File No: EX/227 (STD/1508)

August 2019

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Butanedioic acid, 1,4-diheptyl ester (INCI name: Diheptyl succinate)

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

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

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

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Director
NICNAS

TABLE OF CONTENTS

This assessment report is for an extension of original assessment certificate for Butanedioic acid, 1,4-diheptyl ester (INCI name: Diheptyl succinate). Based on the submission of new information by the extension notifier, some sections of the original assessment report have been modified. These modifications have been made under the heading *'Extension Application'* in the respective sections.

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
EX/227 (STD/1508)	Johnson & Johnson Pte Limited	Butanedioic acid, 1,4-diheptyl ester (INCI name: Diheptyl succinate)	ND*	≤ 1 tonne per annum	Component of 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 for the Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

Human health risk assessment
Provided that the recommended controls are being adhered to, under the conditions of the occupational setting 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, 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 implement the following engineering controls to minimise occupational exposure to the notified chemical during reformulation process:
  - Enclosed, well-ventilated automated process, where possible.

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical during handling of unfinished product undergoing reformulation process at a concentration of up to 100%:
  - Avoid contact with skin and eyes and inhalation of aerosols.

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System for the 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

- 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 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 chemical is proposed to be used at greater than 25% concentration in cosmetic products.

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from being used as a component of cosmetic products, 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.

No additional secondary notification conditions are stipulated.

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

Extension Application (EX/227):
Applicant for the extension application has provided SDS for products containing the notified polymer. The accuracy of the information on the SDS remains the responsibility of the extension applicant.

ASSESSMENT DETAILS

This notification has been conducted under the cooperative arrangement with Canada. The health and environmental hazard assessment components of the Canadian report were provided to NICNAS and, where appropriate, used in this assessment report. The other elements of the risk assessment and recommendations on safe use of the notified chemical were carried out by NICNAS.

1. APPLICANT AND NOTIFICATION DETAILS

Holders of Original Assessment Certificates (STD/1508)
Bronson & Jacobs Pty Ltd (ABN: 81 000 063 249)
70 Marple Avenue
VILLAWOOD NSW 2163

Applicant for an Extension (EX/227) of the Original Assessment Certificate:
Johnson & Johnson Pte Limited (ABN: 24 922 851 374)
45 Jones Street
ULTIMO NSW 2007

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)
No variation to the schedule of data requirements is claimed.

NOTIFICATION IN OTHER COUNTRIES
Canada (2014)

2. IDENTITY OF CHEMICAL

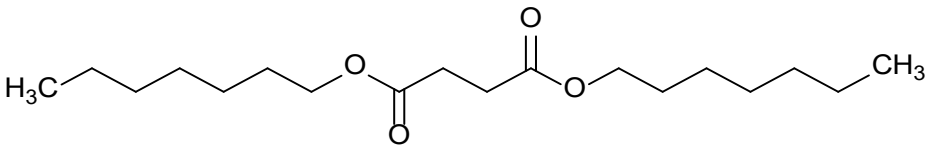
MARKETING NAME(S)
Diheptyl succinate (INCI name)
LexFeel N5, LexFeel N20, LexFeel N50, LexFeel N100, LexFeel N200, LexFeel N350 & LexFeel DHS

CAS NUMBER
15872-89-6

CHEMICAL NAME
Butanedioic acid, 1,4-diheptyl ester

MOLECULAR FORMULA
$C_{18}H_{34}O_4$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
314.5 Da

ANALYTICAL DATA
Reference IR spectra were provided.

3. ANALOGUE DATA

Toxicological data on two analogue chemicals were provided for the human health effects assessment of the notified chemical.

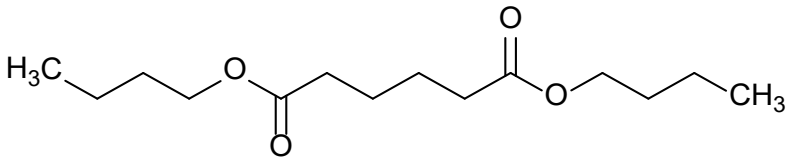
Analogue 1

CHEMICAL NAME
Hexanedioic acid, 1,6-dibutyl ester

CAS NUMBER
105-99-7

MOLECULAR FORMULA
$C_{14}H_{26}O_4$

STRUCTURAL FORMULA



JUSTIFICATION
Analogue 1 is a close analogue of the notified chemical and contains the same di-ester functional group. The alkyl chains derived from butyl alcohol are three carbon atoms shorter than the notified chemical, while the di-ester contains two more central carbon atoms than the notified chemical. Analogue chemical 1 is expected to be metabolised similarly to the notified chemical (to alcohols and a di-acid). However, the metabolites of the analogue may be more toxic than the notified chemical due to the shorter chain length alcohols (C4) compared to that of the notified chemical (C7).

