File No: STD/1619

October 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Propanedioic acid, 2-[(4-hydroxy-3,5-dimethoxyphenyl)methyl]-, 1,3-bis(2-ethylhexyl) ester (INCI name: Bis-Ethylhexyl Hydroxydimethoxy Benzylmalonate)

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment and Energy.

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1619	Merck Pty Ltd	Propanedioic acid, 2-[(4-hydroxy-3,5-dimethoxyphenyl)methyl]-, 1,3-bis(2-ethylhexyl) ester (INCI Name: Bis-ethylhexyl hydroxydimethoxy benzylmalonate)	ND*	≤ 2 tonnes per annum	Ingredient in cosmetics

*ND – Not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia.

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

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable risk to public health.

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

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Avoid eye contact

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

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

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

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

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

(1) Under Section 64(1) of the Act; if
  - the concentration in cosmetic products is intended to exceed 4%;

or

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

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

Safety Data Sheet
The SDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

This notification has been conducted under the cooperative arrangement with the Australian Therapeutic Goods Administration (TGA). The health hazard assessment component of the TGA report was provided to NICNAS and, where appropriate, used in this assessment report. The other elements of the risk assessment and recommendations on the safe use of the notified chemical were carried out by NICNAS and the Department of Environment and Energy.

APPLICANT(S)
Merck Pty Ltd (ABN: 80 001 239 818)
Ground Floor, Building 1, 885 Mountain Highway
BAYSWATER VIC 3137

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: dissociation constant, explosive properties, oxidising properties, genotoxic damage *in vivo* and bioaccumulation.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
TGA (2011)

NOTIFICATION IN OTHER COUNTRIES
BAuA Germany (2008)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
RonaCare® AP

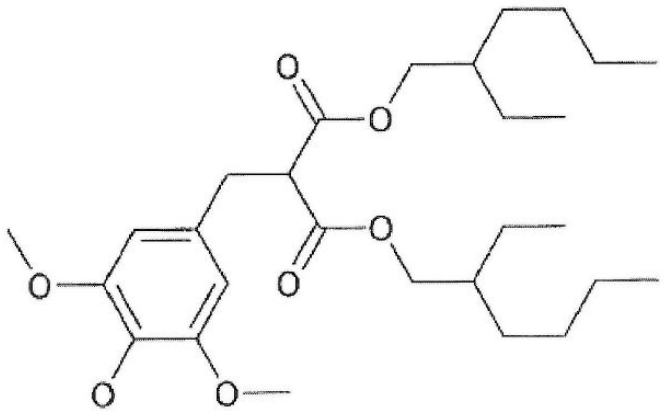
CAS NUMBER
872182-46-2

CHEMICAL NAME
Propanedioic acid, 2-[(4-hydroxy-3,5-dimethoxyphenyl)methyl]-, 1,3-bis(2-ethylhexyl) ester

OTHER NAME(S)
2-[hydroxyl-3,5-dimethoxyphenyl)methyl]malonic acid bis(2-ethylhexyl) ester
Bis-ethylhexyl hydroxydimethoxy benzylmalonate (INCI name)

MOLECULAR FORMULA
$C_{28}H_{46}O_7$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
494.66 g/mol

ANALYTICAL DATA
1H-NMR, IR, HPLC, and UV-Vis spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
≥ 97.5%

IDENTIFIED IMPURITIES (> 1% BY WEIGHT)
None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Clear, slightly yellowish liquid.

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -37°C	Measured
Boiling Point	342.7°C at 101.3 kPa	Measured
Density	1040 kg/m^3 at 20°C	Measured
Vapour Pressure	1.2 x 10^{-6} kPa at 25°C	Measured
Water Solubility	< 0.02 mg/L at 20°C	Measured
Hydrolysis as a function of pH	Not determined	The notified chemical contains hydrolysable functionality, however, due to its low water solubility, it is expected to hydrolyse slowly in the environmental pH (4-9)
Partition Coefficient (n-octanol/water)	log P_{ow} > 5.7 at 25°C	Measured
Adsorption/Desorption	log K_{oc} > 4.2 at 25 °C	Measured
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	No clear flash point up to 260°C	Measured
Flammability	Not flammable	Estimated
Autoignition Temperature	315 °C	Measured

Property	Value	Data Source/Justification
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidative properties

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

Reactivity
The notified chemical is expected to be stable under normal conditions of use.

