File No: STD/1364

August 2010

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

1-Propanaminium, 2,3-dihydroxy-N,N,N-trimethyl-, chloride (1:1)
(INCI Name: Dihydroxypropyltrimonium Chloride)

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

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FULL PUBLIC REPORT

1-Propanaminium, 2,3-dihydroxy-N,N,N-trimethyl-, chloride (1:1)
(INCI Name: Dihydroxypropyltrimonium Chloride)

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Unilever Australia Ltd (ABN 66 004 050 828)
20 Cambridge Street, 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: Hydrolysis as a Function of pH, Adsorption/ Desorption, Dissociation Constant, Particle Size, Explosive Properties, Acute Inhalation Toxicty, In Vivo Genotoxicity and Bioaccumulation

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Canada (2009)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
G Quat
Glycerol Quat
PD Quat

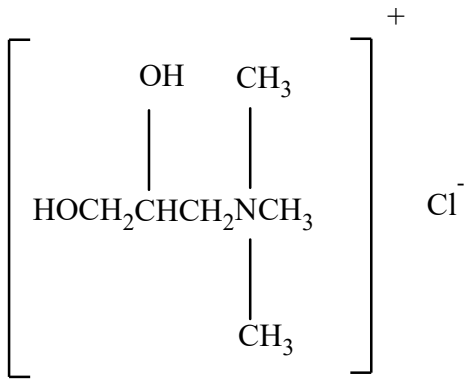
CAS NUMBER
34004-36-9

CHEMICAL NAME
1-Propanaminium, 2,3-dihydroxy-N,N,N-trimethyl-, chloride (1:1)

OTHER NAME(S)
INCI Name: Dihydroxypropyltrimonium Chloride,
(2,3-Dihydroxypropyl)trimonium chloride,
Ammonium, (2,3-dihydroxypropyl)trimethyl-, chloride

MOLECULAR FORMULA
$C_6 H_{16} NO_2 \cdot Cl$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
169.65

ANALYTICAL DATA
Reference IR, Ion Pair Liquid Chromatography spectra were provided.

3. COMPOSITION

DEGREE OF PURITY 99%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name	Methanamine, N,N-dimethyl-, Hydrochloride (1:1) (Trimethylamine Hydrochloride).		
CAS No.	593-81-7	*Weight %*	0.0002%
Hazardous Properties	R36/37/38		

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)

Chemical Name	1-Propanaminium, 3-chloro-, 1,3-dihydroxy-N,N,N-trimethyl-, chloride. (3-chloro-1,3-Dihydroxypropyltrimonium Chloride)		
CAS No.	Unknown	*Weight %*	0.0045%

ADDITIVES/ADJUVANTS

Chemical Name	Water		
CAS No.	7732-18-5	*Weight %*	44.46 to 54.34%
Chemical Name	Ethanol, 2-phenoxy		
CAS No.	122-99-6	*Weight %*	0.36 to 0.44%
Hazardous Properties	Xn; R22 Xi; R36		
Chemical Name	Benzoic acid, 4-hydroxy-, methyl ester		
CAS No.	99-76-3	*Weight %*	0.18 to 0.22%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: White crystalline solid at 20°C.

Property	Value	Data Source/Justification
Melting Point	88ºC	Measured
Boiling Point	282ºC at 100.07 kPa	Measured
Density	1290 kg/m^3 at 22ºC	Measured
Vapour Pressure	<6.7 x 10^{-7} kPa at 25ºC	Measured
Water Solubility	838-861 g/L at 20ºC	Measured
Hydrolysis as a Function of pH	Not determined	The notified chemical is not expected to hydrolyse over the environmental pH range (4–9) based on the absence of readily hydrolysable functional groups
Partition Coefficient (n-octanol/water)	log Pow = 1.15 at 22.7ºC	Measured
Adsorption/Desorption	Not determined	The notified chemical is expected to sorb strongly to negatively charged sites on sludge, soil and sediment.
Dissociation Constant	Not determined	The notified chemical is a salt which will dissociate in water.
Flash Point	224ºC at 101.37 kPa	Measured
Autoignition Temperature	300ºC	Measured
Explosive Properties	Not expected to be explosive	The structural formula contains no explosophores.

DISCUSSION OF PROPERTIES

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

Reactivity

The notified chemical is stable up to its boiling point but decomposes under normal ambient conditions at its boiling point of 282°C at 100.07 kPa.

The notified chemical shelf life is set at 6 months to assure raw material product quality, to control any formation of trimethylamine hydrochloride which can increase over time.

Dangerous Goods classification

Based on the physical-chemical data provided in the above table the notified chemical is not classified according to the Australian Dangerous Goods Code (NTC, 2007). However the data above does not address all Dangerous Goods endpoints. Therefore consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

5. INTRODUCTION AND USE INFORMATION

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

The notified chemical will not be manufactured in Australia. The notified chemical will be imported as a component of finished cosmetic products at up to 10%. The raw material will also be imported with up to 50% notified chemical for further local formulation/blending into other cosmetic products containing up to 10% notified chemical.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	10	10	10	10	10

PORT OF ENTRY

The notified chemical will be imported into Sydney, NSW.

IDENTITY OF MANUFACTURER/RECIPIENTS

The imported raw material containing the notified chemical will be transported to contract packing facilities for formulation. Imported finished products containing the notified chemical will be delivered to the notifier's

warehouse.

TRANSPORTATION AND PACKAGING
The finished products containing the notified chemical will be imported in sizes up to 400 mL bottles and tubes suitable for retail sale, packed in cardboard cartons. The cartons (12 cartons) will be packed to a cardboard shipper. The shippers will be transported from the wharf to the notifier's warehouse by road transport and then for retail distribution.
When imported at 50% for formulation of cosmetics, the notified chemical will be in 1000L high density polyethylene (HDPE) Schutz containers.

USE
The notified chemical will be used as a cosmetic ingredient at levels of up to 5% in leave on products and up to 10% concentration in rinse off products.

OPERATION DESCRIPTION

Imported Finished Products
Finished products will be transported from the wharf to the central distribution centres and workers in the notifier's warehouse will be involved in transferring pallets in the central warehouses and distributing stocks to the retailer's central distribution depots.

Formulation of imported raw material.
Store Persons will receive the ingredient when first delivered and store it in the raw material store. The imported raw material will be tested for quality assurance (QA) purposes by a chemist. The sample will be taken using a scoop by the chemist who will be wearing appropriate personal protective equipment (PPE).

Once cleared by QA, quantities of the ingredient will be issued to the compounder for production. The compounder will weigh an appropriate amount of the notified chemical into a separate container then add the amount directly into a flame proof mixing tank containing other ingredients. The compounder will wear safety glasses with shields, gloves, apron or coverall. Local ventilation will be used in the formulation area.

The chemist will sample and test the finished product for QA purposes, wearing PPE. A sample will be taken using a scoop.

Packers will monitor the line filler and the capper where the finished product was filled into retail bottles. Packers would wear safety glasses, and apron or coverall. Store Persons will remove the pallets of finished product from the end of the packing line and store the finished product for distribution to retail outlet or to salons.

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
Salon workers	100	1	300

EXPOSURE DETAILS
Transport, distribution and store workers are not expected to be exposed to the notified chemical except in an event of an accident. In case of such accidental exposure, main routes of exposure would be dermal and ocular.

6.1.2. Public exposure

However, the likelihood of such an accidental exposure is minimal.