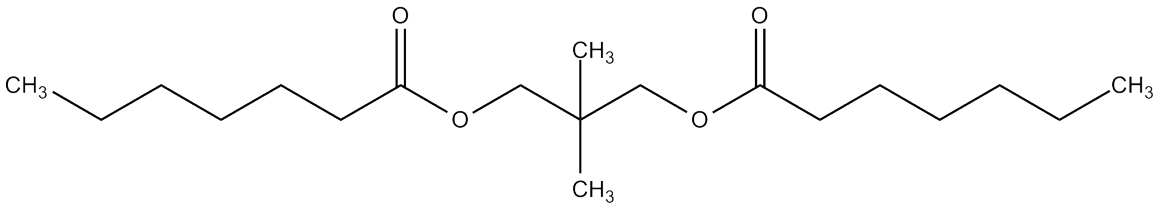
Analogue 2

CHEMICAL NAME
Heptanoic acid, ester with 2,2-dimethyl-1,3,propanediol

CAS NUMBER
68855-18-5

MOLECULAR FORMULA
$C_{19}H_{36}O_4$

STRUCTURAL FORMULA



JUSTIFICATION
Analogue 2 is a close analogue of the notified chemical. It has similar functional groups and has one more carbon atom than the notified chemical. The degradation of analogue 2 is also expected to give products similar in chain length to the expected degradation products of the notified chemical.

4. COMPOSITION

DEGREE OF PURITY
100%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None

ADDITIVES/ADJUVANTS
None

5. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Viscous liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	5 °C	Measured
Boiling Point	294 °C at 101.3 kPa	Measured
Density	929 kg/m^3 at 20 °C	Measured
Vapour Pressure	1.4 kPa at 30 °C	Measured (Reid vapour pressure)
Water Solubility	< 1.0×10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{½}$ > 1 year	Measured
Partition Coefficient (n-octanol/water)	Log Kow = 5.1	Measured
Adsorption/Desorption	Log Koc = 5.1 (extrapolated)	Measured
Dissociation Constant	pKa not applicable	Does not contain dissociable groups
Flash Point	188°C at 101.3 kPa	Measured
Autoignition Temperature	Not determined	Estimated to be high, based on flash point
Explosive Properties	Non explosive	Measured
Oxidising Properties	Non oxidising	Measured

DISCUSSION OF PROPERTIES
The experimental vapour pressure for the notified substance is higher than expected.

The water solubility test was conducted with only four measurements per run in the column elution method. "OECD Test No. 105: Water Solubility" (OECD 105) recommends that 5 measurements per run are made. In addition, the flow rate does not appear to have been reduced for the second run, as is specified in OECD 105. The pH of the aqueous solution was not provided, as it should be according to OECD 105. These deviations from the OECD guideline are not considered to significantly impact on the outcome of the test; the detection limit for the analytical method is high (1 mg/L) and as such, more helpful or detailed information is not expected if the test were run without these deviations.

The hydrolysis test as a function of pH was performed at 50°C and pH of 4, 7, and 9, and less than 10% of hydrolysis was detected.

It is not clear in the octanol-water partition coefficient test report whether the measurements were taken on multiple test replicates, or if duplicate samples from one replicate were measured. "OECD Test No. 107: Partition Coefficient (n-octanol/water): Shake Flask Method" (OECD 107) recommends that three runs are conducted with duplicate test vessels for each run. This deviation from the OECD test guideline is not considered to significantly impact on the results of the test. The detection limit for analysis of the substance in water is high (1 mg/L). Therefore, a more accurate value for the partition coefficient is not expected from more replicates being run. It should also be noted that due to the high detection limit for analysis of the substance in water, the log Kow value of 5.1 is considered the lowest potential value for this parameter. In determining the log Kow value, a concentration of 1 mg/L in water was used (i.e. the detection limit) and it is not certain how much lower the concentration in water may be.