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. It will be imported into Australia contained in 25 kg PE drums or 1 kg bottles at 100% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.2	0.4	0.8	1.2	2

PORT OF ENTRY
Port of Melbourne or Melbourne Tullamarine Airport

IDENTITY OF RECIPIENT
Merck Pty Ltd
Ground Floor, Building 1, 885 Mountain Highway
BAYSWATER VIC 3137

TRANSPORTATION AND PACKAGING
The notified chemical will be imported into Australia by air (Melbourne's Tullamarine Airport) or sea (Port of Melbourne) in its neat form packaged in 25 kg PE drums or 1 kg bottles. Within Australia, the notified chemical stored in the original packaging will be distributed to the customer sites by commercial transporters by air and road.

USE
The notified chemical will be used as an ingredient in cosmetic formulations. In the finished products the notified chemical will be present at concentrations of up to 4% and will be used mostly for leave-on application on the skin of consumers. The notified chemical may also be used in spray applications.

OPERATION DESCRIPTION

Reformulation
The notified chemical at 100% concentration will be weighed and transferred to mixing vessels for preparation of pre-mixes or final cosmetic formulations. Blending and packaging of the liquid formulations will be conducted in enclosed systems. The finished cosmetic products will contain the notified chemical at 0.5 to 4 % concentration.

End Use
The finished cosmetic products containing the notified chemical at ≤ 4% concentration will be used by consumers and professionals such as beauticians. Depending on the nature of the products, application of the finished leave-on and rinse-off skin care products is expected to be by hand or spraying.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse workers	0.5	100-150
Quality control	0.5	100-150
Formulators	6	100-150
Packaging	6	100-150

EXPOSURE DETAILS

Transport and storage workers are not expected to be exposed to the notified chemical except in the unlikely event of an accidental spill.

Reformulation

Dermal exposure to the notified chemical at up to 100% may occur during weighing and addition to the mixer or sampling for quality control testing. Dermal and ocular exposure to the notified chemical at up to 0.5% may occur during cleaning of the blending vessels. Since blending and packaging of the liquid formulations will be conducted in enclosed systems, exposure to the notified chemical is not expected during these processes. The proposed use of impervious gloves, coveralls and safety glasses by all workers should limit the exposure.

End-use

Exposure to the notified chemical at ≤ 4% concentration in end-use products may occur in professions where the services provided involve the application of cosmetic products to clients (e.g. workers in beauty salons). The principal route of exposure will be dermal, while ocular exposure is also possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using the same products containing the notified chemical.

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 ≤ 4% concentration. Given the low vapour pressure of the notified chemical, inhalation exposure is not expected. Oral exposure due to hand-to-mouth transfer is possible, although not considered to pose a risk to the public. The principal route of exposure will be dermal.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following table (SCCS, 2012). For the purposes of the exposure assessment via the dermal route, Australian use patterns for the various product categories were assumed to be similar to those in Europe. A conservative dermal absorption (DA) of 100% was assumed for the notified chemical (ECHA, 2014) and an average female body weight (BW) of 64 kg (enHealth, 2012) was used for calculation purposes.

Cosmetic products (dermal exposure)

Product type	*Amount (mg/day)*	*C (%)*	*RF (unitless)*	*Daily systemic exposure (mg/kg bw/day)*
Body lotion	7820	4.000	1.000	4.88750
Face cream	1540	4.000	1.000	0.96250
Hand cream	2160	4.000	1.000	1.35000
Facial cleanser	800	4.000	0.01	0.00500
Total				**7.2050**

C = concentration (%); RF = retention factor.

