File No: LTD/1972

June 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

4-Dodecenal, (4*Z*)-

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
LTD/1972	International Flavours and Fragrances (Australia) Pty Ltd	4-Dodecenal, (4*Z*)-	ND*	≤ 1 tonne per annum	Fragrance ingredient in household products and 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.

The environmental hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute Category 1	H400 – Very toxic to aquatic life
Chronic Category 1	H410 – Very toxic to aquatic life with long lasting effects

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 PEC/PNEC ratio and the reported 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 safe work practices to minimise occupational exposure during handling of the notified chemical during formulation:
  - Avoid contact with skin

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

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

- A copy of the 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 physical containment, collection and subsequent safe disposal.

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;
- the notified chemical is to be used at > 0.01% concentration in cosmetic and personal care products.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from fragrance ingredient in household products and cosmetics, 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 a product containing 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

APPLICANT(S)
International Flavours and Fragrances (Australia) Pty Ltd (ABN:77 004 269 658)
310 Frankston-Dandenong Road
DANDENONG VIC 3175

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for all physico-chemical endpoints except for density and flash point.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None.

NOTIFICATION IN OTHER COUNTRIES
US (TSCA), Canada (NDSL) and China (IECSC).

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Tangerinal

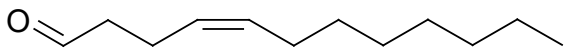
CAS NUMBER
21944-98-9

CHEMICAL NAME
4-Dodecenal, (4*Z*)-

OTHER NAME(S)
(*Z*)-4-Dodecenal
cis-Dodec-4-en-1-al

MOLECULAR FORMULA
$C_{12}H_{22}O$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
182.31 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 84%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name	Dodecanal		
CAS No.	112-54-9	*Weight %*	2.4
Hazardous Properties	H315 (Causes skin irritation) (classification by the notifier)		

Chemical Name	(E)-4-Dodecenal		
CAS No.	174255-48-7	*Weight %*	12.7
Hazardous Properties	The notifier advised that this impurity is expected to have similar hazards to the notified chemical		

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

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

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

Property	Value	Data Source/Justification
Melting Point/Freezing Point	13°C	Modelled (EPI Suite v4.11)
Boiling Point	258°C at 101.3 kPa	Modelled (EPI Suite v4.11)
Density	844-848 kg/m^3	Measured
Vapour Pressure	2.37 Pa at 25°C	Modelled (EPI Suite v4.11)
Water Solubility	0.0073 g/L at 25°C	Modelled (EPI Suite v4.11)
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionalities
Partition Coefficient (n-octanol/water)	log Pow = 4.53 at 25°C	Modelled (EPI Suite v4.11)
Adsorption/Desorption	log K_{oc} = 3.2 at 25°C	Modelled (EPI Suite v4.11)
Dissociation Constant	Not determined	No dissociable functionality
Particle Size	Not determined	Not relevant since the substance is liquid
Flash Point	> 94°C	Measured
Autoignition Temperature	Not determined	Not determined since the flash point is > 94°C.
Explosive Properties	Not explosive	Contains no functional groups that imply explosive properties.
Oxidising Properties	Not oxidizing	Contains no functional groups that 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 as a component of finished fragrance oils. The typical concentration of the notified chemical present in the finished fragrance oil is not more than 0.01%.

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

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

PORT OF ENTRY
Melbourne

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

TRANSPORTATION AND PACKAGING
The notified chemical in finished fragrance oil will be imported in polypropylene-lined steel drums (usually 55 gallons), then transported, primarily by road, from the port of Melbourne to the IFF facility, and then to customer sites.

The finished consumer products containing the notified chemical will be transported, primarily by road, to retail stores or other distribution points.

USE
The notified chemical will be used as an ingredient in fragrance oils that will be incorporated into soaps, detergents, cleaners and other household products, as well as cosmetics and personal care products. The concentration of the notified chemical in the fragrance oil is typically not more than 0.01%. Depending on the amount of the fragrance oil in the final product, the concentration of the notified chemical in the household products and cosmetics may vary significantly, however, it will not exceed 0.001% by weight.

OPERATION DESCRIPTION
No manufacturing, processing, reformulating or repackaging of the notified chemical will occur at the IFF facility. The drummed finished fragrance oil, which will typically contain up to 0.01% of the notified chemical, will be stored at this facility until it is sold and shipped to customers.

