PECs and PNECs. The Q value of <<1 indicates the notified chemical is not expected to pose an unacceptable risk to the aquatic environment from its proposed use pattern.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

Based on the available data the notified chemical is not classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

In addition, the notified chemical is not classified using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations, 2003).

Human health risk assessment

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

When used in the proposed manner at concentrations of up to 10% in cosmetics/cosmetic products, the notified chemical is not considered to pose an unacceptable 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 expected to pose a risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- 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:1008(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.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by 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:

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from component of cosmetic products, or is likely to change significantly;
- the notified chemical is intended for use in cosmetic products at >10% concentration;
- if 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 MSDS of the notified chemical and products containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Density 974-982 kg/m^3

Method Specific gravimeter (Vibration method)
Remarks No further information available

Flash Point 105°C

Method Closed cup method
Remarks No further information available

Vapour Pressure 1.3 kPa at 92°C

Method Not provided
Remarks No further information available

Partition Coefficient (n-octanol/water) log Pow = 0.16 at 20°C

Method Estimated using EPISuite: KOWWIN v1.67
Remarks The estimated value for the lower homologue 1,3-butanediol is -0.29 (Celanese, 2002)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical at 100% concentration
METHOD	In-house method equivalent to OECD TG 401 Acute Oral Toxicity.
Species/Strain	Mouse/CD-1
Vehicle	Distilled water
Remarks - Method	No deaths were noted in the dose ranging test (2M/2F per dose) at concentrations up to 5000 mg/kg bw so only 2 dose levels were used in the main study (2000 and 5000 mg/kg bw). No other significant protocol deviations.
RESULTS	
	No deaths were observed in 5M/5F dosed at 2000 mg/kg bw or 5M/5F dosed at 5000 mg/kg bw.
LD50	>5000 mg/kg bw
Signs of Toxicity	None
Effects in Organs	No effects noted upon gross necropsy.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Inveresk Research Institute (1987a)

B.2. Irritation – skin

TEST SUBSTANCE	Notified chemical at 100% concentration
METHOD	In-house method. Variation of OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3M/3F
Vehicle	0.5 mL of the notified chemical was applied undiluted
Observation Period	72 hrs
Type of Dressing	Occlusive.
Remarks - Method	The following deviations from OECD TG 404 are noted: 1. Mean minimum temperature was 15°C, less than 20°C (±3°C). 2. One test application site on each rabbit was abraded using a sterilin blood lancet prior to application of the test substance. 3. The patch was applied to the test application site for 24 hrs rather than 4 hrs. 4. Skin reactions were assessed at 24 and 72 hrs after patch application but not at 1 hr and 48 hrs as per OECD TG 404. No other significant protocol deviations.
RESULTS	
Remarks - Results	No signs of irritation were observed at any of the treated sites on test animals at 24 or 72 hrs after patch application.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	Inveresk Research Institute (1987b)

B.3. Irritation – eye

TEST SUBSTANCE	Notified chemical at 100% concentration

METHOD: In-house method equivalent to OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).

Species/Strain: Rabbit/New Zealand White
Number of Animals: 3 M, 3 F
Observation Period: 7 days
Remarks - Method: No significant protocol deviations.

RESULTS

Remarks - Results: No effects were observed in any animals 1 hr, 24 hrs, 48 hrs, 72 hrs or 7 days after application of the notified chemical. The Primary Irritation Index was reported as 0.

CONCLUSION: The notified chemical is non-irritating to the eye.

TEST FACILITY: Inveresk Research Institute (1987c)

B.4. Skin sensitisation

TEST SUBSTANCE: Notified chemical at 100% concentration

METHOD: OECD TG 406 Skin Sensitisation – Magnusson & Kligman
EC Directive 96/54/EC B.6 Skin Sensitisation – Magnusson & Kligman.

Species/Strain: Guinea pig/Dunkin-Hartley
PRELIMINARY STUDY: Maximum Non-irritating Concentration:
intradermal: 10% in distilled water
topical: 50% in distilled water

MAIN STUDY
Number of Animals: Test Group: 20 Control Group: 10
INDUCTION PHASE: Induction Concentration:
intradermal: 10% in distilled water
topical: 100% (undiluted)
Signs of Irritation: Moderate and confluent erythema was seen in test animals at intradermal injection sites and topical application sites 24 hrs after treatment. Slight or discrete erythema was observed in control animals.