Daily systemic exposure = (Amount × C × RF × dermal absorption)/body weight

Aerosol products (Inhalation exposure)

Product type	Amount (g/day)	C (%)	Inhalation Rate (m^3/day)	Exposure Duration (Zone 1) (min)	Exposure Duration (Zone 2) (min)	Fraction Inhaled (%)	Volume (Zone 1) (m^3)	Volume (Zone 2) (m^3)	Daily systemic exposure (mg/kg bw/day)
Hairspray	9.89	4.0	20	1	20	50	1	10	**0.1288**

Daily systemic exposure = [(Amount x C x Inhalation Rate x Fraction Inhaled x 0.1)/(body weight x 1440)] x [(Exposure Duration (Zone 1)/Volume (Zone 1)) + (Exposure Duration (Zone 2)/Volume (Zone 2))]

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemical. This would result in a combined internal dose of 7.33 mg/kg bw/day.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies assessed by NICNAS refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 1,000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Photomutagenicity – bacterial reverse mutation	non photomutagenic
Genotoxicity – *in vitro* mammalian cell gene mutation test	non genotoxic
Phototoxicity – *in vitro* mammalian cell test	non phototoxic

Toxicokinetics, metabolism and distribution

Based on the low molecular weight (< 500 Da) of the notified chemical, absorption across biological membranes may occur. However, due to its high hydrophobicity (partition coefficient log P_{ow} > 5.7), dermal absorption is expected to be limited. In an *in vitro* percutaneous absorption test conducted on a porcine skin with a test substance formulation containing 4% of the notified chemical, dermal absorption was estimated to be 0.94% based on the cumulative total in the skin and receptor fluid.

The notified chemical is an ethylhexyl ester, which can hydrolyse to 2-ethylhexanol via chemical or enzymatic processes (CIR, 2013). 2-Ethylhexanol can be further metabolised to 2-ethylhexanoic acid. Both metabolites are classified as having reproductive and developmental toxicity (IMAP, 2016a and b).

Acute toxicity

In an acute oral toxicity study in Wistar rats, the notified chemical was of low oral toxicity (LD50 >2000 mg/kg). It is noted that the number of animals used was low (3/sex), but there were no deaths in the tested animals. In another study in rats, the notified chemical was also found to be of low acute toxicity by the dermal route. The LD50 was >2000 mg/kg and there were no deaths observed.

Irritation and sensitisation

In a skin irritation study the notified chemical was slightly irritating to the skin when tested in rabbits. When applied undiluted to the intact skin, the test substance caused a barely perceptible erythema in all animals that lasted for 7 days, and barely perceptible oedema in one animal on days 3-5.

In an eye irritation study in female rabbits, the notified chemical caused conjunctival redness, (score = 1 according to the Draize scale) that was seen in all animals at 1 and 24 h. The notified chemical is considered to be a slight eye irritant.

In a skin sensitisation (Magnusson and Kligman maximisation) study in female guinea pigs, the notified chemical was not a skin sensitiser when tested with a 20% induction concentration and a 5% challenge concentration. The challenge concentration was the maximum non-irritant concentration in the preliminary test or when applied occlusively for 24 hours to both the control (vehicle) and treated groups.

Repeated dose toxicity
In a 28-day repeated dose oral (gavage) toxicity study, rats were treated with the notified chemical at 0, 100, 300 or 1000 mg/kg bw/day. The only potential test substance-related effects included slightly decreased total locomotor activity observed in males at 1000 mg/kg/day. Since similar differences were not present in females and no other correlating clinical signs were observed, this possible test-item effect was considered non-adverse. Based on this observation, the No Observed Adverse Effect Level (NOAEL) was established as 1000 mg/kg bw/day for the notified chemical.

Reproductive toxicity/Developmental toxicity
No data are available on the reproductive and developmental toxicity of the notified chemical.

Both the potential metabolite of the notified chemical 2-ethylhexanol and a further metabolite 2-ethylhexanoic acid are classified as hazardous for reproductive toxicity. The IMAP report (2016c) on another diester of ethylhexanol estimated a NOAEL of 200 mg/kg bw/day for reproductive and developmental toxicity. This chemical, hexanedioic acid, bis(2-ethylhexyl) ester (CAS 103-23-1), has lower molecular weight than the notified chemical.

Based on the proportion of 2-ethylhexanol formed on hydrolysis of the smallest (2-ethylhexyl nonoanoate) and the largest (2-ethylhexyl (Z)-13-docosenoate) esters in a group of monoesters of ethylhexanol, equivalent doses of the esters required to reach the level of toxicity reported for 2-ethylhexanol (NOAEL of 130 mg/kg bw/day), range from 270-450 mg/kg bw/day (IMAP 2016d).