At the customers' facilities, the drummed fragrance oil will be blended with other ingredients for the manufacture of soaps, detergents, cleaners and other household products, as well as personal care and cosmetic products. The procedures for incorporating the notified chemical into end-use products at the customers' sites will vary depending on the nature of the formulated final products. It is expected that the blending process is highly automated and uses closed systems with adequate ventilation.

The anticipated concentration of the notified chemical in the final consumer products should not exceed 0.001%. The finished household products or cosmetics containing the notified chemical will be used by consumers and professionals (such as beauticians, hairdressers or cleaners). The applications may be in closed systems or open manual processes which include spraying, wiping and rinsing.

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	None	Incidental exposure only
Plant operators -- Mixing compounding (customer site)	4	250
Plant operators -- Drum handling (customer site)	1	250
Plant operators -- Drum cleaning/washing (customer site)	2	250
Plant operators -- Equipment cleaning/washing (customer site)	2	250
Plant operators -- Quality control (customer site)	1	250
Professional users – e.g. hairdressers, beauty salon workers,	8	250

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
cleaners		

EXPOSURE DETAILS

Transport and storage
Transport and storage workers may come into contact with the notified chemical as a component of fragrance oils only in the event of accidental rupture of the drum containers.

At the IFF facility, the primary work activity (transport and warehouse workers) will include handling, loading and off- loading of drums containing the notified chemical diluted in finished fragrance oils at concentration of up to 0.01% by weight. Exposures of workers to the notified chemical will be limited to situations involving product sampling for quality control, in the event of a discharge, clean up from a spill or leaking drum. If such an event occurs, a worker can be exposed through dermal and/or ocular contact. The notifier states that such exposures will be minimised to the extent possible through the use of personal protective equipment (PPE) including protective coveralls, impervious gloves and safety glasses.

Reformulation
During reformulation at the consumer product manufacture facilities, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical (at ≤ 0.01% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. Exposure is expected to be minimised through the use of PPE such as coveralls, goggles and impervious gloves. The notifier also states that adequate local ventilation and self-contained breathing apparatus are expected to be provided if required.

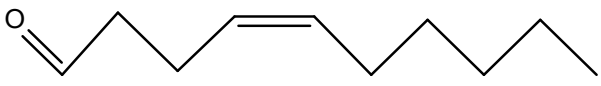
End-use
Exposure to the notified chemical in end-use products (at ≤ 0.001% concentration) may occur in professions where the services provided involve the application of cosmetic products to clients (i.e. hair and beauty salons) or the use of household products in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure
The notified chemical is intended for use in a wide range of cosmetic, personal care and household products. Therefore, public exposure during the end use will be widespread and diffuse. Given the intended use of the aforementioned products, the main route of exposure to the notified chemical is expected to be via dermal contact, while ocular and inhalation exposure (e.g. through the use of spray products) is possible. It is assumed that aggregate exposure to the notified chemical may occur through use of multiple products containing it.

6.2. Human Health Effects Assessment
No toxicity data were submitted for the notified chemical, however, analogue data were provided as read-across for some endpoints (acute oral toxicity, acute dermal toxicity, skin irritation, eye irritation, skin sensitisation, mutagenicity and genotoxicity).

The analogues used in this report are:

Analogue 1: (*Z*)-4-Decenal (CAS No. 21662-09-9)
Analogue 1 is structurally similar to the notified chemical differing only in a two carbon shorter chain length. It is therefore considered acceptable to estimate the acute oral toxicity, acute dermal toxicity and skin sensitisation of the notified chemical.



Analogue 1

Analogue 2: (*E*)-4-Decenal (CAS No. 65405-70-1)
Analogue 2 is structurally similar to the notified chemical also differing in a two carbon shorter chain length. It is therefore considered acceptable to estimate skin irritation, eye irritation, skin sensitisation, mutagenicity and genotoxicity *in vivo* of the notified chemical.

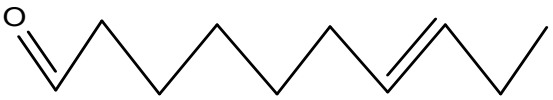
Analogue 2

Analogue 3: (*E*)-2-Dodecenal (CAS No. 20407-84-5)
Analogue 3 is a structural isomer of the notified chemical and is therefore considered acceptable to estimate the skin sensitisation and *in vivo* genotoxicity of the notified chemicals.