A single determination was done for the adsorption/desorption test, while "OECD Test No. 121: Estimation of the Adsorption Coefficient (Koc) on soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)" (OECD 121) recommends that duplicate determinations be conducted. In addition, only two reference points (for two reference substances) were measured and used for the calibration curve in this test. OECD recommends that a minimum of six reference points be used. As well, the reference points on the curve are to be above and below the expected log Koc value according to OECD 121. The two reference points used in the test were both below the determined log Koc value for the notified substance. This is considered acceptable for the purposes of risk assessment since the log Koc of above 5.1 indicates that the notified chemical is immobile in soil/sediment.

The dissociation constant test for the notified substance was not conducted because the substance was considered by the study author to be insoluble in water. Therefore, dissociation is not applicable.

Reactivity
The notified chemical is expected to be stable under normal conditions of use. It is not explosive, non-oxidising and not auto-ignitable under normal conditions. The notified chemical presents no significant reactivity hazard by itself or in contact with water. However, direct sources of heat and contact with strong acids, alkali or oxidising agents should be avoided.

Dangerous Goods classification
Based on the submitted physico-chemical data in the above table the notified chemical is not classified according to the Australian Dangerous Goods Code (NTC, 2007). However, the data above do 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.

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

6. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured within Australia. The notified chemical will be imported into Australia either as a blended bulk raw material (≤ 100% concentration) for reformulation into cosmetics or as a component of finished cosmetic products (typically ≤ 10% concentration with the exception of anhydrous products where it may be present at ≤ 25% concentration).

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

Original Introduction Volume

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤ 10	≤ 20	≤ 30	≤ 50	≤ 60

Extension Application Introduction Volume (EX/227)

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

PORT OF ENTRY
Various ports throughout Australia

TRANSPORTATION AND PACKAGING
When imported as a blended bulk raw material for reformulation into cosmetics the notified chemical will be transported by ship into Australia in 7 gallon (26.5 L) HDPE pails or 55 gallon (208.2 L) stainless steel drums. The notified chemical will also be imported as a component of finished cosmetic products in a variety of containers suitable for retail sale. The products containing the notified chemical will be circulated to distribution centres/reformulation sites and retail outlets within Australia by road.

USE
The notified chemical will be used as an emollient or skin conditioning ingredient and will be sold to industrial customers to be incorporated into cosmetic and personal care products. The notified chemical will also be imported as a component of finished cosmetic products. The concentration of the notified chemical in the cosmetic products will typically be ≤ 10%; however, anhydrous formulations may contain the notified chemical at concentration of ≤ 25%.

The notified chemical will be used as a component of both leave-on and rinse-off cosmetic products including products with spray applications. Product categories include creams, deodorant, body washes, hair care, moisturisers, and makeup (including foundation and lip care). The notified chemical will be used as an excipient in sunscreen formulations.

Extension Application:
The notified chemical will be used in cosmetics at concentrations of approximately 1%.

OPERATION DESCRIPTION
The notified chemical will not be manufactured within Australia. The notified chemical may be imported as a blended bulk raw material for reformulation into cosmetics or as a component of finished cosmetic products.

Reformulation
If imported as a blended bulk raw material (≤ 100% concentration) for reformulation, the notified chemical will be weighed and added to the mixing tank where it will be blended with additional additives to form the finished cosmetic products. The notifier states that the mixing facilities are expected to be mostly automated, well ventilated (local exhaust ventilation) and use closed systems. After being reformulated, the finished products containing the notified chemical will be transferred into the retail packaging.

End use
The finished cosmetic products containing the notified chemical may be used by consumers and professionals, such as workers in beauty salons. Application of products could be by hand, spray or through the use of an applicator.

7. HUMAN HEALTH IMPLICATIONS

7.1. Exposure Assessment

7.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	1–2	30
From dock to warehouse	1–2 / site	30
Warehouse to formulators	1–2	20
Reformulation	1–3 per site	30
Retail workers	> 8	240
Salon professionals	> 8	240

EXPOSURE DETAILS

Transport and storage
The notified chemical will not be manufactured in Australia. It will be imported as a blended bulk raw material (≤ 100% concentration) or as a component of finished formulation/cosmetic/personal care products at a concentration ≤ 25% w/w.

The notified chemical will be transported and stored in sealed HDPE closed head pails or consumer packaging (plastic tubes, jars, bottles, sticks) protected by cartons and on secure pallets. Therefore, exposure to the notified chemical during transport and storage is expected only in the unlikely event of an accident where a container is damaged. In case of such accidental exposure, the main route of exposure would be dermal and ocular.