Mutagenicity/Genotoxicity
The notified chemical tested negative in a bacterial reverse mutation assay and negative in an *in vitro* mammalian cell gene mutation test.

The notified chemical was also considered negative in a photomutagenicity study, using two irradiation levels. The levels of increased revertants in one strain only (TA1535) in the unirradiated group were not dose related and were attributed to a low level of revertants in the solvent control.

Phototoxicity
In an *in vitro* phototoxicity test conducted in Balb/c 3T3 fibroblast cells, the notified chemical was not phototoxic.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

6.3. Human Health Risk Characterisation
The notified chemical was of low acute oral and dermal toxicity in rats, and was a slight skin and eye irritant in rabbits. Inhalation toxicity data are not available. The notified chemical was not a skin sensitiser in guinea pigs and repeated dose toxicity was low (NOAEL 1000 mg/kg bw/day). In *in vitro* assays, the potential for genotoxicity, photogenotoxicity and phototoxicity was not indicated. The notified chemical will be used as a cosmetic ingredient with dermal exposure. Dermal absorption is likely to be low (<1%) as evidenced by an *in vitro* dermal absorption study. No reproductive and developmental toxicity data for the notified chemical are available. The potential metabolite 2-ethylhexanol is classified as a developmental toxicant, with an estimated oral NOAEL of 130 mg/kg bw/day.

6.3.1. Occupational Health and Safety
Reformulation
During reformulation, workers may be exposed to the notified chemical at up to 100% concentration. The notifier anticipates that worker exposure will be limited through the use of engineering controls such as enclosed systems, automated processes and local exhaust ventilation. The use of appropriate PPE (coveralls, impervious gloves and eye protection) will also be used to limit worker exposure.

End-Use
Workers involved in professions where the services involve application of cosmetic products containing the notified chemical to clients (*e.g.* beauty salon workers) may be exposed to the notified chemical at ≤ 4%

concentration. Dermal, and to a lesser extent, ocular and inhalation exposure may occur. PPE, such as gloves, may be used by workers to minimise repeated dermal exposure, and good hygiene practices are expected to be in place. If PPE is used, the risk to such workers is expected to be of a similar or lesser extent than that for consumers using the various products containing the notified chemical.

Therefore, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health

Members of the public will experience widespread and frequent exposure to the notified chemical at ≤ 4% concentration through daily use of cosmetic products. The main route of exposure is expected to be dermal with some potential for accidental ocular and inhalation exposure.

Local Effects

The notified chemical is slightly irritating to skin and eyes. Given the low proposed use concentration (≤ 4%) irritation effects are not expected.

Systemic effects

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical using the worst case exposure scenario from use of multiple products. Total exposure was calculated to be 7.33 mg/kg bw/day (see Section 6.1.2). Using a 100% dermal exposure and NOAEL of 1000 mg/kg bw/day derived from a 28 day repeated dose oral toxicity study, the margin of exposure was estimated to be 138.79. A MoE value ≥ 100 is generally considered to be acceptable for taking into account intra- and inter-species differences. Using a dermal absorption of 1% as indicated in the *in vitro* study, the MoE would be 13,879.

Based on the high MoE for the notified chemical, the MoE for the metabolite is expected to be much higher than 100, even taking into account lower NOAEL for the metabolite,.

Overall, based on the information available, the risk to the public associated with use of the notified chemical at ≤ 4% concentration in cosmetic products is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia in its neat form for reformulation into finished cosmetic formulations for leave-on application on the skin. There is unlikely to be any significant release of the notified chemical to the environment from transport and storage, except in the case of accidental spills and leaks. In the event of spills, the products containing the notified chemical is expected to be collected with absorbents, and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve blending operations that will be highly automated, and is expected to occur within a fully enclosed environment. Wastes containing the notified chemical generated during reformulation include equipment wash water, residues in empty import containers and spilt materials. It is estimated by the notifier that up to 0.5% of the import volume of the notified chemical may be released from reformulation processes. These will be collected and released to on-site wastewater treatment facilities, sewers, or disposed of to landfill in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The notified chemical is expected to be released to the aquatic compartment through sewers during its use in personal care products across Australia.

