File No.: LTD/2126

June 2020

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Zanthoxylum piperitum, ext.

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 Agriculture, Water and the Environment.

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 on our website:

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/2126	International Flavours and Fragrances (Australia) Pty Ltd	Zanthoxylum piperitum, ext.	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard Classification
Based on the available information, the notified chemical is a hazardous chemical according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The hazard classification applicable to the notified chemical is presented in the following table.

Hazard Classification	*Hazard Statement*
Flammable liquids (Category 3)	H226 – Flammable liquid and vapour
Skin corrosion/irritation (Category 2):	H315 – Causes skin irritation
Sensitisation, skin (Category 1)	H317 – May cause an allergic skin reaction

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*
Chronic Aquatic Toxicity (Category 2)	H411 – 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 the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Flammable liquids (Category 3): H226 – Flammable liquid and vapour
  - Skin corrosion/irritation (Category 2): H315 – Causes skin irritation
  - Sensitisation, skin (Category 1): H317 – May cause an allergic skin reaction

The above should be used for products/mixtures containing the notified chemical, if applicable, based on the concentration of the notified chemical present.

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:
  - Enclosed/automated processes
  - Local exhaust ventilation

- 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 reformulation:
  - Avoid contact with skin and eyes
  - Avoid inhaling aerosols or mists

- 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:
  - Impervious gloves
  - Safety glasses or goggles
  - Protective clothing
  - Respiratory protection if aerosols or mists are expected to be generated

- 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.

Public Health

- Formulators of end-use products available to the public, especially oral care products, should take into account the potential for the notified chemical to cause tingling, numbing and pungent effects. Formulators should be aware of when these effects may occur to avoid any adverse effects to consumers using the products containing the notified chemical.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

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

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.

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 final use concentration of the notified chemical exceeds 0.1% in cosmetic and household products;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from fragrance ingredient, 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 SDSs of the notified chemical and product containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the SDSs 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 exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Schedule data requirements are varied for all physical and chemical properties except for vapour pressure and flash point

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Pepper Sichuan extract

CAS NUMBER
97404-53-0

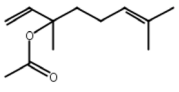
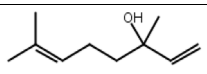
CHEMICAL NAME
Zanthoxylum piperitum, ext.

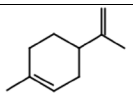
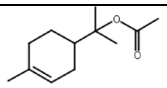
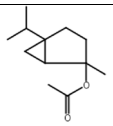
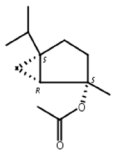
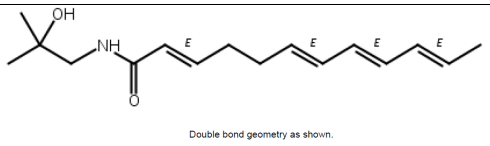
OTHER NAME(S)
Zanthoxylum piperitum extract;
Sichuan pepper extract;
Sichuan pepper CO_2 extract

MOLECULAR FORMULA
Unspecified (UVCB)

STRUCTURAL FORMULA
Based on the GC results, individual components for the notified chemical were characterised (accounting for 72.77%). The chemical identity, concentrations and structural formulae for these components are presented in the table below.

Gas Chromatography results for the notified chemical

Chemical name	CAS number	Area %	Likely range of concentration %	Structure
1,6-Octadien-3-ol, 3,7-dimethyl-, 3-acetate (Linalyl acetate)	115-95-7	37.9	30-50	
1,6-Octadien-3-ol, 3,7-dimethyl- (Linalool)	78-70-6	11.28	10-20	