The notifier states that dockside and warehouse workers routinely wear personal protective equipment (PPE) such as impervious gloves, coveralls, safety glasses and boots to minimise exposure to the notified chemical.

Reformulation
Limited dermal and ocular exposure of workers to the notified chemical (≤ 100% w/w) may occur during transfer from the transport containers to the manufacturing equipment. Exposure to the notified chemical at levels ≤ 25% w/w may occur during manufacturing (connection and disconnection of transfer filling lines), quality control and packaging of the finished product as well as during maintenance and cleaning of equipment.

The notifier states that exposure to the notified chemical during reformulation is expected to be minimised by the use of automated equipment and closed systems for reformulation, as well as the requirement for PPE such as safety glasses, safety shoes, impervious gloves and coveralls. Local exhaust ventilation is recommended and assumed to be used at exposure points. Overall the exposure of workers to the notified chemical is expected to be low.

Retail workers
Retail workers will unpack shippers and place the consumer-packaged products (containing ≤ 25% w/w notified chemical) on retail shelves. There will be no exposure during this task, except for any unexpected spills from damaged packaging.

End-use
Exposure to the notified chemical in end-use products (at ≤ 25% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hair dressers, workers in beauty salons). The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure, but this is not expected to occur in all workplaces. However, good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

7.1.2. Public Exposure

There will be widespread and repeated exposure of the public to the notified chemical (at up to 25% concentration) through the use of a wide range of cosmetic and personal care products. The principal routes of exposure will be dermal, while ocular, oral (during facial use), and inhalation exposures (through the use of spray products) are also possible. Use of leave-on products such as moisturisers and sunscreens is expected to give the highest single exposure.

Data on typical use patterns of product categories in which the notified chemical may be used are shown in the following table (SCCS, 2012; Cadby *et al.*, 2002). For the purposes of the exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. A dermal absorption of 100% is recommended (European Commission, 2003) for chemicals with molecular weight < 500 Da, in the absence of chemical-specific data. Based on an *in vitro* dermal absorption study submitted by the notifier on Analogue 2, which has a dermal absorption of 2%, a dermal absorption value of 10% was considered reasonable to derive the margin of exposure for the notified chemical. An adult bodyweight of 60 kg has been used for calculation purposes.

Product type	**Amount** (mg/day)	**C** (%)	**RF**	**Daily systemic exposure** (mg/kg bw/day)
Body lotion	7820	10	1	1.303
Face cream	1540	10	1	0.257
Hand cream	2160	10	1	0.360
Deodorant (non-spray)	1500	25	1	0.625
Liquid Foundation	510	25	1	0.213
Lipstick, lip salve*	57	25	1	0.024
Makeup remover	5000	25	0.1	0.208
Hair styling products	4000	10	0.1	0.067
Shower gel	18670	10	0.01	0.031
Hand wash soap	20000	10	0.01	0.033
Shampoo	10460	10	0.01	0.017
Hair conditioner	3920	10	0.01	0.007
Facial cleanser	800	10	0.01	0.001
Total				**3.146**

C = concentration; RF = retention factor.
Daily exposure = mg/day × C (%) × RF; Daily systemic exposure = daily exposure × dermal absorption (%) /body weight (60 kg)

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above table that contain the notified chemical. This would result in a combined internal dose of 3.146 mg/kg bw/day.

7.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical or the analogue are summarised in the following table. For full details of the *in vitro* percutaneous absorption study, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity*	LD50 11,260 mg/kg bw; low toxicity*
Rabbit, acute dermal toxicity*	LD50 20 mL/kg bw; low toxicity*
Rat, acute inhalation toxicity*	No deaths occurred during 8 hour exposure
Eye irritation – in vitro (HET-CAM)	non-irritating
Human, skin sensitisation – RIPT (100%)	no evidence of irritation or sensitisation
In vitro Percutaneous absorption #	2.08 ± 0.21 % dermal absorption #
Rat, repeat dose oral toxicity – 28 days*	NOAEL > 1,000 mg/Kg bw*
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro (Micronucleus assay)	non genotoxic

* Tests conducted on analogue chemical 1– Hexanedioic acid, 1,6-dibutyl ester
\# Tests conducted on analogue chemical 2 – Heptanoic acid, ester with 2,2-dimethyl 1,3-propanediol

Toxicokinetics, metabolism and distribution

Based on the low molecular weight (<500 Da) of the notified chemical, there is potential for it to cross the gastrointestinal (GI) tract by passive diffusion or to be dermally absorbed. However in an *in vitro* dermal absorption study on Analogue 2 using cadaver skin, low absorption (approximately 2%) was seen.