RELEASE OF CHEMICAL FROM DISPOSAL

It is estimated by the notifier that 1% of the import volume of the notified chemical may remain in end-use containers once the consumer products are used up. Wastes and residues of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in Australia, the majority of the notified chemical is expected to be released to sewers on a nationwide basis. The submitted biodegradation study indicates that the notified chemical is not expected to be rapidly degraded in sewage treatment plants (STPs). For the details of the environmental fate study please refer to Appendix C.

In STPs the notified chemical is expected to be efficiently removed (based on its low water solubility and high partition coefficients) from effluent by adsorption to sludge. Therefore, only a small portion of the notified chemical may be released to surface waters. A proportion of the notified chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation, or disposed of to landfill. The notified chemical residues in landfill and soils are expected to have low mobility based on its calculated soil adsorption coefficient (Log K_{OC} > 4.2). The notified chemical has the potential to bioaccumulate based on its high octanol-water partition coefficient value (log P_{OW} > 5.7) and lack of ready biodegradability. However, the notified chemical is not expected to be significantly released to surface waters and is not harmful to aquatic life up to the limit of its water solubility. In the aquatic and soil compartments, the notified chemical is expected to degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the predicted environmental concentration (PEC) is summarised in the table below. Based on the reported use in cosmetic products, it is assumed that 100% of the total import volume of the notified chemical is released to the sewer. The release is assumed to be nationwide over 365 days per year. It is conservatively assumed that there is no removal of the notified chemical during sewage treatment processes.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	24.386	million
Removal within STP	0%	
Daily effluent production:	4,877	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.56	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 3.75 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 18.7 µg/kg and 37.5 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
<u>*Acute toxicity*</u>		
Fish Toxicity	96 h LL50 > 0.02 mg/L	Not harmful to fish up to its water solubility limit
Daphnia Toxicity	48 h EL50 > 0.02 mg/L	Not harmful to aquatic invertebrates up to its water solubility limit
Algal Toxicity	72 h EL50 > 0.02 mg/L	Not harmful to algae up to its water solubility limit
Inhibition of Bacterial	EC50 >1000 mg/L	Not inhibitory to bacterial respiration

Respiration		
Chronic Toxicity		
Daphnia Toxicity	21 d NOEL = 0.1 µg/L	Not harmful to aquatic invertebrates up to its water solubility limit

Based on the above ecotoxicological endpoints for the notified chemical, it is not expected to be harmful to aquatic organisms up to the limit of its solubility in water. Therefore, the notified chemical is not formally classified under the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* (United Nations, 2009) for acute and chronic toxicities.

7.2.1. Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) for the aquatic compartment has not been calculated, since the notified chemical is not considered to be harmful to aquatic life up to the limit of its solubility in water.

7.3. Environmental Risk Assessment

The Risk Quotients (Q = PEC/PNEC) have not been calculated since the PNEC was not calculated. Although the notified chemical is not readily biodegradable and has the potential for bioaccumulation, it is not expected to be harmful to aquatic life up to the limit of its water solubility. Therefore, based on the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -37°C

Method OECD TG 102 Melting Point/Melting Range, July 27 1995.
Remarks Freezing temperature method.

A preliminary test was carried out to estimate the freezing temperature of the test substance. In the preliminary test no phase transition was observed, although the temperature of the teste item decreased continuously.
The experiment was repeated with a new test item aliquot in a main test study. Starting from 20°C the test item was cooled down to -37°C. No crystallization point of the test item was observed. At the end of the experiment the test item was clear, highly viscous and gelatinous.
Test Facility IBACON (2006a)

Boiling Point 342.7°C at 101.3 kPa

Method OECD TG 103 Boiling Point, July 27 1995.
EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks Capillary method.

In the preliminary test, a stream of air bubbles was visible at 358°C. Therefore, the main test was performed by quickly heating the test item to 340°C and afterwards slowly using a heating rate of 1 K/min. Starting at 310°C the colour of the sample changed and darkening of the test item was observed.
Due to the darkening of the test item during the heating phase, determination of the boiling point was ambiguous. A decomposition of the test item was also possible. The boiling point (mean value) was determined to be 342.7°C (615.8 K) at 101.3 kPa.
Test Facility IBACON (2006b)

Density 1040 kg/m^3 at 20°C

Method OECD TG 109 Density of Liquids and Solids, July 27 1995.
EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks Pycnometer method.
Test Facility SIEMENS (2007a)

Vapour Pressure 1.2 x 10^{-6} kPa at 25°C

Method OECD TG 104 Vapour Pressure, 2006.
EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks Effusion method.