CHALLENGE PHASE
1st challenge: topical: 50% in distilled water
Remarks - Method: No significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge:*	
		24 h	*48 h*
Test Group	50% in water	0/20	0/20
Control Group	Distilled water	0/10	0/10

Remarks - Results: A positive control test was conducted using 10 animals (Albino Dunkin-Hartley Guinea pigs) treated with Dinitrochlorobenzene (DNCB) in the following concentrations in propylene glycol for induction 0.1% (intradermal injection) and 1% (topical application). Slight or discrete erythema was observed in all animals 24 hrs after topical challenge with 1% DNCB indicative of a contact sensitisation reaction. However, DNCB is one of the strongest known sensitisers and it is unclear whether this test method is suitable for detecting weaker sensitisers.

CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Inveresk Research Institute (1987d)

B.5. Repeat dose irritation

TEST SUBSTANCE	Notified chemical at 100% concentration
METHOD	No standard test guideline available
Species/Strain	Rabbit/New Zealand White
Route of Administration	Dermal –semi-occluded
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days/week Duration of exposure (dermal): ~24 hours/day Post-exposure observation period: None
Remarks - Method	Nine male New Zealand White rabbits were acclimatised for at least one week prior to the experiment in standard conditions, with food and water provided *ad libitum*. Body weights, and food and water consumption were recorded in the week prior to the test, immediately prior to the first patch application and then at weekly intervals afterwards. 15 µL of the notified chemical (dose not specified) was applied to a clipped dorsal area of the trunk with an adjacent control site for comparison. The sites were covered with tape and the trunk was securely bound with elastic bandage for approximately 24 hrs. After this time, the tape and bandages were removed and the treated skin sites assessed immediately prior to the next application. This process was repeated every day over 28 days. Assessment of the treated skin sites was performed according to OECD guidelines for dermal irritation. One animal died on Day 10 and an additional animal was added to the test group on Day 11 (see below). After assessment of the treated skin sites on Day 29, the animals were sacrificed and the treated and control sites excised and placed in buffered formalin. After fixation, they were trimmed and embedded in wax. Sections of the skin 4-6 µm thick were cut and stained with haemotoxylin and oesin for histopathological examination.

RESULTS

Mortality and Time to Death

Two animals died during the study. One animal died on Day 10 due to a gastrointestinal disease (unrelated to treatment). Another died on Day 22 but the cause of death was not established.

Clinical Observations

Slight erythema was observed in 2 animals on Day 18. There were no signs of irritation the following day.
Very slight erythema and oedema was observed in one animal on Day 15 and another animal on Day 27. However, there were no signs of irritation in either of these animals the following day.

Histopathological assessment

Mild inflammatory cell infiltration was observed in 4 animals at the site treated with the notified chemical. In 2 of these animals similar lesions were noted at the control site.

Remarks – Results

The signs of irritation are not considered to be significant due to their sporadic incidence and mild severity.

CONCLUSION

The notified chemical did not cause skin irritation upon repeated application to rabbit skin under the conditions of the test. As the dose level tested was not provided, a dermal NOAEL cannot be established.

TEST FACILITY	Inveresk Research Institute (1987e)

B.6. Genotoxicity – bacterial reverse mutation test

TEST SUBSTANCE	Notified chemical at 100% concentration
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Pre incubation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA (pKM101)
Metabolic Activation System	Aroclor 1254 induced rat liver microsome preparations (S9 mix)
Concentration Range in Main Test	a) With metabolic activation: 33 - 10000 µg/plate b) Without metabolic activation: 33 - 10000 µg/plate
Vehicle	DMSO
Remarks - Method	The method was equivalent to OECD TG 471 except for the maximum concentration (10000 µg/plate). This exceeds the maximum recommended concentration for soluble non-cytotoxic substances (5000 µg/plate).
RESULTS	
Remarks - Results	No precipitation or toxicity to the bacteria was observed at concentrations up to 10000 µg/plate. The positive control substances (2-Aminoanthracene, Methyl methanesulfonate, N-ethyl-N-nitro-N-nitrosoguanidine, 9-Amino-acridine and 2-Nitrofluorene) induced the appropriate increases in revertant colonies, implying the validity of the test method.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Inveresk Research International (1987f)

B.7. Genotoxicity – bacterial DNA repair assay

TEST SUBSTANCE	Notified chemical at 100% concentration
METHOD	*rec*-assay baed on the methods of Kada et al., 1980
Species/Strain	*Bacillus subtilis*: M45, H17.
Metabolic Activation System	Aroclor 1254 induced rat liver microsome preparations (S9 mix)
Vehicle	DMSO
Method	<u>*Rapid Streak Test*</u> A preliminary test was conducted to determine suitable dose levels of the notified chemical using the rapid streak method. Five 25 µL aliquots of the notified chemical at concentrations from $2.5x10^{-3}$ mg/mL to 25 mg/mL were pipetted onto a filter paper disc in the centre of a Petri dish containing agar. The plates were stored at 4°C to facilitate diffusion of the notified chemical. After 17 hrs, a single loop of bacteria was applied to the surface of the agar and the plates were incubated for 2 days at 37°C. Growth inhibition of the bacteria was measured. <u>*Liquid Suspension Assay*</u> As no toxicity was observed in the preliminary test, the main test was conducted using the liquid suspension method at the following concentrations: 6.25, 12.5, 25, 50 and 100 mg per plate in triplicate. Cultures were diluted and added to a plastic tube with:

S9 mix (or 0.5 mL of PO_4 buffer pH 7.4, for controls), and vehicle, positive, negative controls or test substance solution.
The following substances were used as vehicle, positive control and negative control respectively: DMSO, ethyl methanesulfonate (EMS) and chloramphenicol. Each tube was mixed and incubated at 37°C for 90 mins, then agar was added.
The contents were mixed and poured onto agar plates and incubated at 37°C for 24 hrs.
The number of surviving bacteria were counted for each strain and the survival index calculated as follows:

S.I. = % Survivors *B. subtilis* M45 / % Survivors *B. subtilis* H17.

If the survival index was < 0.5 then this was considered indicative of preferential inhibition of DNA repair-deficient strains.

RESULTS

Remarks - Results

No inhibition of bacterial growth was observed in the rapid streak test at concentrations up to 25 mg/mL.
In the liquid suspension assay, no preferential inhibition was observed in either strain in the presence or absence of metabolic activation at concentrations between 6.25 and 100 mg/plate.
The responsiveness of the *Bacillus subtilis* M45 or H17 strains was confirmed by the preferential toxicity observed when the strains were treated with EMS. In the absence of metabolic activation, the survival index was 0.29 and in the presence of metabolic activation, the survival index was 0.77.
No preferential toxicity was observed when the strains were treated with chloramphenicol (negative control) or DMSO (vehicle).

CONCLUSION

The notified chemical was not mutagenic to *Bacillus subtilis* M45 or H17 under the conditions of the test.

TEST FACILITY

Inveresk Research International (1987g)

B.8. Photoirritation

TEST SUBSTANCE

Notified chemical at 100% concentration

METHOD

The back of each guinea pig was shaved and chemically depilated, then 0.025 mL of the notified chemical (undiluted) and the positive control, 8-methoxysporalen (8-MOP), were applied epicutaneously to marked sites on each of the 10 animals in the test group.
The animals in the test group were placed in a restraining cage with 10 individual compartments and exposed to 20 J/cm^2 of UVA radiation (320-400 nm) for an unspecified period of time. After exposure to 2.5 J/cm^2 of UVA radiation, the positive control site on each guinea pig was covered with lightproof tape.
The animals in the control group were also placed in a restraining cage with 10 individual compartments but were not exposed to UVA radiation.
All animals were examined 24, 48 and 72 hours after application of the test substance for signs of erythema and oedema.

Species/Strain	Guinea Pig/Dunkin-Hartley	
Number of Animals	Test Group: 10	Control Group: 10
Vehicle	Distilled water	

RESULTS

Remarks - Results	No skin reactions were observed 24, 48 or 72 hrs after treatment at sites treated with the notified chemical. Slight to moderate reactions were observed at up to 72 hours after treatment in all animals at the site treated with 8-MOP confirming the sensitivity of the positive control in the Dunkin-Hartley Guinea Pig.
CONCLUSION	The notified chemical does not exhibit a photoirritant potential under the conditions of the test.
TEST FACILITY	Inveresk Research International (1987h)

B.9. Photosensitisation

TEST SUBSTANCE	Notified chemical at 100% concentration
METHOD	Two tests were conducted. The first test was conducted with the notified chemical undiluted and the second with a positive control substance, tetrachlorosalicylanilide (TCSA) 0.1% w/w in Petrolatum. Induction The back of each guinea pig was shaved and chemically depilated, then 0.025 mL of the notified chemical (undiluted) was applied epicutaneously to marked sites on each animal in the test group. These animals were then placed in a restraining cage with 10 individual compartments and exposed to approximately 485 mJ/cm^2 of UVA radiation 185 mJ/cm^2 of UVB radiation for 10 mins. This process was repeated another 5 times, at intervals of approximately 48 hrs (excluding weekends), resulting in 6 applications in a 2 week period. Shaving and depilation were repeated as necessary. Control group animals and positive control group animals were treated in the same way, with the notified chemical replaced by distilled water, and TCSA, respectively. All animals were examined 24, 48 and 72 hours after application of the test substance for signs of erythema and oedema. Challenge Twelve days following the final induction exposure, the notified chemical was applied open epicutaneously to the shaved and depilated backs of the animals of the test and control groups in the same way as induction. Approximately 30 mins after application the animals of the test and control groups were exposed to 10 J/cm^2 of UVA radiation. After exposure, the notified chemical was applied to the adjacent site of animals from both the test and control groups without being irradiated. All animals were examined 24, 48 and 72 hours after application of the test substance for signs of erythema and oedema.
Species/Strain	Guinea Pig/Dunkin-Hartley
Number of Animals	Test Group: 10 Control Group: 10 Positive Control Group: 10
Vehicle	Distilled water
Remarks - Method	One animal was killed prior to challenge (suspected pneumonia).