Acute toxicity

No studies on the acute toxicity endpoints were available for the notified chemical. Acute toxicity studies via the oral, dermal and inhalation routes were conducted on analogue chemical 1, before the introduction of relevant OECD guidelines (Smyth *et al.* 1951). An LD50 of 11,210 mg/kg bw was calculated for the oral route, and 20 mL/kg body weight for the dermal route. In order to estimate acute inhalation toxicity, rats were exposed to air saturated with analogue chemical 1 for up to eight hours. No deaths were observed at the end of the study. The NOAEL of >1000 mg/kg bw/day in a repeated dose study on analogue 1 also indicates low acute oral toxicity for this chemical.

Irritation and sensitisation

Hen's egg chorioallantoic membranes (white leghorn chicken eggs) were exposed to the notified chemical to evaluate the eye irritation potential of the material. Chick embryo membranes were exposed to 10% test material for 5 minutes. Irritation scoring was done continuously, while severity scoring was done at 1 and 5 minutes during test material exposure. Additional membranes were also exposed to two positive control materials, sodium hydroxide and dodecyl sulphate sodium salt, and to the vehicle, olive oil, for irritation comparison. The notified substance had an average irritation score of 0.00, while sodium hydroxide was 17.07, dodecyl sulphate sodium salt was 10.39, and olive oil was 0.00. According to the classification criteria provided in the study report, the notified substance has no to slight eye irritation potential. However, the HET-CAM assay has not yet been validated as a replacement test for the *in vivo* Draize test, and is not to be used for regulatory hazard classification purposes, based on a lack of adequate data (ICCVAM, 2010).

In a dermal sensitization and irritation study on the notified chemical using 57 human subjects, an unspecified amount of notified substance was applied to the upper back and covered with a semi-occlusive patch. Following a 24-hour exposure period, the test patches were removed. Induction patches were applied 3 times per week for 3 consecutive weeks until 9 applications had been made. The test sites were scored for reaction 24 hours after patch removal. Following a 2-week rest period, challenge patches were applied to a new site on the back and allowed to remain in contact with the skin for 24 hours. Challenge sites were scored at 24, 48 and 72 hours after patch application. A total of 50 test subjects successfully completed the test procedure, while 7 test subjects did not, for reasons unrelated to the test. No skin reactions were noted in any test subject during the induction phase or during the challenge phase of the test. The test substance is not an irritation

hazard, and is not a sensitization concern under the conditions of this study in humans. It should be noted that the amount of test substance applied was not provided. In addition, it is not clear whether the test substance was applied directly to the skin of the test area, or applied to a test patch which was then applied to the skin of the test area.

Repeated dose toxicity
A subchronic toxicity study on analogue 1 was provided. In the subchronic study, the analogue substance (purity of 99.8%) was administered to SD rats (6 animals/sex/dose plus 6 additional animals/sex/dose for the control and high dose groups) by oral gavage at dose levels of 0, 20, 140, or 1,000 mg/kg bw/day for 28 days. There were no mortalities. Salivation after dosing was noted in the high dose males and females throughout the study. Mean body weights and mean food consumption were similar among all groups during the study. Sporadic mean increases or decreases were observed in haematology parameters, with no dose-response relationships observed. There were changes observed in clinical chemistry, organ weights, necropsy and histopathology. These changes were not slight but were noted in the absence of related findings. As such, the findings were not considered toxicologically significant. No treatment-related changes were observed in the urinalysis parameters measured. The recovery groups showed no significant findings. Under the conditions of this test, the NOAEL is the highest dose tested of 1,000 mg/kg bw/day in both sexes of rat.

It is noted that the study does not meet all the requirements of "OECD Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents" (OECD 407). Several tissues were not collected and weighed during the course of this study and several other tissues were not collected and subject to a histopathological examination. OECD 407 recommends that these tissues be weighed or subject to histopathological examination. OECD 407 also recommends that individual animal data be provided, which has not been done for the current study. Finally, necropsy appears to have been done several days after dosing was done.