The vapour pressure was measured in the temperature range of 23°C to 149°C. Above 79°C vapour pressure could be measured. Vapour pressure values were calculated for 20, 25 and 50°C using the Antoine constants. The vapour pressure at 25°C was determined to be 1.2 x 10^{-6} kPa.
Test Facility SIEMENS (2006)

Water Solubility <0.02 mg/L at 20 °C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Column elution method.
The water solubility of the test substance was determined to be lower than the detection

limit of the analytical method.
Test Facility IBACON (2006c)

Partition Coefficient (n-octanol/water) log Pow > 5.7 at 25 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks High Performance Liquid Chromatography (HPLC) method.
The logarithmic partition coefficient was extrapolated to be 7.4.
Test Facility IBACON (2006d)

Adsorption/Desorption log K_{oc} > 4.2 at 25 °C

Method OECD TG 121 Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge Using HPLC
Remarks High Performance Liquid Chromatography (HPLC) method.
Test Facility SIEMENS (2008)

Flash Point No clear flash point up to 260ºC

Method EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks The study authors noted that no flash point was indicated in the pre-experiment. Ignition of the test substance vapour was conducted in a series of experiments at a temperature range from 119 to 300°C, however, a flash point was not indicated. The testing was stopped at 300°C due to safety precautions.
Test Facility IBACON (2006e)

Autoignition Temperature 315°C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks The preliminary test indicated the lowest self-ignition temperature of the test substance to be 325°C. The autoignition temperature determined in the main test was 315°C.
Test Facility SIEMENS (2007b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents, 27 July 1995. EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral), 30 September 1996.
Species/Strain	Rat/Wistar (HanRcc, SPF)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure period: 14 days
Vehicle	PEG 300
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M, 5F	0	0/10
low dose	5M, 5F	100	0/10
mid dose	5M, 5F	300	0/10
high dose	5M, 5F	1000	0/10
control recovery	5M, 5F	0	0/10
high dose recovery	5M, 5F	1000	0/10

Mortality and Time to Death

There was no mortality reported. All animals survived to scheduled necropsy.

Clinical Observations

One male treated with 100 mg/kg bw/day showed scabs and a wound starting in week 2 and additional hair loss from week 3 to the end of treatment. Breathing noises were observed in one male treated with 1000 mg/kg bw/day on 2 days in week 2. These findings were considered to be incidental.

In males treated with 1000 mg/kg bw/day of the test substance, the total locomotor activity showed dose-dependent decrease with statistical significance. Since similar differences were not present in females and no other correlating clinical signs were observed, this possible test-item effect was considered non-adverse.

The mean body weight of females during treatment and recovery, and of treated males, was comparable to that of the respective controls. Males treated with 1000 mg/kg bw/day had slightly higher mean body weight during recovery than the respective controls.

The mean body weight gain of treated and recovery group of males was not affected by treatment. In treated females at all dose levels, the mean body weight gain during treatment was slightly lower than in the respective controls. This effect was statistically significant on day 8 in females of the 100 mg/kg bw/day group and at the end of treatment in females treated at 100 and 300 mg/kg bw/day. The noted differences were small, did not show a dose-relationship and were inconsistent across sexes. Therefore, they were considered not to be test item-related.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical Biochemistry

After 4 weeks of treatment, urea was decreased with statistical significance in females treated at 1000 mg/kg bw/day. This change was considered to be biologically not relevant.

Total protein levels were also significantly increased in females treated at 300 mg/kg bw/day. However, these changes were inconsistent across dose levels and sexes and they were considered not to be test item-related.

Haematology
No significant changes in haematology parameters were observed in females. In males at 100 mg/kg bw/day, a slight but statistically significant decrease in the red blood cell count, haemoglobin concentration and haematocrit were observed after 4 weeks of treatment. This change was not detected at other doses. In male animals of the 1000 mg/kg bw/day group, significantly increased number of monocytes was reported.

After the recovery period, males at 1000 mg/kg bw/day were reported to have slightly decreased white blood cell count, increased neutrophils, decreased lymphocytes and decreased basophils.