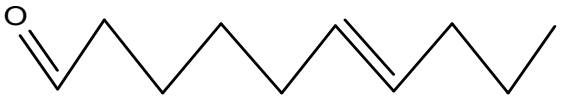
Analogue 3

Analogue 4: Isomer mixture of (*E*)-8-Decenal (CAS No. 174155-47-6), (*E*)-7-Decenal (CAS No. 21661-97-2), (*E*)-6-Decenal (CAS No. 147159-48-6), (*Z*)-8-Decenal (CAS No. 174155-46-5) and (*Z*)-6-Decenal (CAS No. 105683-99-6).
Analogue 4 is a mixture of isomers structurally similar to the notified chemical, differing only in two carbon shorter chain length. It is therefore considered acceptable to estimate skin sensitization of the notified chemical.

(*E*)-8-Decenal



(*E*)-7-Decenal



(*E*)-6-Decenal

(*Z*)-8-Decenal

(*Z*)-6-Decenal

The results from toxicological investigations conducted on the analogue chemicals are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Mouse, acute oral toxicity*	LD50 > 5000 mg/kg bw; low toxicity
Guinea Pig, acute dermal toxicity*	LD50 > 5000 mg/kg bw; low toxicity
Rabbit, skin irritation**	non-irritating
Rabbit, eye irritation**	non-irritating
Mouse, skin sensitisation – Local lymph node assay****	evidence of weak skin sensitisation
Human skin sensitisation– HMAX*	no evidence of sensitisation
Human, skin sensitisation – HRIPT (0.5%)**	no evidence of sensitisation
Human, skin sensitisation – HRIPT (0.25%)***	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation**	non mutagenic
Genotoxicity – *in vivo* mouse micronucleus test**	non genotoxic
Genotoxicity – *in vivo* mouse micronucleus test***	non genotoxic

*Analogue 1
**Analogue 2
***Analogue 3
****Analogue 4

Toxicokinetics
Based on the water solubility (0.0073 g/L at 25ºC), partition coefficient (log Pow = 4.53) and the low molecular weight (182.31 Da) of the notified chemical, passive diffusion across the gastrointestinal (GI) tract and dermal absorption are expected to occur. The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity
No acute toxicity data were provided for the notified chemical. However, analogue data for acute oral and dermal toxicity studies were provided. These studies (not conducted according to the OECD guidelines or GLP compliance) indicated that analogue 1 is of low acute oral and dermal toxicity in mice and guinea pigs, respectively.

Irritation
The notified chemical contains a structural alert for skin irritation (aldehyde group) (Hulzebos *et al.,* 2005).

Two *in vivo* dermal studies were considered to estimate the skin irritation potential of the notified chemical. The results of the acute dermal toxicity study in guinea pigs indicated that analogue 1 is slightly irritating to the skin, whereas the skin irritation study in rabbits indicated that analogue 2 is not a skin irritant. Overall, the skin irritation potential of the notified chemical is expected to be low.

One *in vivo* ocular study was also presented. The eye irritation study in rabbits indicated that analogue 2 is slightly irritating to the eyes.

Sensitisation
The notified chemical contains a structural alert for skin sensitisation (aldehyde group) (Barratt *et al.,* 1994 and Gerner *et al.,* 2004). The quantitative structure-activity relationship (QSAR) modelling using the QSAR Toolbox 3.4.0.17, predicted the notified chemical as a weak skin sensitiser.

Analogue 4, an isomer mixture, was found to be sensitising in a mouse Local Lymph Node Assay (LLNA). The EC3 value was calculated to be 66%, indicating it as a weak skin sensitiser. Information relevant to the sensitising potential of the notified chemical was also available from a human maximisation test (HMAX) for analogue 1 and human repeat insult patch tests (HRIPT) for analogues 2 and 3. Analogue 1 was not a skin sensitiser when tested at 100% concentration on 24 subjects that completed the study. Analogue 2 and 3 also showed no evidence of skin sensitisation when tested at 0.5% on 45 subjects or at 0.25% on 103 subjects, respectively. No skin allergic reactions were noted in subjects during the induction or challenge phases.