Mutagenicity/Genotoxicity
In a bacterial reverse mutation assay conducted according to the "OECD Test No. 471: Bacterial Reverse Mutation test", strains of Salmonella typhimurium (TA98, TA100, TA102, TA1535, and TA1537) were exposed to the notified substance in DMSO at concentrations ranging from 50 to 5,000 µg/plate in triplicate in both the presence and absence of S9 mammalian metabolic activation. In tests 1 (plate incorporation) and 2 (pre-incubation), there were no significant increases in the number of revertant colonies observed in any of the strains at any of the concentrations tested either in the presence or absence of metabolic activation. Precipitate was observed at 1,600 and 5,000 µg/plate in each strain both in the presence and absence of metabolic activation. Cytotoxicity was noted in test 1 with metabolic activation in strains TA98 and TA1537 at 5,000 µg/plate, in test 2 with metabolic activation in TA1537 at 1,600 and 5,000 µg/plate. In both tests, the positive control substances induced the appropriate responses in the corresponding strains, confirming the performance of the test system and the metabolic activation. The notified substance is not considered mutagenic under the conditions of this study in selected strains of *S. typhimurium*.

In a mammalian *in vitro* micronucleus assay conducted according to the "OECD Test no. 487: In Vitro Mammalian Cell Micronucleus Test", human peripheral lymphocytes were exposed to the notified substance at concentrations of 0.05, 0.1, or 0.2 µg/mL with or without S9 mammalian metabolic activation. The cells were exposed either for 3 hours followed by 24 hours expression period with or without metabolic activation, or 24 hours continuous exposure without metabolic activation. A preliminary test was performed to aid in dose selection. In the main test, in the presence of metabolic activation, cytotoxicity was observed at 48.5%, 53.9%, and 54.4% in the 0.05, 0.1, and 0.2 µL/mL treatments, respectively. In the absence of metabolic activation, cytotoxicity was 44.4, 46.9, and 47.5% with 3-hour exposure and 48.0, 50.4, and 58.1% after 24 hours of exposure at 0.05, 0.1, and 0.2 µg/mL respectively. There were no significant increases in the number of micronuclei observed in any of the groups treated with the test substance when compared with the control and vehicle controls either in the presence or absence of metabolic activation. The positive control substances elicited increases of roughly double the number of micronuclei observed in the control/vehicle control groups. The increases were small but statistically significant, confirming the performance of the test system. The test material is not considered clastogenic in human lymphocyte cells under the conditions of this study.

Health effects summary
The notified chemical has a structural alert for irritation; however, available test information indicates that it had no to slight potential for eye irritation in an *in vitro* test (non-validated method), and was not irritating to human skin. It was not sensitising in a repeat insult patch test (RIPT), and not mutagenic in bacterial cells or genotoxic in human cells *in vitro*. The available information for analogue substance 1 showed the substance to have low acute and repeated dose oral toxicity in rats.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

7.3. Human Health Risk Characterisation

7.3.1. Occupational Health and Safety

Transport and Reformulation
Workers may experience dermal and accidental ocular exposure to the notified chemical (at up to 100% concentration) during transport and formulation processes. This exposure may occur during handling of the drums, cleaning and/or maintenance of the equipment. At these facilities, exposure may also extend to compounders and laboratory staff involved in the formulation of the end products containing the notified chemical and the sampling and quality control testing of these products. The notifier has stated that processes will include use of enclosed, automated processes and the use of PPE (impervious gloves, safety glasses and coveralls) should minimise the potential for exposure.

Therefore, under the expected scenarios for transport and reformulation, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Workers involved in professions where the services provided involve the application of cosmetic products to clients (e.g. hairdressers or beauty salon workers), may be exposed to the notified chemical during their application of products to salon clients. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. The risk to these workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical on a regular basis (for details of the public health risk assessment, see Section 6.3.2.).

Based on the information available, the risk to workers associated with use of the notified chemical at ≤ 25% concentration in cosmetic products is not considered to be unreasonable.

7.3.2. Public Health
Members of the public may be repeatedly exposed to the notified chemical during the use of cosmetic, hair care and personal care products containing the notified chemical at the proposed concentration up to 25%.

Local effects
Based on the information available, the notified chemical is not expected to cause adverse local effects.

Systemic effects
The potential systemic exposure to the public from the use of the notified chemical in cosmetic products was estimated to be 3.15 mg/kg bw/day (see Section 6.1.2). Using a NOAEL of 1,000 mg/kg bw/day, which was derived from a repeated dose toxicity study on analogue chemical 1, the margin of exposure (MOE) was estimated to be 317.86. Under the most conservative assumption that the concentration in all cosmetic products was 25%, the potential cumulative systemic exposure would be 6.26 mg/kg bw/day, which corresponds to an MOE of 160. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences, therefore, the MOE is considered to be acceptable.