Although, statistically significant, the observed changes were not dose-dependent and were within the normal range of the historical data. Changes noted during the recovery period at 1000 mg/kg bw/day were different from those noted during treatment. Therefore, it was concluded that the observed changes during recovery were not test item-related.

Urinalysis
A significant increase in erythrocytes in the urine in males treated at 300 or 1000 mg/kg bw/day was within the historical control levels for rats of this strain and age.

Effects in Organs
No statistically significant difference in the organ weights was noted in the treated animals when compared to controls. Significant increase in liver, kidney and spleen weights in males at 1000 mg/kg bw/day was observed after the recovery period. Adrenal weights were significantly decreased in these males. These findings were considered to be incidental, reflecting the usual individual variability.

After 28 days of treatment, a watery cyst was noted in the left kidney of one male treated at 300 mg/kg bw/day. One male treated with 100 mg/kg bw/day had sores and eschars in the skin. These isolated findings were considered incidental, reflecting the usual individual variability.

Remarks – Results
In regards to the general toxicity by repeated administration, slightly decreased total locomotor activity was the only treatment related effect observed in males at 1000 mg/kg bw/day. Based on this observation, the NOAEL was established at 1000 mg/kg bw/day.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1000 mg/kg bw/day in this study, based on the slightly decreased total locomotor activity in males at 1000 mg/kg/day.

TEST FACILITY	RCC (2008)

B.2. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (*Salmonella typhimurium*), January 1998. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria, 2000 Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S-9 fraction from Aroclor 1254-induced rat liver
Concentration Range in Main Test	Test 1 (with and without metabolic activation): 0.016 – 5000 µg/plate Test 2 (with and without metabolic activation): 20.48 – 2000 µg/plate
Vehicle	Dimethyl sulphoxide (DMSO)
Remarks - Method	In Test 2, treatments in the presence of S-9 included a pre-incubation step. An extended does-range of the test substance (0.016 – 2000 µg/plate) was applied to strain TA102 in Test 2.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	*Cytotoxicity in Preliminary Test**	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	>5000	>5000	>1000	Negative
Test 2		>2000	>2000	Negative
Present				
Test 1	>5000	>5000	>1000	Negative
Test 2		>2000	>2000	Negative

*The highest concentration in the preliminary test was 5000 µg/plate

Remarks - Results

Statistically significant increase in the revertant colony numbers were observed in TA100 with metabolic activation and TA102 without metabolic activation.

To determine the reproducibility of the positive results in Test 1, in Test 2, a pre-incubation step was included in all treatments in the presence of S-9 and additional treatments (dose range 1.6 – 2000 µg/plate) were included for strain TA102.
Since the increases in the revertant numbers from Test 1 did not provide a clear indication of a dose-relationship (i.e. they occurred at one or more low or intermediate dose levels), and they were not reproducible in the second independent experiment despite employing either additional dose levels or challenge methodology, it was concluded that the notified chemical did not cause increase in the revertant colony numbers in any of the tester strains used, following treatment with the test substance at any dose level, in the presence or absence of metabolic activation.

Positive controls performed as expected, confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

Covance (2006)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Oxygen Demand (ThOD)
Remarks - Method	The test and reference items were directly weighted and stirred in the test flasks.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% Degradation*[*]	*Day*	*% Degradation*
4	0	4	64
7	5	7	83
14	19	14	99
21	25	21	102
28	26	28	105

[*]Mean value of two replicates

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate surpassed the threshold level of 60 % within 4 days indicating the suitability of the inoculums. The toxicity control exceeded 40% biodegradation after 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical after 28 days was 26%.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	IBACON (2006f)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Static.
Species	*Danio rerio*
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	267 mg $CaCO_3$/L
Analytical Monitoring	Not determined as the water solubility of the test substance was determined to be lower than the detection limit of the analytical method.
Remarks – Method	The test solution was prepared as water accommodation fractions (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of test substance into the test medium followed by ultrasonication for one hour and stirring for 23 hours. The filtrate was used for this study.

RESULTS

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

LL50	> 0.02 mg/L at 96 hours.
NOEL	Not determined.
Remarks – Results	All validity criteria for the test were satisfied.