Dermal, ocular and inhalation exposure of the chemist to the notified chemical at up to 50% may occur infrequently during sampling and testing of the raw and finished products for QA purposes.

The compounder may also be exposed to the notified chemical through dermal, ocular and inhalation routes during weighing, mixing and formulation processes.

Packers, during monitoring the line filler and the capper where the finished product will be filled into retail bottles, may also be exposed to the notified chemical via dermal and ocular routes.

However exposure is likely to be minimised through the automation of the process and the use of safety equipment such as safety glasses, gloves and apron or coveralls. Moreover, mixing and dispensing will be carried out in a closed system with flame proof mixers and pumps designed not to create aerosols and earthed for static discharges. In addition, adequate ventilation and appropriately located exhaust will be used. Overall, the exposure of these workers to the notified chemical is expected to be low.

Workers in hair and beauty salons will experience extensive dermal exposure during application of products containing the notified chemical by hand. Such professionals may use some personal protective equipment to minimise repeated exposure, and good hygiene practices are expected to be in place. Exposure of such workers is expected to be of either a similar or higher level than that experienced by consumers using products containing the notified chemical.

End-use products are designed to be sold to consumers. The general public will be repeatedly exposed to levels of the notified chemical up to 5% in leave-on cosmetic products and up to 10% in rinse-off products.

Public exposure from transport, storage, reformulation or disposal is considered to be negligible.

Public exposure to the notified chemical is expected to be widespread and frequent through daily use of personal care products containing the notified chemical. Exposure to the notified chemical will vary depending on individual use patterns. The principal route of exposure will be dermal, and accidental ocular exposure may also occur. Inhalation exposure is also possible if products are applied by spray. Accidental ingestion from the use of these types of products is also possible from 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 (BW) of 60 kg for females (SCCP, 2006);
- The maximum concentration of the notified chemical in rinse-off cosmetic products 10%;
- The maximum concentration of the notified chemical in leave-on cosmetic products 5%;
- 2% dermal absorption (in vivo dermal absorption study, see Sec. 6.2)
- An individual uses all product types containing the notified chemical.

Product type	**mg/event**	**events/day**	**C** (%)	**RF**	**Daily exposure** (mg/day)	**Daily systemic exposure*** (mg/kg bw/day)
Leave on						
Body lotion	7820	1	5	1	391	0.1303
Face cream	1540	1	5	1	77	0.0257
General purpose cream	1200	2	5	1	120	0.04
Total (Leave on)						**0.196**
Rinse off						
Facial cleansers	4060	1-2 (1 used for calculation)	10	0.01	4.06	0.0014
Make up remover	2500	2	10	0.1	50	0.0167
Shower gel	5000	2	10	0.01	10	0.0033
Shampoo	10460	1	10	0.01	10.46	0.0035
Hair conditioner	14000	0.28	10	0.01	3.92	0.0013
Hair styling products	5000	2	10	0.1	100	0.0333
Total (Rinse off)						**0.06**
Total						**0.26**

C = concentration; RF = retention factor; Daily exposure = mg/event x events/day x C(%) x RF;
*Daily systemic exposure = [daily exposure x dermal absorption %] / BW

Total systemic exposure was calculated as 0.26 mg/kg bw/day for a female of 60 kg bw (SCCP, 2006) using all types of rinse-off cosmetic products containing 10% notified chemical and leave-on cosmetic products containing 5% notified chemical.

This exposure estimate was calculated assuming 2% dermal absorption as per the in vivo rat dermal absorption study provided by the notifier, and use of multiple cosmetic products simultaneously by an individual.

6.2. Human health effects assessment

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

Endpoint	*Result and Assessment Conclusion*
Reconstructed Human epidermis Episkin, skin irritation **	non-irritating
Bovine, Corneal opacity & permeability assay, eye irritation**	non-corrosive or not a severe irritant
Mouse, skin sensitisation – Local lymph node assay*	no evidence of sensitisation
Rat, repeat dose <oral> toxicity – 14 days.**	NOAEL 300mg/kg bw/day
Rat, repeat dose <oral> toxicity – 90 days.**	NOAEL 300mg/kg bw/day
Mutagenicity – bacterial reverse mutation*	non mutagenic
Genotoxicity – in vitro Mammalian Chromosomal Aberration test*	non genotoxic
Genotoxicity – in vitro Mammalian Cell Gene Mutation Test**	non genotoxic
Skin Irritation - Human Volunteer Study Repeated Use - 14 days***	no visual signs of irritation

*100% notified chemical concentration tested,
** ~50% notified chemical concentration tested,
***4% notified chemical concentration tested

Toxicokinetics, metabolism and distribution.
Limited data are provided to describe the likely toxicokinetic properties of the notified chemical. The low molecular weight (169.65 Da) and the partition coefficient (log Pow = 1.15 measured) indicate that absorption following ingestion and dermal exposures may occur.

In an in-vivo dermal absorption study in rats with carbon -14 labelled notified chemical, the total amount of the notified chemical absorbed through the skin under occlusive conditions was approximately 2% of the applied dose (176 μg/cm^2), indicating low percutaneous absorption of the notified chemical under the conditions of the test. The majority of ^{14}C material penetrating the skin was excreted in the urine. Of the applied dose of ^{14}C material 65% was excreted in the urine, 2.5% in the faeces, 1% was expired as ^{14}CO2, with 31.5% remaining the carcass.

Acute toxicity.
The notified chemical is reported in the manufacturer's MSDS to be of low acute toxicity via oral and dermal routes, however no studies were provided. The oral LD50 was reported to be >2000 mg/kg bw in female rats, and the dermal LD50 to be >2000 mg/kg bw in male rabbits.

No acute inhalation toxicity study was conducted using the notified chemical.

Irritation.
Skin irritation
The notified chemical was tested in vitro using the reconstructed Human epidermis Episkin at ~50% for 15 minutes treatment period followed by a post exposure incubation period of 42 hours. Based on the results, the notified chemical at this concentration is considered non-irritating to skin.

In a 14-day human volunteer study, a body skin lotion containing the notified chemical at 4% showed no significant irritation potential compared to a similar product without the notified chemical.

Eye irritation
The notified chemical at ~50% was tested in a Bovine Corneal Opacity/Permeability Assay (BCOP), which focuses on corneal injury. The test results were very similar to the negative control. This study protocol has been formally validated for identification of corrosion and severe irritation and the results indicate that at ~50% the chemical is not a severe eye irritant. The ICCVAM 2009 Panel Report considered the usefulness of the method for lesser degrees of irritation, and concluded that it can be used as a screening test to distinguish non-irritants from substances classified as irritant. It is noted on the manufacturer's MSDS that the chemical at 50% can cause temporary irritation and pain. Based on the BCOP results at 50% and the proposed use concentration of up to 10%, the chemical is not expected to cause significant irritation if there is accidental ocular exposure,

however it is not possible to conclude the notified chemical as a non eye irritant based on the test results.

Sensitisation.
The notified chemical was tested in a Local Lymph Node Assay (LLNA) in mice ~50%, and did not show any sensitisation potential up to this concentration.

Repeated Dose Toxicity (sub acute, sub chronic, chronic).
A subchronic 90 day oral study in rats (preceded by a 14-day screening study) established a no observed adverse effect level (NOAEL) of 300 mg/kg bw/day. This level was set on the basis of effects seen at 300 and 1000 mg/kg bw/day, including changes in locomotor activity that may be indicative of neurotoxicity**.**

Mutagenicity.
The notified chemical was not mutagenic to Salmonella typhimurium bacteria strains, and did not induce chromosome aberrations in human peripheral lymphocytes, in the presence or absence of metabolic activation. It was not genotoxic in a mammalian cell gene mutation test using mouse lymphoma cells.