RESULTS

Remarks - Results	No skin reactions were observed 24, 48 or 72 hrs after treatment at sites treated with the notified chemical either during the induction or challenge phase. Positive responses were observed in 4/10 animals at 48 hrs and 5/10 animals at 72 hours after treatment with TCSA, confirming the sensitivity of animals to the positive control.

CONCLUSION	The notified chemical did not exhibit photosensitising potential under the conditions of the test.
TEST FACILITY	Inveresk Research International (1987i)

B.10. Skin irritation – human volunteers

TEST SUBSTANCE	Notified chemical at 100% concentration
Study Group	13 M/17 F (aged 20 to 66 yrs)
Vehicle	Fin chamber
METHOD	
Remarks - Method	No standard test method available. Filter paper was soaked with an unspecified quantity of the (1) notified chemical at 100% concentration, (2) 1,3-butanediol and (3) purified water (control) and applied to the skin of the medial brachium area. After 48 hrs, the treatment was removed from the subjects and the treated site was assessed for effects after 30 mins, 24 hrs and up to 7 days following removal of the fin chamber.
RESULTS	
Remarks - Results	Slight erythema was observed at the treated site 30 mins after removal of the fin chamber in a 66 year-old female and a 49 year-old female after removal of the fin chamber. However, 24 hrs later there were no signs of erythema at the treated site.
CONCLUSION	The notified chemical was found to have very slight potential for irritation under the conditions of the test.
TEST FACILITY	Kuraray Co., Limited (year not stated)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I)
Inoculum	Activated mixture of sewerage, river, lake, bay and synthetic sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	GC analysed the concentration of the test substance and TOC analyser measured the DOC content
Remarks - Method	There were no significant deviations from the standard protocol. The concentrations of the notified chemical and reference substance (aniline) were both 100 mg/L. Inoculum concentration was 30 mg/L. A blank control was used consisting of only the culture medium.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation**	*Day*	*% Degradation*
7	62	7	41
14	77	14	81
21	88	21	83
28	94	28	84

*Calculated from BOD. Mean of three measurements.

Remarks - Results	The oxygen uptake of the inoculum blank (4.3 – 17.3 mg O_2 / L) was lower than the recommended (20 – 30) mg O_2 / L suggested in the OECD guideline. On the 28th day the oxygen uptake of the inoculum blank was 21.7 mg O_2 / L which was well within the guideline recommendation of uptake being less than 60 mg O_2 / L after 28 days. All other validity criteria were met. There was over 60% degradation of the notified chemical within a 10 day window.
CONCLUSION	The notified chemical is readily biodegradable
TEST FACILITY	Kurume Research Laboratories (1993a)

C.2. Ecotoxicological Investigations

C.2.1. Inhibition of microbial activity

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test, 1986
Inoculum	Mixture of activated synthetic sewage nutrition and sewerage sludge
Exposure Period	30 min and 3 h
Concentration Range	62.5 – 1000 mg/L
Remarks – Method	Tests were conducted by exposing activated sewage sludge to synthetic sewage and 62.5, 125, 250, 500 and 1000 mg/L concentrations of the test substance for a period of 30 min and 3 h at 20 ± 2°C. Reference material (3,5–dichlorophenol), at concentrations of 5 and 10 mg/L, was prepared in order to confirm the suitability of the inoculum. The total hardness of the test water was not reported.

RESULTS

IC50	>1000 mg/L (30 min) >1000 mg/L (3 h)
Remarks – Results	Variation in respiration rates of the two controls after 3 h contact time was ≤15%, and the IC50 (3-hour contact time) for reference substance 3,5-dichlorophenol was 26.1 mg/L, thus validating the test. There was a weak dose-response between inhibition rate and concentration of test substance, with approximately 10-12% inhibition observed at the highest dose.
CONCLUSION	The notified chemical is not harmful to microbial respiration
TEST FACILITY	Kurume Research Laboratories (1993b)

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