In light of the exposure scenario considered and based on the information available, the risk to the public associated with the use of the notified chemical at up to 25% concentration is not considered to be unreasonable.

8. ENVIRONMENTAL IMPLICATIONS

8.1. Environmental Exposure & Fate Assessment

8.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported into Australia as a blended bulk raw material (< 56% notified chemical) or as a component of finished formulations/cosmetic/personal care products.

Reformulation by blending with other ingredients is expected to occur in Australia. Release from blending is expected to be very low. Empty pails are likely to be rinsed and the aqueous rinsate is likely to be disposed of into the sewer for the worst case scenario. Spills would be contained and disposed of to landfill. Any exposed surfaces would be washed down with the rinsate that is likely to be disposed of to the sewer.

RELEASE OF CHEMICAL FROM USE
Most of the notified chemical is expected to be washed to the sewer as a result of personal uses including skin care (eg. moisturisers and washes) and hair care (e.g. shampoos and conditioners).

RELEASE OF CHEMICAL FROM DISPOSAL
Waste is expected to be disposed of to landfill after containment. Container residues would either be disposed of to landfill with the containers or washed to the sewer when containers are rinsed. Residues removed as a result of cleaning the manufacturing equipment are likely to be flushed to the sewer.

8.1.2. Environmental Fate

A ready biodegradation study was provided (OECD 301 B) for the notified chemical. The test showed that the notified chemical degraded 75.22% after 28 days. The test chemical reached the pass criteria of 60% $ThCO_2$ within a 10-day window, indicating that the chemical is readily biodegradable. Based on this information, the substance is not expected to be persistent in the aquatic environment. The log Kow value for the notified chemical is at least 5.1. Based on this information, the notified chemical may be bioaccumulative. However, this potential to be accumulative is expected to be significantly reduced by the ready biodegradability.

Most of the notified chemical is expected to be released to sewer after use or washing/collection of residues/spills. Due to the low water solubility and high log K_{OC}, the majority of the notified chemical is expected to be removed in a sewage treatment plant (STP) via adsorption to sludge sediment and biodegradation. The sludge is expected to be eventually sent to landfill. In the water column or landfill, the notified chemical is expected to be decomposed, through biotic and abiotic pathways, into water and oxides of carbon.

8.1.3. Predicted Environmental Concentration (PEC)

The Predicted Environmental Concentration (PEC) can be estimated as outlined below based on the hypothetical worst case assumptions of complete discharge to the sewer nationwide and no removal from sewage treatment plants (STPs). Hence the PEC estimated below should be regarded as an over estimate as the notified chemical would be degraded and associated to sludge during sewage treatment.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	60,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	60,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	164.38	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	**Mitigation**
Daily effluent production:	4,523	ML
Dilution Factor – River	1.0	
Dilution Factor – Ocean	10.0	
PEC - River:	36.35	µg/L
PEC - Ocean:	3.63	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 36.348 µg/L may potentially result in a soil concentration of approximately 0.2423 mg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 1.212 mg/kg and 2.423 mg/kg, respectively. These calculations are considered over estimates since the majority of notified chemical is expected to be removed from the effluent via adsorption to sludge sediment and biodegradation in sewage treatment processes.

8.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical are summarised in the table below.

Endpoint	*Result*	*Assessment Conclusion*
Daphnia Toxicity	48 h EC50 > 100 mg/L (nominal)	Not harmful to *Daphnia*
Algal Toxicity	72 h E_rC50 > 100 mg/L (nominal)	Not harmful to algae

Based on the above endpoints the notified chemical is not considered to be harmful to aquatic organisms up to the limit of water solubility. The notified chemical is not considered to be harmful to aquatic organisms under the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) (United Nations, 2009). Therefore, the notified chemical is not formally classified under the GHS.

Based on its measured acute toxicity and biodegradability, the notified chemical is not formally classified under the GHS for the chronic hazard.