Health hazard classification
Based on the provided, 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
The notified chemical is of low acute oral and dermal toxicity. At around 50% concentration, it is not a skin irritant or a severe eye irritant and not a skin sensitiser. Information on inhalation toxicity of the notified chemical was not provided.

Dermal and ocular exposure to transport and storage workers could only occur in the event of an accident of breakage or spillage of sealed containers containing the notified chemical at up to 50% concetration.

Dermal and ocular exposure of the compounders and chemists to the raw material premixes containing up to 50% concentration of the notified chemical could occur during formulation of cosmetics. The use of PPE such as protective clothing, gloves and safety glasses will minimise exposure.

Employees in hair and beauty salons may experience dermal exposure during application of products containing the notified chemical (up to 5% in leave-on products and up to 10% in rinse-off products) by hand. The exposure of these employees would be similar or higher to that of consumers. However, the use of some personal protective equipment and good hygiene practices in place would minimise exposure, and are expected to be used if any irritation effects are experienced. Therefore, the risk of health effects following repeated exposure is not anticipated to be unacceptable.

Overall, the notified chemical in leave on and rinse off products at the specified concentrations is not expected to pose an unacceptable risk to workers under the occupational conditions described.

As no information is available on inhalation toxicity of the notified chemical, the risk of use of spray products cannot be evaluated.

6.3.2. Public health

The public may come into contact with the notified chemical at up to 5% through the use of a range of leave-on cosmetic products and at up to 10% through the use of a range of rinse-off cosmetic products. Irritation effects are not expected to occur at these concentrations.

Consumers are expected to use cosmetic products containing the notified chemical repeatedly. A quantitative risk assessment was conducted below using the NOAEL established in the 90 day repeat dose toxicity study.

The margin of exposure (MOE) for the notified chemical could be estimated as follows using the systemic exposures estimated in sec. 6.1.2:

MOE (combined use of leave on and rinse off products) = NOAEL / Estimated combined daily systemic exposure = 300 mg/kg bw/day / 0.26 mg/kg bw/day = 1154

MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Based on a NOAEL of 300 mg/kg bw/day established in the 90-day repeat dose toxicity study, and 2% dermal absorption, the MOE is calculated as >1000 for a female using all types of products containing the notified chemical.. Therefore, the risk of repeated exposure is considered to be acceptable. Dermal absorption of the notified chemical may vary with the formulation types of cosmetics. The MOE could change if the usage pattern of the cosmetics differed or if the dermal absorption from products varied from 2%. The risk is acceptable (MOE >100) up to 20% dermal absorption if formulation types affect the dermal absorption at the maximum specified concentrations in cosmetics.

Overall, based on the data provided, the notified chemical is not considered to pose an unacceptable risk to public health at concentrations up to 5% in leave-on and 10% in rinse-off cosmetic products. As no information is available on inhalation toxicity, the risk of use of spray products cannot be evaluated.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported as a component of finished cosmetic products and will also be imported as a raw material (up to ~50% aqueous solution) for formulation of cosmetics. The notified chemical is expected to be released to landfill as residue in containers (estimated to be up to 1% of the annual import volume) and released to sewer from the cleaning of blending equipment (up to 3%).

Accidental spills during transport or reformulation are expected to be collected with inert material and sent to landfill.

RELEASE OF CHEMICAL FROM USE

The notified chemical is a component in cosmetic products. Therefore, it is expected that the majority of the imported quantity of notified chemical will be released to sewer.

RELEASE OF CHEMICAL FROM DISPOSAL

Residue of the notified chemical in the empty containers (1%) is likely either to share the fate of the container and be disposed of to landfill, or to be washed to the sewer when containers are rinsed before recycling.

7.1.2 Environmental fate

The majority of the notified chemical will be disposed of to the sewer where it is expected to biodegrade and partition to sludge and sediment. The notified chemical is not likely to bioaccumulate in fish due to its high water solubility, low log Pow, and its potential biodegradability. In landfill, the notified chemical is likely to be immobile as it sorbs strongly to negatively charged sites on soil and sediment. It is expected to degrade through biotic or abiotic processes to form water and oxides of carbon and nitrogen. For the details of the environmental fate studies, refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

Assuming that most of the notified chemical will be washed into the sewer, the following Predicted Environmental Concentration (PEC) in sewage effluent on a nationwide basis was calculated.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	10,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	10,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	27.40	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	21.161	million
Removal within STP	0%	
Daily effluent production:	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	6.47	µg/L
PEC - Ocean:	0.65	µg/L

The notified chemical is expected to partition to sludge and to be readily biodegradable, hence the removal of the notified chemical from influent by sewage treatment plant (STP) processes is expected. However, in this worst case model, the majority of the notified chemical is assumed to be released in effluent. STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 6.474 µg/L may potentially result in a soil concentration of approximately 43.16 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 215.8 µg/kg and 431.6 µg/kg, respectively. However, given the expected degradation and the adsorptive nature of the notified chemical, these values should be considered as theoretical maximum concentrations only.

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on the neat notified chemical are summarised in the table below. The chronic daphnia ecotoxicological test was conducted on an aqueous solution of the notified chemical (53.4%), thus the result has been corrected to reflect the endpoint of the notified chemical. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Acute		
Fish Toxicity	LC50 (96 h) >100 mg/L	Not harmful to fish
Daphnia Toxicity	EC50 (48 h) >100 mg/L	Not harmful to aquatic invertebrates
Algal Toxicity	E_rC50 (72 h) >100 mg/L	Not harmful to algae
Inhibition of Bacterial Respiration	IC50 (17 h) >94.4 mg/L	Not harmful to microbial activity
Chronic		
Daphnia Toxicity	NOEC (21 d) = 5.34 mg/L*	No long lasting harmful effects to aquatic invertebrates**

*Corrected to reflect the endpoint of the notified chemical.
**Classification based on the notified chemical's expected ready biodegradability, daphnia chronic NOEC value,

and the absence of other reasons for concern.

Under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) the notified chemical is considered to be not harmful to fish, aquatic invertebrates, algae or microbial activity.

7.2.1 Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the chronic daphnia toxicity endpoint (NOEC (21 d) = 5.34 mg/L) of the notified chemical using an assessment factor of 50, as acute endpoints for three trophic levels and a chronic NOEC were available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (Invertebrates).	5.34	mg/L
Assessment Factor	50	
PNEC:	106.80	µg/L

7.3. Environmental risk assessment

Based on the above PEC and PNEC values, the following Risk Quotients (Q) have been calculated:

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	6.47	106.8	0.061
Q - Ocean:	0.65	106.8	0.006

The risk quotient is <1 and, therefore, the notified chemical is not expected to pose a risk to the environment based on the reported use in cosmetics and the maximum annual importation volume.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

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

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, 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

- Employers should ensure that the following safety directions are used by workers to minimise occupational exposure to the notified chemical during formulation of cosmetics:
  - Avoid contact with eyes

- A copy of the MSDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC: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 physical containment, collection and subsequent safe removal.