While Analogue 4 was a weak skin sensitiser (EC3 = 66%), the notified chemical has a higher molecular weight compared with the isomers in Analogue 4 (182 vs 154). Based on the weight of evidence, the notified chemical could be a weak skin sensitiser. However, the available data are insufficient to classify it as a skin sensitiser according to the GHS criteria.

Mutagenicity/Genotoxicity
The notified chemical has structural alerts for carcinogenicity (Benigni *et al.,* 2008). No carcinogenicity data on the notified chemical was provided.
Analogue data showed no genotoxic potential. Analogue 2 was negative in a bacterial reverse mutation assay and analogue 3 was negative in an *in vivo* micronucleus test. Analogue 2 was also negative in an *in vivo* micronucleus test (Bhatia *et al.,* 2010).

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

Health hazard classification
Based on the available toxicity data, the notified chemical cannot be classified 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

6.3.1. Occupational Health and Safety

Reformulation
Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemicals (at ≤ 0.01%) during reformulation. The notified chemical may be a slight skin irritant. However, irritation is not expected at the low concentration at which the chemical is imported. The notified chemical may be a weak skins sensitiser. Therefore, caution should be exercised when handling the notified chemical during reformulation and quality control processes.

The use of enclosed, automated processes and PPE (i.e., coveralls, goggles and impervious gloves) should minimise the potential for exposure. The risk to workers of skin sensitisation would be reduced by the low concentration at which it is introduced into Australia (≤ 0.01%). Therefore, provided that adequate control measures are in place to minimise worker exposure, the risk to workers from use of the notified chemicals is not considered to be unreasonable.

End use
Cleaners, hair and beauty care professionals will handle the notified chemical at ≤ 0.001% concentration. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or lesser extent than that experienced by consumers using products containing the notified chemical (for details of the public health risk assessment, see Section 6.3.2).

6.3.2. Public Health
Considering the available data, the notified chemical is expected to have slight skin irritation potential. However, irritation effects are not expected from use of the notified chemical at the proposed use concentration. The notified chemical is also expected to have weak skin sensitisation potential. Given the very low levels in the end products (0.001%), the notified chemical is not expected to present a skin sensitisation concern to the public. Information regarding repeated dose toxicity is not available, however human exposure from use of products is considered to be very low, and therefore the risk of systemic effects is considered to be low.

Based on the available information, the risk to the public associated with the use of cosmetic and household products containing the notified chemicals at ≤ 0.001%, 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 as a component in fragrance oil. Significant release of the notified chemical to the environment is not expected from transport and storage, except in the case of accidental spills

and leaks. In the event of a spill, wastes containing the notified chemical are expected to be contained and collected with an inert absorbent material and disposed of in accordance with local regulations.

At the customers' facilities, the fragrance oil containing the notified chemical will be blended with other ingredients for the manufacture of household products, personal care and cosmetic products. The blending operations are expected to be highly automated in closed systems with adequate ventilation. Therefore, significant release of the notified chemical from this process to the environment is not expected. Any wastes containing the notified chemical residues during reformulation/repacking processes are expected to be discharged to an on-site wastewater treatment plant and/or a local municipal treatment plant according to the local government regulation. Empty import containers containing the notified chemical will be either recycled or be disposed of through an approved waste management facility.

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 and household products. There may be minor air fugitive emissions to air with product sampling and use but exposures to these emissions are expected to be low.

RELEASE OF CHEMICAL FROM DISPOSAL
Wastes and residues of the notified chemical in empty containers are likely to either share the fate of the containers 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

No environmental fate data were submitted. The notified chemical is expected to be readily biodegradable based on Analogue 4 data. The analogue chemicals are structurally similar to the notified chemical with the difference that the carbon chain of the notified chemical is 2 carbons longer than the analogue chemicals. The analogue and the notified chemical are expected to have similar environmental fate.

Following its use in personal care and household products in Australia, the majority of the notified chemical is expected to be released to sewer on a nationwide basis. During the wastewater treatment process, the majority of the notified chemical is expected to be removed by degradation, based on the expected ready biodegradation, and/or by partitioning to sludge, based on the expected low water solubility.

Notified chemical remaining in the treated sewage effluents is likely to be released to surface waters or applied to land when used for irrigation. Notified chemical in sewage sludge is anticipated to be disposed of to landfill or applied to land when sludge is used for soil remediation. The notified chemical is expected to degrade in sewage treatment plants, surface waters, soils and landfill due to its ready biodegradability to form water and oxides of carbon.