CONCLUSION The notified chemical is not harmful to fish up to its water solubility limit

TEST FACILITY Merck KGaA (2007a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	Not determined as the water solubility of the test substance was determined to be lower than the detection limit of the analytical method.
Remarks - Method	The test solution was prepared as water accommodation fractions (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of test substance into the test medium followed by ultrasonication for one hour and stirring for 23 hours. The filtrate was used for this study.

RESULTS

Concentration (mg/L)		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
100	Not determined	20	0	0

EL50	> 0.02 mg/L at 48 hours.
NOEL	Not determined.
Remarks - Results	All validity criteria for the test were satisfied.

CONCLUSION The notified chemical is not harmful to aquatic invertebrates up to its water solubility limit

TEST FACILITY Merck KGaA (2006)

C.2.3. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction test.
Species	*Daphnia magna*
Exposure Period	21 d
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	LC-MS/MS

Remarks - Method	The test solution was prepared as water accommodation fractions (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of test substance into the test medium followed by stirring for 96 hours. The test medium was incubated for an equilibration period of 24 hours in the dark and then filtered.

	Test Concentration (mg/L)	
	Control	*Loading rate 100 mg/L (mean measured 0.1 µg/L)*
Mortality (%)	5	5
Total no. offspring released by survived *Daphnia*	124.9	132.2
Mean reproduction rate in % of control	100	106

NOEL	0.10 µg/L at 21 days
Remarks - Results	The measured concentrations of the notified chemical at the start of the test renewal periods were between 0.025 and 0.43 µg/L. In the stability control samples the measured concentrations were between <LOQ and 0.13 µg/L. The low recoveries at the end of the test medium renewal periods were considered to be caused by the degradation of the test item in the test water. The 21-d NOEL of the test substance was determined to be at least 100 mg/L based on loading rate or the mean measured concentrations of 0.10 µg/L calculated as a time-weighted mean of the test item The notified chemical had no toxic effects on survival and reproduction of *Daphnia magna* after the exposure period of 21 days up to its water solubility limit.
CONCLUSION	The notified chemical is not harmful to daphnias on a chronic basis up to the limit of its water solubility.
TEST FACILITY	Harlan Laboratories Ltd. (2009)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Desmodesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 0, 100 mg/L Actual: not determined
Auxiliary Solvent	None
Water Hardness	Not determined
Analytical Monitoring	Not determined as the water solubility of the test substance was determined to be lower than the detection limit of the analytical method.
Remarks - Method	The test solution was prepared as water accommodation fractions (WAFs) due to low water solubility of the test substance. The WAF was prepared by adding the weighed amount of test substance into the test medium followed by ultrasonication for one hour and stirring for 23 hours. The filtrate was used for this study.

RESULTS

Biomass		*Growth*	
EL50 mg/L at 72 h	*NOEL mg/L*	*EL50 mg/L at 72 h*	*NOEL mg/L*
> 0.02	0.02	> 0.02	0.02

Remarks - Results	All validity criteria for the test were satisfied. The 72 h EC50 was determined to be > 0.02 mg/L based on growth rate.
CONCLUSION	The notified chemical is not harmful to algae up to the limit of its water solubility.
TEST FACILITY	Merck KGaA (2007b)

C.2.5. Inhibition of microbial activity

Test Substance	Notified chemical
Method	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Aerobic activated sludge
Exposure Period	3 hours
Concentration Range	Nominal: 10, 32, 100, 320, 1000 mg/L Actual: not determined
Remarks – Method	The notified chemical is not soluble in water. Therefore, it was directly dosed into each test flask and tap water was added. For complete emulsification of the test chemical, this mixture was stirred for about 24 hours at test temperature (18-22°C) in the dark before adding the inoculum. The test flasks were tightly closed to avoid water loss by evaporation. After approximately 24 hours, the test water containing the test chemical was slightly red coloured and the test chemical was not completely dissolved.
Results	
IC50	>1000 mg/L
NOEC	Not determined
Remarks – Results	The EC50 could not be quantified because up to the highest nominal test concentration of 1000 mg/L, no inhibition was observed after three hours incubation.
Conclusion	The notified chemical is not considered to be inhibitory to microbial respiration.
Test Facility	IBACON (2007)

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