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 notified chemical is used in cosmetic products applied by spraying;

or

(1) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from ingredient of cosmetic products at up to 5% in leave-on products and up to 10% in wash-off products, or is likely to change significantly;
  - the amount of chemical being introduced has increased from 10 tonnes, or is likely to increase, significantly;
  - the chemical has begun to be manufactured in Australia;
  - additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

Material Safety Data Sheet
The 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

Melting Point/Freezing Point 88°C

Method	EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	Differential scanning calorimetry Method.
Test Facility	Harlan Laboratories (2009).

Boiling Point 282°C at 110.07 kPa.

Method	EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	Differential scanning calorimetry Method. Boiling was accompanied by decomposition as indicated by a black residual stain at the end of the determination.
Test Facility	Harlan Laboratories (2008).

Density 1290 kg/m^3 at 22°C

Method	EC Directive 92/69/EEC A.3 Relative Density.
Remarks	Gas comparison pycnometer Method.
Test Facility	Harlan Laboratories (2008).

Vapour Pressure <6.7 x 10^{-7} kPa at 25°C

Method	EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	Vapour Pressure Balance with measurements at several temperatures and linear regression analysis used
Test Facility	Harlan Laboratories (2008).

Water Solubility 838-861g/L at 20°C

Method	Modification of EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	Flask Method. The standard A.6 method was not applicable to the test substance as samples at five times the saturation level were not able to be prepared due to the high indeterminable saturation level of the notified chemical. Concentration analysis was reportedly unable to be performed due to high solubility producing unfilterable mixtures, thus, water solubility was estimated based on visual estimation. A clear colourless single phase solution with no excess test item present was found at 838 g/L, however excess test item was observed at 861 g/L. The water solubility was predicted to be 1000 g/L by the estimations program WSKOW (v1.41) (US EPA, 2009).
Test Facility	Harlan Laboratories Ltd. (2009a)

Partition Coefficient (n-octanol/water) log Pow = 1.15.at 22.7°C

Method	EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks	Shake-Flask Method. The test substance (50% notified chemical in water) was diluted in n-octanol saturated water (pH 7) and combined with n-octanol (water saturated). Six partitions were performed by inverting the flasks ~180° over a period of 5 min. After separation, the concentrations in both phases were determined by HPLC. The partition coefficient of the test substance was determined to be 14.2, log Pow 1.15 at 22.7°C. The notified chemical is water soluble but has a tendency to partition from water to oil.
Test Facility	Harlan Laboratories Ltd. (2009b)

Flash Point 224°C at 101.37 kPa

Method	EC Directive 92/69/EEC A.9 Flash Point.
Remarks	Closed Cup method
Test Facility	Harlan Laboratories (2008).

Flammability (Solids)

Method	EC Directive 92/69/EEC A.10 Flammability (Solids).

Remarks	The test item did not propagate combustion over the 200 mm of the preliminary screening test and determined to be not highly flammable.
Test Facility	Harlan Laboratories (2008).

Autoignition Temperature 300ºC

Method	EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	In a separate study was carried out to EC method A16- Relative self-ignition temperature for solids, it was confirmed that the notified chemical did not have a relative self-ignition temperature below the melting temperature.
Test Facility	Harlan Laboratories (2008).

Viscosity 5.99 cSt (10ºC).

Method	ASTM D445
Remarks	Data Ex MSDS. Test Substance PD Quat (Notified chemical 50% in water).
Test Facility	Dow Chemical Company (2009)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Skin irritation – human study 14 days

TEST SUBSTANCE	Product containing notified chemical at 4%.
METHOD	In house method. (Study summary only was supplied) The test substance was Glycerol Quat at 8% (4% of notified chemical) in a commercial skin lotion Vaseline Intensive Care Lotion (VICL) Antioxidant (Giant) Sample Number S2910000. Vaseline Intensive Care Lotion (VICL) Total Moisture Sample Number S2909900 containing no notified chemical was run as the control. The study was designed to compare the irritation potential of the two products in human volunteers.
Study Design	The test article and the control were applied four times a day over the 14 day treatment period (Days 0 to 13).Each subject received both the test article and the control, each being applied to a predetermined test site on the left or right forearm according to a randomisation schedule and a template applied to mark the 4cm x 2 cm test site. Each product was applied and gently rubbed in with a finger using sufficient product to cover the entire test area. The weight of the study products were recorded at the start and end of the study. Each subject kept a diary card with times of application per day and times test sites were washed/showered/bathed. Skin condition was visually assessed according to a scoring scale on days 0 to 4, days 7 to 11 and day 14. Skin reactions caused by the test article were compared statistically using a two tailed, all pairs modified Sign test. All hypothesis tests were performed using a 5% level of significance.
Study Group	32 adult humans aged 18-65 screened, 26 (25 females and 1 male) began the study and 25 completed the study. One female subject was terminated after missing 8 applications on both arms on days 5 and 6.
Observation Period	14 days.
Type of Dressing	Open.
Remarks - Method	The test was carried out during summer where the weather was warm.
RESULTS	
Remarks - Results	The visual assessment scores were compared statistically in the same subject by assessment time. There were no significant differences between the number of times the skin condition of the test product was unequal to the skin condition of the control for any of the time points. Neither of the two products elicited any skin reaction sufficient to terminate a subject from further repeated applications. There was a high degree of variability in the weight of each product applied in both groups; it is not possible to make any meaningful statement about the amount of study product used by the subjects. No safety concerns related to the use of either study product were identified. Two adverse events were reported. One subject developed a headache on one day and another subject had hotness of the right arm on one day. Both events were considered unrelated to the products used in the study.
CONCLUSION	According to the experimental conditions used, the notified chemical at 4% in a body skin lotion showed no significant differences in visually assessed irritation potential to a control product without the notified chemical in a repeated use test with 4 applications a day for 14 days.
TEST FACILITY	4-Front (2009).

B.2. Irritation – skin (In vitro Human reconstructed epidermis Episkin)

TEST SUBSTANCE Notified chemical (53.4%) in water as a clear colourless liquid.

METHOD Episkin™ Method. (draft OECD method using ECVAM SOP)
Species/Strain Human reconstructed epidermis Episkin.
Observation Period Treatment period 15 minutes followed by a post exposure incubation period of 42 hours.
Type of Dressing
Remarks - Method The testing was done in triplicate. An initial test was carried out to exclude direct MTT [[3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] reduction.
Positive (Sodium Lauryl Sulfate) and negative (Phosphate Buffered Saline) controls were also run in triplicate.
Criteria for in vitro interpretation-
If mean tissue viability is ≤ 50% classification is (Irritant (Xi) and R38).
If mean tissue viability is >50% classification is Non Irritant.

RESULTS

Batch & Concentration	Viability Score (average)	Mean OD_{540} Score	Conclusion
Negative Control	100+	0.828	Predicted non irritant
Positive Control	8.1	0.067	Predicted irritant, R38
Test Material	94.1	0.779	Predicted non irritant

Remarks - Results

CONCLUSION The notified chemical at 53.4% in water is non-irritating to the skin.

TEST FACILITY Harlan (2009a).

B.3. Irritation – eye (Bovine Corneal opacity & permeability assay)

TEST SUBSTANCE Notified chemical (53.4%) in water as a clear colourless liquid.