The notified chemical is moderately volatile from water (vapour pressure = 2.37×10^{-3} kPa at 25 °C) and may slowly volatilise to air during sewage treatment. The half-lives of the notified chemical in air is calculated to be 1.3 and 1.4 hours, for *Z* and *E* isomers respectively, based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2012). Therefore, the notified chemical is not expected to persist in the air compartment.

Although the notified chemical has a small molecular size (MW = 182) and high calculated water/octanol partition coefficient (log Kow = 4.53), significant bioaccumulation is not expected due to the expected rapid biodegradation and surface activity, based on analogue data.

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 cosmetics and household cleansing products, it is assumed that 100% of the total import volume of the notified chemical is released to the sewer treatment plants (STPs) in 365 days. Of this, an estimated 94% is predicted to be removed by biodegradation or partitioning to sludge and air during sewage treatment plant (STP) processes (SimpleTreat, European Commission, 2003).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1,000	kg/year
Days per year where release occurs	365	days/year

Daily chemical release:	2.74	kg/day
Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	94%	**Mitigation**
Daily effluent production:	4,523	ML
Dilution Factor - River	1	
Dilution Factor - Ocean	10	
PEC - River:	0.036	µg/L
PEC - Ocean:	0.0036	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 0.036 µg/L may potentially result in a soil concentration of approximately 0.242 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 1.21 µg/kg and 2.42 µg/kg, respectively.

7.2. Environmental Effects Assessment

No ecotoxicity data were submitted for the notified chemical. As the notified chemical contains functional groups that have a demonstrated toxicity to aquatic organisms, the ecotoxicity effects of the notified chemical were predicted using ecological structure activity relationship (ECOSAR v1.11, US EPA 2012). The conservative toxicity results are summarised in the table below.

Endpoint	*Result (*)*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 0.493 mg/L	Potentially very toxic to fish
Daphnia Toxicity	48 h LC50 = 0.226 mg/L	Potentially very toxic to aquatic invertebrates
Algal Toxicity	96 h EC50 = 0.610 mg/L	Potentially very toxic to algae

**Modelled estimate ((ECOSAR v1.10, class – Aldehydes (Mono), US EPA, 2012).*

The modelling data indicates that the notified chemical is potentially very toxic to fish, aquatic invertebrates and algae under the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS). Therefore, the notified chemical is formally classified as "Acute category 1; Very toxic to aquatic life" under the GHS.

Based on its potential acute toxicity, ready biodegradability and the log Kow ≥ 4, the notified chemical is considered to be potentially very toxic to aquatic life with long lasting effects. Therefore, the notified chemical is formally classified as as "Chronic category 1; Very toxic to aquatic life with long lasting effects" under the GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the estimated invertebrate toxicity of the notified chemical using an assessment factor of 1000. Although acute endpoints for three trophic levels are available, these data are not measured endpoints. Therefore, using the conservative assessment factor of 1000 is more appropriate in this case.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Invertebrates)	0.23	mg/L
Assessment Factor	1,000	
Mitigation Factor	1.00	
PNEC:	0.23	µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River	0.036	0.23	**0.158**
Q - Ocean	0.0036	0.23	**0.016**

The Risk Quotients (Q = PEC/PNEC) have been conservatively calculated to be < 1 for both river and ocean compartments, indicating that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in aquatic environments based on its annual importation quantity and the removal of the chemical from waste water by degradation, adsorption to sewage sludge and partitioning into air. The notified chemical has a low potential for bioaccumulation and is unlikely to persist in surface waters, air or soils.

Therefore, on the basis of the PEC/PNEC ratio, maximum annual importation volume and assessed use pattern in cosmetic and domestic products, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Density 844-848 kg/m^3 at 20°C

Method	OECD TG 109 Density of Liquids and Solids. EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks	Oscillating densitometer method (Protocol provided)
Test Facility	International Flavours and Fragrances (Australia) Pty Ltd

Flash Point > 94°C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Closed cup equilibrium method (Protocol provided)
Test Facility	International Flavours and Fragrances (Australia) Pty Ltd

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Analogue 1

METHOD
- Species/Strain: Mice
- Vehicle: Not stated
- Remarks - Method: The description of the procedure was very short. It was not possible to compare the method used with methods in OECD guidelines. The purity of the test substance was not reported. There was no information on the batch that was tested, the study was not carried out according to GLP, and no data were presented on the development of the body weights.