Daphnia acute toxicity

In an acute daphnid immobilisation test (OECD 202), groups of 20 *Daphnia magna* per concentration were exposed to the notified chemical at nominal concentrations of 0 (control), 0 (solvent control), 6.3, 13, 25, 50, or 100 mg/L for 48 hours under static conditions. Dimethylformamide was used to solubilise the notified chemical due to its low water solubility. In addition, the stock solution or test solutions were siphoned to avoid oily droplets, possibly the test material, on the surface. Because the test concentrations were not measured, the amount of notified chemical to which the daphnids were exposed remains uncertain. An initial main test exposure was stopped after 24 hours due to sporadic immobilisation observed. The experiment was repeated. In the new test, no immobilised daphnids were observed at any concentration after 24 and 48 hours of exposure. The 48 hour EL50 for immobilisation was greater than 100 mg/L (nominal). Based on these findings, the notified chemical can be considered a low toxicity concern for daphnids under the conditions of this test. Although the test concentrations were not confirmed during this test, as is specified in OECD 202, this test is considered acceptable. The notified chemical is considered to be not harmful to *Daphnia* up to the limit of water solubility.

Algal growth inhibition

In an algal growth inhibition study (OECD 201), cultures of *Pseudokirchneriella subcapitata* green algae were exposed at nominal concentrations of 0 or 100 mg/L for 72 hours. A range finding test showed little inhibition at the highest concentration tested of 100 mg/L. The water solubility of the notified chemical is low, and no solubilizing agent was used in this test. In addition, the stock solution was filtered, possibly removing the test material. Because the test concentrations were not measured, the amount of notified chemical the algae were exposed to remains uncertain. The test substance-treated group showed 0.23% inhibition in cell density, 0.24% inhibition in yield, and 0.49% inhibition in growth rate. The 72 hour EL50 for algal growth rate (E_rL50) and the 72 hour EL50 for algal yield (E_yC50) were greater than 100 mg/L (nominal). The 72 hour NOEC for growth rate and yield was 100 mg/L (nominal), the highest concentration tested. Based on the results of this study, the notified chemical can be considered a low acute toxicity concern for green algae under the conditions of this test. Although the test concentrations were not confirmed during this test, as is specified in OECD 201, this test is considered acceptable. The notified chemical is considered to be not harmful to green algae up to the limit of water solubility.

8.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) was not calculated since the notified chemical is not considered to be harmful up to the limit of solubility.

8.3. Environmental Risk Assessment

The Risk Quotient (RQ = PEC/PNEC) was not calculated since the PNEC was not available.

The notified chemical is not expected to pose an unreasonable risk to the aquatic environment based on the low ecotoxicity, biodegradability and assessed use pattern.

8. RISK ASSESSMENT FOR EXTENSION APPLICATION

There are no changes under the proposed extension to the use, or to the occupational, public and the environmental exposure and the overall introduction volume has not increased significantly. Therefore, the circumstances in the extension are not expected to impact on the original human health and environment risk assessment and recommendations.

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Dermal absorption – in vitro

TEST SUBSTANCE	Analogue chemical 2 (Heptanoic acid, ester with 2,2-dimethyl 1,3-propanediol)
METHOD	Percutaneous absorption of radioactive test substance using the human cadaver skin model (similar to OECD 428 – Skin Absorption: in vitro method)
Remarks - Method	No major deviations from the OECD guideline except for the vehicle used. The test substance was diluted in ethanol. Test substance was ^{14}C- radiolabeled and absorption was measured in human cadaver skin, in vitro, using the finite dose technique and Franz diffusion cells. The test substance was evaluated on six sections from six different cadaver skin donors for the percutaneous absorption of ^{14}C-labeled test substance over a 48-hour dose period. Test samples were collected at different time intervals (1, 2, 4, 6, 8, 10, 24, 32 and 48 hour) for analysis to estimate rate of absorption of the test substance. Following the last sample and surface wash, each chamber was tape-stripped with 10 sequential strips that were combined and saved for subsequent analysis. At preselected times after dosing (1, 2, 4, 6, 8, 10, 24, 32 and 48 hour); the dermal receptor solution was removed in its entirety, replaced with fresh receptor solution, and an aliquot saved for subsequent analysis. All samples were analysed for ^{14}C- isotope content using liquid scintillation counting.
RESULTS	Total penetration through skin – 2.08 ± 0.21 % (6.8 ± 0.7 ng) of given dose (327 ng)
Remarks - Results	The results showed that the test substance did penetrate the skin but in extremely low levels when measured as the ^{14}C-labeled isotope. Total penetration through the skin was 2.08% of the applied dose over 48 hours. Total recovery of the isotope was around 87%.
CONCLUSION	The dermal absorption of the test substance was considered to be poor from the test results. Considering the structural similarity of the test substance to the notified chemical a dermal absorption of 10% was considered reasonable.
TEST FACILITY	DermPharm (2003)

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