METHOD Bovine Corneal Opacity & Permeability Assay. (Sina JF et al. A collaborative evaluation of seven alternatives to the Draize eye irritation test using pharmaceutical intermediates).
Species/Strain Corneas from eyes of adult cattle with iris and lens removed.
Number of Animals 3 corneas per test material.
Test Period 10 minutes exposure followed by an incubation period of 120 minutes.
Remarks - Method The ocular irritancy potential of a test substance is measured by its ability to induce opacity and increase permeability in an isolated bovine cornea. The effects are measured by a) decreased light transmission through the cornea (opacity) and b) increased passage of sodium fluorescein dye through the cornea (permeability) and c) evaluation of fixed and sectioned cornea at the light microscopic level if applicable.
Positive control used was ethanol undiluted. Negative control was 0.9%w/v sodium chloride solution.

RESULTS

Cornea Opacity Measurements after 10 minutes of exposure

Treatment	Opacity Post Incubation Av of 3	Permeability Av of 3	In vitro Irritancy Score
Negative Control	0.3	0.053	1.1
Positive Control	20.3 Corrected Value	0.986 Corrected Value	35.1

Test Material	1.3 Corrected Value	0.000 Corrected Value	1.3

Cornea Epithelium Condition after 10 minutes of exposure

Treatment 3 tests	Observation Immediately after Rinsing	Observation Post Incubation
Negative Control	Clear/Clear/Clear	Clear/Clear/Clear
Positive Control	Cloudy/Cloudy/Cloudy	Cloudy/Cloudy/Cloudy
Test Material	Clear/Clear/Clear	Clear/Clear/Clear

Remarks - Results

A test material that induces an in vitro irritancy score of ≥ 55.1 is defined as an ocular corrosive or serve irritant. Such substances will be labelled within the European Union with the risk phase R41- "Risk of Serious Damage to Eyes".
However, there are limitations for this test method based on false and positive rates for certain chemical and physical classes (eg. Alcohols, ketones and solids). In some circumstances, the assay may be useful for identification of categories of ocular irritants other than corrosive or severe, but the accuracy and reliability of the assay have not yet been formally evaluated for this purpose.
The positive control in vitro irritancy score must fall within the range 30.9-67.7 to meet the test criteria. The positive control material induced an in vitro irritancy score of 35.1 and the corneas treated with the positive control material were cloudy post treatment and post incubation.
The Test Substance with an in vitro irritancy Score of 1.3 and the corneas treated with the test substance were clear post treatment and post incubation.

CONCLUSION

The notified chemical is not an ocular corrosive or severe eye irritant.

TEST FACILITY

Harlan (2009b).

B.4. Repeat dose toxicity (14 Day Oral Toxicity Study in Rodents)

TEST SUBSTANCE

Notified chemical (53.4%) in water as a clear colourless liquid.

METHOD

OECD TG 407 Repeated Dose 14 Day Oral Toxicity Study in Rodents
EC Directive 92/54/EEC B.7 Repeated Dose (14 days) Toxicity (Oral)

Species/Strain: Rat/HanBri: WIST SPF 20 male + 20 female (Groups 1 to 4: each 5 male + 5 female).

Route of Administration: Oral – gavage

Exposure Information: Daily doses administered as a 10 mL/kg body weight.
Group 1: 0 mg/kg bw.
Group 2: 100 mg/kg bw.
Group 3: 300 mg/kg bw.
Group 4: 1000 mg/kg bw.
Dosage was adjusted for the purity of the test material.

Vehicle: Distilled water.

Physical Form: Liquid.

Remarks - Method: No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 male + 5 female	0	0
low dose	5 male + 5 female	100	0
mid dose	5 male + 5 female	300	0
high dose	5 male + 5 female	1000	0

Mortality and Time to Death
All animals survived until scheduled necropsy.

Clinical Observations
No clinical signs were evident at any dose level tested. There were no test item-related changes in mean daily food consumption or in water consumption. The mean daily body weights of the test item-treated rats compared favourably with those of the control rats.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
No toxicologically relevant differences in the haematological parameters were noted. No differences of toxicological relevance were noted in males or females after two weeks treatment.

Effects in Organs
No test item related differences were noted in the mean absolute or relative organ weights at any dose level.

Remarks – Results
Only typical macroscopic background findings were noted in rats treated with 100, 300 or 1000 mg/kg bw/day.

CONCLUSION
The no observed adverse effect level (NOAEL) of the notified chemical administered orally daily to rats by gavage for a period of 14 days was established at 1000mg/kg body weight/day.

TEST FACILITY (RCC 2008b)

B.5. Repeat dose toxicity (90 Day Oral Toxicity Study in Rodents)

TEST SUBSTANCE Notified chemical (53.4%) in water as a clear colourless liquid.

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
EC Directive 88/302/EEC B.26 Sub-Chronic Oral Toxicity Test: 90-Day Repeated Oral Dose Study using Rodent Species (with additional testing for neurotoxicity).

Species/Strain Rat/HanRcc: WIST(SPF).
Group 1: 18 male + 18 female. (includes recovery groups)
Group 2: 12 male + 12 female.
Group 3: 12 male + 12 female.
Group 4: 18 male + 18 female. (includes recovery groups)
Reserve animals Group 10: 2 male + 2 female.

Route of Administration Oral – gavage

Exposure Information Daily doses administered as a 10 mL/kg body weight.
Group 1: 0 mg/kg bw.
Group 2: 100 mg/kg bw.
Group 3: 300 mg/kg bw.
Group 4: 1000 mg/kg bw.
Dosage was adjusted for the purity of the test material.
Recovery animals for groups 1 and 4 were examined 28 days after cessation of dosing
No significant protocol deviations.

Vehicle	Distilled water.
Physical Form	Liquid.
Particle Size	µm
Remarks - Method	One reserve animal was exchanged during the acclimatization period.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	18 male + 18 female	0	0
low dose	12 male + 12 female	100	0
mid dose	12 male + 12 female	300	0
high dose	18 male + 18 female	1000	0

Mortality and Time to Death

No mortality was seen in the test or recovery animals.

Clinical Observations

In a functional observational battery carried out in week 13, statistically significant changes to locomotor activity were noted at all dose levels in males, that are considered to be possibly indicative of neurotoxicity. Significant changes in activity were also noted in mid and high dose females. Most of the locomotor effects had resolved in recovery animals. No effects were seen in mean daily food consumption or mean body weights. No changes evident in test item-related ophthalmoscopic changes and no evidence of changes in duration of estrus.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

The urinalysis parameters showed no evidence of systematic changes. In the hematology parameters of high dose males and females,, the mean relative thromboplastin time was elevated when compared with the controls, and the differences exceeded the ranges of the historical control data. Although considered test item-related the cause is unclear. A greater incidence of clotted samples (five) were noted in high dose females when compared with the control females (none), but the significance of this finding is not clear. All other differences remain within the ranges of the respective historical control data. In the clinical biochemistry parameters of high dose males, potassium, phosphorus and protein levels were elevated. No other parameters were affected in these males and no toxicologically relevant differences were noted in mid or low dose males. Differences noted in high and mid dose females included elevations in sodium, chloride, calcium, phosphorous, protein and globulin, whereas low dose females showed elevations in sodium, phosphorous and globulins when compared with the controls. Although most remained within the historical control ranges, the differences noted in some parameters (sodium in all test item-treated females, protein in high and mid dose females, globulin in high dose females), exceeded the upper ranges. At mid and high doses, the pH of the urine was slightly lower in males and females at the end of the treatment period, and considered to be a test tem-related finding, but non adverse.

The differences noted in these parameters were reversible during the recovery period.