RESULTS

Main Study

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	10	5000	4/10

- LD50: > 5000 mg/kg bw
- Signs of Toxicity: Diarrhea, lethargy, piloerection, dyspnea, ptosis and left eye crusted shut were noted. Four animals died during the study period, on days 0 (2 animals), 3 and 11.
- Effects in Organs: Necroscopy of the animals showed red/dark discolouration of the stomach, intestine, liver and lungs.
- Remarks - Results: The necropsy results were labelled for rats rather than mice (presumably in error).

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

TEST FACILITY: M B Research (1978)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Analogue 1

METHOD
- Species/Strain: Guinea pigs
- Vehicle: Not stated
- Type of dressing: Not stated
- Remarks - Method: The description of the procedure was very short. It was not possible to compare the method used with methods in OECD guidelines. The purity of the test substance was not reported. The exposure period was not stated. There was no information on the batch that was tested, the study was not carried out according to GLP, and no data were presented on the development of the body weights.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5	5000	0/5

- LD50: > 5000 mg/kg bw
- Signs of Toxicity: Adipsia, anorexia and emaciation were noted.

Effects in Organs	There were no deaths or test substance-related clinical signs during the study period.
Remarks - Results	Moderate redness of skin and slight oedema were observed in 4 and 3 animals, respectively. No adverse results were seen at necropsy. The necropsy results were labelled for rabbits rather than guinea pigs (presumably in error).

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

TEST FACILITY M B Research (1978)

B.3. Irritation – skin

TEST SUBSTANCE Analogue 2

METHOD Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	3M, 3F
Vehicle	None
Observation Period	72 hours
Type of Dressing	Occlusive
Remarks - Method	The test substance was added to one abraded and one intact site. The test substance was applied for 24 hours. Skin reaction to treatment was evaluated according to the method of Draize at 24 and 72 hours after the application of the test substance.

RESULTS

Remarks - Results	All six animals showed no evidence of discomfort on application of the test substance and remained healthy for the duration of the study. Almost all individual scores were zero. The Primary Dermal Irritation Index for the test substance was 0.041, non-irritating.

CONCLUSION The test substance is non-irritating to the skin.

TEST FACILITY CSE (1979)

B.4. Irritation – eye

TEST SUBSTANCE Analogue 2

METHOD Similar to OECD TG 405 Acute Eye Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	5M, 1F
Observation Period	7 days
Remarks - Method	The test substance (0.1 ml) was applied once into the right eye of each of the six rabbits. The eyes were examined at 24, 48, and 72 hours and at 4 and 7 days. On Day 1 and Day 7 the eyes were examined with fluorescein. The irritation was scored by the method of Draize.

RESULTS

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Conjunctiva: redness	0.67	0.33	0.67	0.67	0.67	0	1	< 72 h	0

Lesion	*Mean Score**						*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3	4	5	6			
Conjunctiva: chemosis	0	0	0.33	0.33	0	0	1	< 48 h	0
Conjunctiva: discharge	0.33	0	0.33	0.67	0.33	0.33	1	< 72 h	0
Corneal opacity	0	0	0	0	0	0	-	-	-
Iridial inflammation	0	0	0	0	0	0	-	-	-

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

Remarks - Results: All six animals remained healthy and of normal behaviour for the duration of the study. Conjunctival effects were seen, that were resolved by the 72 h observation. The primary Ocular Irritation Score was 3.67.

CONCLUSION: The test substance is slightly irritating to the eye.

TEST FACILITY: CSE (1978)

B.5. Skin sensitisation – mouse Local Lymph Node Assay (LLNA)

TEST SUBSTANCE: Analogue 4 (isomer mixture)

METHOD: OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010)
EC Council Regulation No 440/2008 B.42 Skin Sensitisation (Local Lymph Node Assay)

Species/Strain: Mouse/CBA/Ca

Vehicle: Acetone/olive oil 4:1

Remarks - Method: An exception to the GLP compliance was noted. No analysis was carried out to determine the homogeneity, concentration or stability of the test item formulation. The study authors assumed that the test item formulation was stable during application.

Positive control: α-hexyl cinnamaldehyde (85%) at 25% v/v in acetone: olive oil (4:1)
Negative control: vehicle only

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)**	*Stimulation Index***
Test Substance			
0 (vehicle control)	5/F	979.18	1.00
25	5/F	1883.16	1.92
50	5/F	1774.7	1.81
100	5/F	5305.24	5.42
Positive Control			
25	5/F	7142.2	7.29

* total number of lymph nodes per animal is 2
**Stimulation Index = Test/Vehicle Control Ratio

EC3: 66%

Remarks - Results: No signs of systemic toxicity or death were noted during the study.

CONCLUSION: There was evidence of induction of a lymphocyte proliferative response indicative of weak skin sensitisation to the test substance.

TEST FACILITY	Harlan (2012)

B.6. Skin sensitisation – human volunteers

TEST SUBSTANCE	Analogue 1
METHOD	HMAX (human maximisation test) – the method was modified after JID 47: 393-409, 1966.
Study Design	Induction Procedure: 32 healthy human volunteers were treated with Analogue 1, (assumed to be neat) using an occlusive patch for 48 hour periods on 5 alternate days. Patch sites were pretested with 5% aqueous sodium lauryl sulfate (SLS) for the first patch only. Rest Period: 10-14 days Challenge Procedure: Following the rest period, occlusive challenge patches of the analogue were applied on a new site. Challenge sites with and without 5% SLS were used. Patches were removed after 24 h and evaluated for dermal reactions. The test sites were re-evaluated at 48 h and 72 h.
Study Group	32 healthy volunteers were screened and 24 completed the study.
Vehicle	Not specified.
Remarks - Method	Occluded.
RESULTS	
Remarks - Results	24/32 subjects completed the study. Eight subjects discontinued study participation for reasons unrelated to the test material. One subject had an equivocal response at 48 hrs following challenge with 5% SLS and the test substance, but no other reactions indicative of irritation or sensitisation due to the test substance were observed.
CONCLUSION	The test substance was not a skin sensitiser under the conditions of the test.
TEST FACILITY	LMC (1978)

B.7. Skin sensitisation – human volunteers (0.5%)

TEST SUBSTANCE	Analogue 2
METHOD	HRIPT (Repeated insult patch test with challenge)
Study Design	Induction Procedure: Occluded patches containing 0.4 mL test substance at 0.5% were applied 3 times per week for a total of 9 applications. Rest Period: ~14 days Challenge Procedure: Patches were applied to previously treated sites and removed after 24 h and evaluated for dermal reactions.
Study Group	50 healthy volunteers.
Vehicle	Not specified
Remarks - Method	Occluded
RESULTS	
Remarks - Results	44/50 subjects completed the study. Six subjects discontinued study participation for reasons unrelated to the test material. The challenge of one person and re-challenge of another one were done later. Only one study subject showed moderate response after the primary irritation. No other adverse responses were noted at induction or challenge phases.
CONCLUSION	The test substance was not a skin sensitiser under the conditions of the test.
TEST FACILITY	Hill Top Research (1978)

B.8. Skin sensitisation – human volunteers (0.25%)

TEST SUBSTANCE	Analogue 3
METHOD	HRIPT (Repeated insult patch test with challenge)
Study Design	Induction Procedure: Patches containing 0.2 mL test substance at concentration of 0.25% (w/w) were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed after 24 h and graded after an additional 24 h (or 48 h for the patches removed on a Saturday). Rest Period: ~14 days Challenge Procedure: Patches were applied to previously untreated sites and were removed after 24 h and evaluated for dermal reactions. The test sites were re-evaluated at 48 h and 72 h.
Study Group	112; age range 18-70 years
Vehicle	Ethanol: Diethyl Phthalate (1:3)
Remarks - Method	Occluded. The test substance was spread on a 3.63 cm^2 patch as received and was allowed to evaporate for at least 30 min, but no longer than 90 min, prior to application.
RESULTS	
Remarks - Results	103/112 subjects completed the study. Seven subjects discontinued study participation for reasons unrelated to the test material. No adverse responses were noted at induction or challenge phases.
CONCLUSION	The test substance was not a skin sensitiser under the conditions of the test.
TEST FACILITY	CRL (2011)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE	Analogue 2
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria (2008). Plate incorporation procedure (Test 1: Range-finding test))/Pre incubation procedure (Test 2: Main test)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S9 microsomal fraction from β-naphthoflavone/phenobarbital-induced rat liver
Concentration Range in Main Test	<u>All *Salmonella* strains</u> With and without metabolic activation: 0.3-5000 µg/plate
Vehicle	Dimethyl sulphoxide (DMSO)
Remarks - Method	A correction for the purity of the test substance was made when the test item formulations were prepared. No other deviation from standard protocol. A preliminary toxicity test (3-5000 µg/plate) was performed to determine the toxicity of the test material in the presence and absence of metabolic activation in all *Salmonella* strains. This test was used as Test 1. Tests 1 and 2 were conducted on separate days using fresh cultures and test substance solutions. The concentration range was amended in Test 2 based on the results of Test 1. <u>Test 1</u>: All *Salmonella* strains with and without S9: 3, 10, 33, 100, 333, 1000,