Effects in Organs

In the absence of any microscopically correlating changes, all difference in mean absolute and relative organ weights were considered to be unrelated to the test item. No test item-related macroscopic changes were noted at any dose level. Minimal and slight tubular atrophy of the testes and associated cellular debris in the epididymes were seen in two high dose recovery animals. Some other microscopic changes were considered spontaneous and to be non-dose related.

Dose-related reductions in the mean testicular and epididymal sperm counts were noted in mid and high-dose males, when compared with controls, although the values were within the range of historical controls. Sperm motility and morphology were not affected. .

Remarks – Results

Changes in the locomotor activity in mid and high dose animals are indicative of some neurotoxic effects. Further investigations may be required to rule out any potential neurotoxic effects at doses over 300 mg/kg bw/day.

CONCLUSION
Based on the results of this study, the no observed adverse effect level (NOAEL) of the notified chemical administered orally daily to rats by gavage for a period of 90 days was established as 300 mg/kg bw/day.

TEST FACILITY (RCC 2008b)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical (99.9%) as a white powder.

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure followed by Pre incubation procedure to increase the range of mutagenic chemicals that could be detected using this assay system.

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102.
Metabolic Activation System	S-9 from Arochlor 1254 induced rat liver
Concentration Range in Main Test	a) With metabolic activation: Range finder Experiment 1: 0-5000 µg/plate. Experiments 2 & 3: 156.25-5000 µg/plate. b) Without metabolic activation: Range finder Experiment 1: 0-5000 µg/plate. Experiments 2 & 3: 156.25-5000 µg/plate.
Vehicle	Deionised water.
Remarks - Method	100 µL of the test article solution in deionised water was used. If greater than two fold increase in revertant count is observed in two experiments than the result was taken as evidence of a positive response. Control treatments were performed using the same addition volumes per plate as the test article: 0.1 ml for plate incorporation treatments and 0.05 ml for pre-incubation treatments. Additional negative controls were performed using the solvent anhydrous dimethyl sulphoxide (DMSO), which was also used to formulate the positive control chemicals (e-nitrofluorene (2NF) for TA98 strain, Sodium azide for TA100 and TA1535, 9-aminoacridine (AAC) for TA1537 and Mitomycin C (MMC) for TA102).

RESULTS

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

Remarks - Results A small but statistically significant increase in revertant numbers was observed in Experiment 2 treatments with strain TA100 in the presence of S-9 when the data were analysed at the 1% level using Dunnett's test. Therefore TA100 treatments in the presence of S-9 were repeated. Following repeat treatments no increases in revertant numbers were observed, and therefore the increase observed in Experiment 2 was not reproducible and was considered to be due to a chance event and not indicative of mutagenic activity.
All positive control chemicals induced large increases in revertant numbers in the appropriate trains.

	Under the experimental conditions employed no further significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test material up to the maximum dose of 5000 µg/plate either with or without metabolic activation.
CONCLUSION	The notified chemical was not mutagenic to five histidine requiring strains of *Salmonella typhimurium* bacteria including treatments at concentrations up to 5000 µg/plate in the absence and in the presence of metabolic activation system under the conditions of the study.
TEST FACILITY	Covalance (2005a).

B.7. Genotoxicity – in vitro - Mouse Lymphoma cells

TEST SUBSTANCE	Notified chemical (51.3%) in water as a clear colourless liquid.
METHOD	OECD TG 476 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Mouse
Cell Type/Cell Line	Mouse lymphoma cell line.
Metabolic Activation System	Liver fraction (S9 mix) from male Sprague-Dawley rats pretreated with Aroclor 1254.
Vehicle	Distilled water.
Physical Form	
Remarks - Method	Cytotoxicity range finding tests were run: Experiment 1- 3 hours with and 3 hours without S9 tests; 6 concentrations from 156.3 to 5000 µg/mL. Experiment 2- 24 hours without S9 tests; 6 concentrations from 19.53 to 5000 µg/mL. Main tests were run: Experiment 1- 3 hours with and 3 hour without S9 tests; 6 concentrations from 187.5 to 5000µg/mL. Experiment 2- 3 hours with and 24 hours without S9 tests; 6 concentrations from 250 to 5000 µg/mL. Negative controls comprised treatments with the vehicle, purified water, diluted 10-fold in the treatment medium. Positive control chemicals were Methyl methane sulphonate (MMS) and Benzo[a]pyrene (B[a]P)

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period (hours)*	*Expression Time (hours)*	*Selection Time (days)*
Absent				
Test 1	250, 500, 1000, 2000, 3500, 5000	3	24 + 24	7-8
Test 2	250, 500, 1000, 2000, 3500, 5000	24	24 +24	7-8
Present				
Test 1	187.5, 375, 750, 1500, 3000, 5000	3	24 +24	7-8
Test 2	187.5, 375, 750, 1500, 3000, 5000	3	24 +24	7-8

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	>5000	>5000	Not observed	Negative
Test 2	>5000	>5000	Not observed	Negative
Present				
Test 1	>5000	>5000	Not observed	Negative
Test 2	>5000	>5000	Not observed	Negative

Remarks - Results	In the cytotoxicity Range-Finder Experiment, 3 hours treatment with 6 concentrations from 156.3 to 5000 µg/mL in the absence and presence of S-9, the highest tested concentration 5000 µg/mL presented 71% and 91% relative total growth (RTG). 24 hour treatment nine concentration (from 19.53 to 5000 µg/mL) were tested in the absence and presence of S-9, the highest concentration 5000 µg/mL gave 178% RTG. This high RTG may due to an unusually high viability count at the high concentration tested. Cell count data were consistent at all lower concentration tested and did not show toxicity or a concentration related increase in cell number. No significant changes in pH in the culture medium were observed upon addition of the test article preparation. Test article precipitation in the culture medium was not observed at up to 5000 µg/mL at the start or end of the test. Significant increases in osmolality (>50 mOsm/kg) were observed at 5000 µg/mL following all treatment conditions in the Range Finder experiment. Measurements were subsequently retaken in the Main Experiments. In Experiment 1, six concentrations ranging from 187.5 to 5000 µg/mL were tested in the absence and presence of S9. Two days after treatment, all concentrations were selected to test viability and trifluorothymidine (TFT) resistance. The highest concentration, 5000 µg/mL, gave 85% and 108% RTG in the absence and presence of S9, respectively. In Experiment 2, six concentrations ranging from 250 to 5000 µg/mL were tested in the absence (24 hours) and presence of S9 (3 hours). Two days after treatment, all concentrations were selected to test viability and TFT resistance. The highest concentration, 5000µg/mL, gave 75% and 102% RTG in the absence and presence of S9, respectively. In Experiments 1 and 2, the mutant frequencies of the concentrations plated were all less than the sum of the mean control MF plus the global evaluation factor (GEF, 126 mutants per 10^6 viable cells), indicating a negative result. Osmolality measurements were repeated in both Experiments 1 and 2 and significant increases in (>50 mOsm/kg over the concurrent controls) were observed at 5000 µg/mL in Experiment 1 and at 3500 µg/mL and above in Experiment 2 (individual data not reported). As there were no significant increases in Mutant Frequency at any concentration tested in either experiment the increases in osmolality were not deemed to have had any impact on the study. For the negative controls, the proportion of small colony mutants in the absence and presence of S-9 ranged from 28% to 38% in Experiment 1 and 35% to 47% in Experiment 2. Marked increases in the number of both small and large colony mutants were observed following treatment with the positive control chemicals MMS and B[a]P.
CONCLUSION	The notified chemical did not induce mutation at the tk locus of L5178Y mouse lymphoma cells when tested under the conditions of the test. These conditions included treatments up to 5000 µg/mL in two independent experiments, in the absence and presence of metabolic activation.
TEST FACILITY	Covalance (2008c).