2500 and 5000 µg/plate

Test 2:
All *Salmonella* strains with and without S9: 0.3, 1, 3, 10, 33, 100, 333 and 1000 µg/plate

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 333 (TA98, 100, 102) ≥ 1000 (TA1535) ≥ 100 (TA1537)	> 5000 for all *Salmonella* strains	Negative
Test 2	≥ 333 (TA98, 100, 102) ≥ 100 (TA1535) ≥ 33 (TA1537)	> 1000 for all *Salmonella* strains	Negative
Present			
Test 1	≥ 1000 for all *Salmonella* strains	> 5000 for all *Salmonella* strains	Negative
Test 2	≥ 1000 (TA98 and 102) ≥ 333 (TA100, 1535 and 1537)	> 1000 for all *Salmonella* strains	Negative

Remarks - Results: No toxicologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test item, either with or without metabolic activation or exposure method. The laboratory's historical control range was exceeded in untreated control of strain TA102 with metabolic activation in experiment 1. This deviation was judged to be due to biologically irrelevant fluctuations in the number of colonies and had no impact on the outcome of the study. The positive and negative controls gave satisfactory results confirming the sensitivity of the test system.

CONCLUSION: The test substance was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY: RCC (2007a)

B.10. Genotoxicity – *in vivo*

TEST SUBSTANCE: Analogue 3 (99.4%)

METHOD: OECD TG 474 (1997). Mammalian Erythrocyte Micronucleus Test.
EC Directive 2000/32/EC B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test (2000).

Species/Strain: Mouse/NMRI
Route of Administration: Oral
Vehicle: Corn oil
Remarks - Method: The ratio between polychromatic and normochromatic erythrocytes was determined in the same sample and reported as number of polychromatic erythrocytes (PCEs) per 2000 erythrocytes to describe a cytotoxic effect due to the treatment with the test item. Doses were determined on the basis of a preliminary toxicity test. The CAS number quoted in the study is less specific to the current CAS number of analogue 3.

The analysis of the test item formulations showed that the analysed samples correspond to the nominal values. The obtained results ranged between 96.3% - 112.9% of the nominal values.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	5/sex	0	24
II (low dose)	5/sex	500	24
III (mid dose)	5/sex	1000	24
IV-A (high dose)	5/sex	2000	24
IV-B (high dose)	5/sex	2000	48
V (positive control*)	5/sex	40	24

*CP=cyclophosphamide

RESULTS

Group	*PCEs with micronuclei (%)*	*Range*	*PCE/2000 erythrocytes*
I (vehicle control)	0.105	0-5	1089
II (low dose)	0.145	0-6	1072
III (mid dose)	0.110	0-4	1039
IV-A (high dose)	0.120	0-5	1100
IV-B (high dose)	0.100	0-6	1158
V (positive control)	2.045	20-71	1142

Doses Producing Toxicity	None seen.
Genotoxic Effects	None
Remarks - Results	There was no statistically significant or biologically relevant enhancement in the frequency of the detected micronuclei at any preparation interval and dose level. The mean values of micronuclei observed after treatment with the test item were below or near to the value of the vehicle control group. The positive and vehicle controls gave satisfactory responses confirming the validity of the test system. No clinical signs of toxicity or of cytotoxicity in the bone marrow were noted at any dose level; therefore it is not certain if the test substance reached the bone marrow.
CONCLUSION	The test substance was not clastogenic under the conditions of this *in vivo* mammalian erythrocyte micronucleus test.
TEST FACILITY	RCC (2007b)

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