B.8. Genotoxicity – in vitro - Human Lymphocytes

TEST SUBSTANCE	Notified chemical (99.9%) as a white powder.
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Human (pooled blood from three females)
Cell Type/Cell Line	Peripheral blood lymphocytes.

Metabolic Activation System	Liver fraction (S9 mix) from male Sprague-Dawley rats induced with Aroclor 1254.
Vehicle	Purified water.
Physical Form	
Remarks - Method	A dose finding test was performed in order to select appropriate test article dose levels for the chromosomal aberration test. Dose levels, 4.883, 7.766, 19.53, 39.06 78.13, 156.3, 312.5, 625.0, 1250, 2500, 5000 µg/mL. Three concentrations were selected for the two main experiments were run with dose levels: 2000, 3000, 4000 µg/mL of the test article. The positive control chemicals were used for the main experiment only. Mitomycin C (MMC) was dissolved in sterile water for injection immediately prior to use and Cyclophosphamide (CPA) was dissolved in sterile anhydrous dimethyl sulphoxide (DMSO). At the highest dose tested (5000 µg/mL), osmolality of 10mM was exceeded.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period (hours)*	*Harvest Time (hours)*	*Precipitation*
Absent				
Test 1	500, 1000, 2000*, 3000*, 4000*, 5000	3	20	Not observed
Test 2	500, 1000, 2000*, 3000*, 4000*, 5000*	20	20	Not observed
Present				
Test 1	500, 1000, 2000*, 3000,* 4000*, 5000	3	20	Not observed
Test 2	500, 1000*, 2000*, 3000, 4000, 5000*	3	20	Not observed

*Cultures selected for metaphase analysis.

RESULTS

Remarks - Results	Test article precipitation in the culture medium was not observed at up to 5000 µg/mL at the start or end of the test. No increases outside the range of background data in the frequency of chromosomal aberrations or polyploidy was observed at any concentration used in the presence or absence of metabolic activation in the short term treatments or in the continuous treatments. It was judged that the chromosomal aberration test was performed satisfactorily. Positive control chemicals MMC and CPA gave statistically significant increases in the number of cells with structural aberrations, confirming the sensitivity of the test system. The results of the mitotic index determination for the treatment in the cytotoxicity range-finding experiments 1 and 2 (experiment 1: 3 hour treatment and 17 hours recovery, experiment 2: 20 hours treatment and 0 hour recovery) were acceptable.

CONCLUSION	The notified chemical did not induce structural or numerical chromosome aberrations in cultured human peripheral blood lymphocytes when tested up to 5000 µg/mL in either the absence or presence of a rat liver metabolic activation system (S-9) under the experimental conditions described.
TEST FACILITY	Covalance (2005b).

B.9. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE	Notified chemical (98.7%) as a white powder.

METHOD: OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
EC Directive 2004/73/EC B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain: Mouse CBA/CaOlaHsd ex Harland Netherlands.
28 female animals. (4 x 5 test item groups, 4 per control group, and 4 per vehicle group).

Vehicle: Propylene Glycol.

Remarks - Method: Volume administered of test item diluted to 2.5%, 5%, 10%, 25% or 50% in propylene glycol and added at 25 µL/ear repeated on three consecutive days (d1, d2 and d3). Evaluations were made on day 6. The positive control, α-hexylcinnamaldehyde, was a moderate sensitiser, tested at 25% concentration.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0% (vehicle control)	219	-
2.5%	267	1.2
5%	190	0.9
10%	230	1.0
25%	292	1.3
50%	296	1.4
Positive Control		
25%	4663	9.0

Remarks - Results: No systemic toxicity was observed during the study. Neither clinical signs on the ears of the animals nor abnormalities of the draining lymph nodes were observed during the study period.
Increased stimulation index with the positive control confirmed the reliability of the test system.

CONCLUSION: Based on the test results the notified chemical does not cause an allergenic potential when tested up to the concentration of 50% (w/v) in propylene glycol.

TEST FACILITY: RCC (2007).

B.10. Dermal Absorption

TEST SUBSTANCE: Notified chemical (>95%) as a white powder.

METHOD: In vivo rat study. In-house method. The study was performed with carbon -14 labelled notified chemical which was administered by topical application. The study investigated the penetration of the test material through rat skin under occlusion. At 8, 24 and 48 hours of the rat topical treatment with the material (five rats with ^{14}C-notified chemical) urine samples were taken for ^{14}C assay and at 24 and 48 hours faeces were collected for ^{14}C assay. Thin layer chromatography (TLC) of the test solution at 1:10 dilutions and of the rat skin rinsings containing ^{14}C- was carried out. The presence of ^{14}C on the developed TLC plates by three different solvent systems was detected using the RITA 4radio-TLC analyser and autoradiography using X-ray film.

Species/Strain: 5 Female Rats / Olac-Wistar

Vehicle: 95% Ethanol / water

Type of dressing: Occlusive

Remarks - Method	Thin layer chromatography (TLC) of the test solution at 1:10 dilutions and of the rat skin rinsings containing ^{14}C- was carried out. The presence of ^{14}C on the developed TLC plates by three different solvent systems was detected using the RITA 4radio-TLC analyser and autoradiography using X-ray film.

RESULTS

Remarks - Results	The topically applied dose of ^{14}C-notified chemical was 176 µg/cm^2 over the skin and during the period of skin contact just over 2% of the dose (approximately 3.5 µg/cm^2) penetrated the skin. Rinsing the treated area of the skin with ethanol removed approximately 30% of the original dose and approximately 31% remained on the skin. 20% of the dose had been transferred to the protective device during 48 hour exposure. TLC of the skin rinsings suggest that the material remained unchanged over the 48 h of skin contact. Of the material that penetrated the skin, 65% was excreted in the urine, 2.5% in the faeces, 1% was expired as $^{14}CO_2$, with 31.5% remaining the carcass. Overall recovery of C-14 was approximately 85%.
CONCLUSION	The total amount of the notified chemical absorbed through the skin in vivo in rats was approximately 2% of the applied dose (176 µg/cm^2) concluding low percutaneous absorption of the notified chemical under the conditions of the test.
TEST FACILITY	Unilever Research Facility (1992)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test. EC Directive 84/449/EEC C.5 Biotic Degradation - Modified Sturm test.
Inoculum	Activated sewage sludge micro-organisms from a pilot scale sewage plant
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Evolved CO_2 was quantified by titrating unreacted $Ba(OH)_2$ in the CO_2 adsorption solution. Carbon concentrations of the test substance solutions were determined by elemental analysis.
Remarks - Method	The test substance was added at nominal concentrations of 9 and 18 mg/L to inoculated mineral medium. The test solutions were aerated with CO_2-free air and incubated at 19-20.5°C for 28 days. Degradation was determined by measuring the amount of CO_2 produced, corrected with the blank inoculum, and expressed as % of theoretical amount of CO_2 ($ThCO_2$). The results are presented below. A reference substance control was not reported in the summary report.

RESULTS

Test substance (9 mg/L)	*Test substance (18 mg/L)*

Day	*% Degradation*	*Day*	*% Degradation*
5	-2	5	0
7	27	7	10
14	74	14	78
28	80	28	91

Remarks - Results: The test material attained >60% degradation within a 10-day window. Whilst the results are not considered valid as the degradation of a reference substance was not reported this is not expected to affect the outcome of the test.

CONCLUSION: The notified chemical is expected to be readily biodegradable.

TEST FACILITY: Unilever Research Facility (1991a)

C.1.2. Bioaccumulation

TEST SUBSTANCE: Notified Chemical

METHOD: Not tested

Remarks - Results: The notified chemical is not likely to bioaccumulate based on its high water solubility, low log Pow (1.15) and its expected biodegradability.

CONCLUSION: The notified chemical is not expected to bioaccumulate.

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test - Semi-static. EC Directive 84/449/EEC C.1 Acute Toxicity for Fish - Semi-static.
Species	Zebra fish (*Brachydanio rerio*)
Exposure Period	96 hour
Auxiliary Solvent	None
Water Hardness	82–102 mg $CaCO_3$/L
Analytical Monitoring	None
Remarks – Method	A limit test of nominal concentration 100 mg test substance/L was conducted in accordance with the guidelines above. The test concentration and a control were prepared and each had ten fish added. The test chambers were maintained at 25.0–25.5°C, pH 7.8–8.5 and 7.5–8.0 mg O_2/L. Test solutions were renewed daily. The fish were observed for mortality and sub-lethal effects over a period of 4 days.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	Not determined	10	0	0	0	0	0
100	Not determined	10	0	0	0	0	0

LC50	>100 mg/L at 96 hours.
NOEC (or LOEC)	100 mg/L at 96 hours.
Remarks – Results	There was no mortality of zebra fish exposed to the test substance at a concentration of 100 mg/L for 96 h. There was no mortality in the control, thus validating the test.
CONCLUSION	The notified chemical is not harmful to fish.
TEST FACILITY	Unilever Research Facility (1991b)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test and Reproduction Test – Semi-static. EC Directive 84/449/EEC C.2 Acute Toxicity for Daphnia – Semi-static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	152-175 mg $CaCO_3$/L
Analytical Monitoring	None
Remarks - Method	The test was conducted according to the guidelines above at nominal test substance concentrations of 10.0, 18.0, 32.0, 56.0, and 100.0 mg/L. A blank control was run in parallel. Test conditions were: 18.0-21.0°C, 16h/8h light dark cycle, pH 7.9-8.4 and 7.8-8.3 mg O_2/L.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	Not determined	4 × 5	0	0
10.0	Not determined	4 × 5	0	0
18.0	Not determined	4 × 5	0	1
32.0	Not determined	4 × 5	0	1
56.0	Not determined	4 × 5	0	2
100.0	Not determined	4 × 5	1	5

EC50 >100 mg/L at 48 hours
NOEC 10.0 mg/L at 48 hours
Remarks - Results There was 25% mortality in the highest concentration of test substance tested (100 mg/L). There was no mortality of *D. magna* in the control, thus validating the test.

CONCLUSION The notified chemical is not harmful to aquatic invertebrates

TEST FACILITY Unilever Research Facility (1991c)

C.2.3. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical (53.4% in water)

METHOD OECD TG 211 *Daphnia magna*, Reproduction test - Semi-static
Species *Daphnia magna*
Exposure Period 21 d
Auxiliary Solvent None
Water Hardness 236-258 mg $CaCO_3$/L
Analytical Monitoring None
Remarks - Method *Daphnia magna* (10 replicates of a single daphnid per group) were exposed to the test substance at nominal concentrations of 0.01, 0.1, 1.0, and 10 mg/L for a period of 21 days under semi-static conditions. Test conditions were: 16h/8h light dark cycle, 18-22°C, pH 6.9-8.7, 6.7-10.1 mg O_2/L. A blank control was run in parallel. The daphnia were fed with algal suspension and supplements, and each day the vessels were assessed for adult survival, time to first brood and the number of neonates produced. Analysis of variance and Dunnett's test was used to determine the 21 day NOEC of mean juvenile production, time to release of first brood and mean size of first brood.

RESULTS

Day 21				
Nominal Concentration (mg/L)	*Mean Percent Adult Survival*	*Mean Number of Offspring Produced per female – cumulative**	*Mean size of first brood*	*Mean time of release to first brood (days)*
0.00	100	74.0	11.3	11.3
0.01	90	79.6	12.1	12.1
0.10	100	73.3	11.5	11.5
1.00	100	76.6	13.0	13.0
10.0	100	74.7	12.4	12.4

*Including dead offspring (<0.1%).

EC50 (reproduction) >5.34 mg/L at 21 days**
NOEC (reproduction) 5.34 mg/L at 21 days**
Remarks - Results There was no statistically significant effect at ≤10 mg test substance/L on adult survival, the number of neonates produced per surviving adult, the size of the first brood, or time to first brood. Observations of all neonates

during the study indicated a low incidence of minor deformities(<5%), severe deformities (<2%) and offspring mortality (<0.1%). There was no concentration dependant effect on the number or type of deformities seen within the neonates.
There was no mortality in the control, and the mean number of live offspring produced per adult was 74, thus validating the test.
**The test was conducted on a solution of the notified chemical (53.4%) in water. Therefore, the results have been corrected to reflect the effects of the notified chemical itself.

CONCLUSION The notified chemical is not harmful to aquatic invertebrates.

TEST FACILITY Safety and Environmental Assurance Centre (2008)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.
EC Directive 87/302/EEC C.3 Algal Inhibition Test.

Species	*Desmodesmus subspicatus* (formerly known as *Scenedesmus subspicatus*)
Exposure Period	72 hours
Concentration Range	Nominal: 0-100 mg/L Actual: Not determined
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	Coulter cell counter for the determination of algal cell density
Remarks - Method	The test was conducted in accordance with the guidelines above at test substance concentrations of 10.0, 32.0 and 100.0 mg/L with an initial algal density of 10^4 cells/mL. A blank control was run in parallel. Test conditions: 24.5°C, pH 7.4-8.4, continuous illumination.

RESULTS

Biomass		*Growth*	
E_bC_{50} *mg/L at 72 h*	E_bC_{10} *mg/L*	E_rC_{50} *mg/L at 72 h*	E_rC_{10} *mg/L*
>100.0	>32.0	>100	>100

Remarks - Results Cell density of the control increased 101-fold over 72 hours, thus validating the test.

CONCLUSION The notified chemical is not harmful to algae.

TEST FACILITY Unilever Research Facility (1991d)

C.2.5. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD In-house method

Inoculum	*Pseudomonas putida*
Exposure Period	17 hours
Concentration Range	Nominal: 0-94.4 mg/L Actual: Not determined
Remarks – Method	*Pseudomonas putida* was grown in a liquid medium at 24 ± 2°C in the presence of either the test substance (0-94.4 mg/L) or the reference material (cetyl trimethyl ammonium bromide, 0-10.1 mg/L). After 17 h

	growth was terminated by the addition of formalin and absorbance read at 600 nm. IC50 and NOEC values were determined by comparing the test substance with inhibition of growth using the SAS 'TOXTEST' computer program.
RESULTS	
IC50	>94.4 mg/L
NOEC	94.4 mg/L
Remarks – Results	The test substance had no apparent effect on the growth of *P. putida* under the conditions of this study. In contrast, the reference material was found to have a significant effect on growth with an estimated IC50 and NOEC of 0.2-0.3 mg/L and 0.101 mg/L, respectively.
CONCLUSION	The notified chemical is not harmful to microbial activity
TEST FACILITY	Unilever Research Facility (1990)

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