Gas Chromatography results for the notified chemical				
Chemical name	CAS number	Area %	Likely range of concentration %	Structure
Cyclohexene, 1-methyl-4-(1-methylethenyl)- (Limonene)	138-86-3	7.16	5-10	
3-Cyclohexene-1-methanol, α,α,4-trimethyl-, 1-acetate	80-26-2	1.28	1-5	
Bicyclo[3.1.0]hexan-2-ol, 2-methyl-5-(1-methylethyl)-, 2-acetate	87553-42-2	9.14	5-15	
Bicyclo[3.1.0]hexan-2-ol, 2-methyl-5-(1-methylethyl)-, 2-acetate, (1*R*,2*S*,5*S*)-*rel*-	77318-47-9 (trans)			
2,6,8,10-Dodecatetraenamide, *N*-(2-hydroxy-2-methylpropyl)-, (2*E*,6*E*,8*E*,10*E*)-	97465-69-5	6.01	1-10	 Double bond geometry as shown.
Unknowns (each peak > 1%, total 7 peaks)	-	15.21		
Unknowns (each peak < 1%)	-	12.03		

MOLECULAR WEIGHT
< 500 g/mol (UVCB components identified)

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

3. COMPOSITION

DEGREE OF PURITY
100% (UVCB)

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: liquid

Property	***Value***	***Data Source/Justification***
Melting Point	< -20 °C - 156 °C	Information provided by the notifier on the main components
Boiling Point	176 - 421 °C	Information provided by the notifier on the main components
Density	898.4 - 928.4 kg/m^3	SDS

Property	*Value*	*Data Source/Justification*
Vapour Pressure	0.0249 kPa at 24 °C	Measured
Water Solubility	5.69×10^{-3} - 1.56 g/L	Estimated using QSAR (US EPA, 2012)
Hydrolysis as a Function of pH	Not determined	The majority of the UVCB constituents contain functionalities which are susceptible to hydrolysis
Partition Coefficient (n-octanol/water)	log Pow = 2.9 – 3.9 = 4.2 – 4.4	Aliphatic terpene constituents Aliphatic cyclic constituents Estimated by KOWWIN v.1.68 (US EPA, 2012)
Adsorption/Desorption	log Koc= 1.88 – 2.71 = 2.4 – 2.79	Aliphatic terpene constituents Aliphatic cyclic constituents Estimated by KOCWIN v.2.00 (US EPA, 2012)
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	39 °C at 101.3 kPa	Measured
Autoignition Temperature	245-280 °C at 99.4-101.2 kPa	Information provided by the notifier on the main components
Explosive Properties	Predicted negative	The main components contain no functional groups that would imply explosive properties.
Oxidising Properties	Predicted negative	The main components contain no functional groups that would imply oxidising properties.

DISCUSSION OF PROPERTIES
For 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 recommended for physical hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard Classification	*Hazard Statement*
Flammable liquids (Category 3)	H226 – Flammable liquid and vapour

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 and will not be imported into Australia in neat form. It will be imported into Australia as a component of finished fragrance oil products. The fragrance oil products will contain the notified chemical at ≤ 1% concentration and will be reformulated locally to produce household and cosmetic products.

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 RECIPIENTS
International Flavours and Fragrances (Australia) Pty Ltd

TRANSPORTATION AND PACKAGING
The finished fragrance oil products containing the notified chemical (at ≤ 1% concentration) will be imported in 208 L polypropylene-lined steel drums. The imported products containing the notified chemical will be transported by road to the International Flavours and Fragrances (IFF) facility in Victoria and then distributed to reformulation sites. The end-use products will be packaged in containers suitable for retail sale.

USE
The notified chemical will be used as a fragrance ingredient and incorporated into a variety of cosmetic, oral care and household products at ≤ 0.1% concentration.

OPERATION DESCRIPTION
The notified chemical will not be manufactured in Australia. The imported finished fragrance oils containing the notified chemical (at ≤ 1% concentration) will be stored at the notifier's facility until they are sold and distributed to customer facilities for reformulation into end-use cosmetic and household products.

Reformulation
At the customer reformulation sites, procedures for incorporating fragrance oil products containing the notified chemical into end-use products will likely vary depending on the nature of the formulated products and may involve both automated and manual transfer steps. In general, it is expected that the products containing the notified chemical will be weighed and added to the mixing tank where mixing with additional additives will occur to form finished cosmetic and household products. Subsequently, automated filling of the reformulated products into containers of various sizes will occur. The blending and filling operations are expected to be typically automated with enclosed systems and adequate ventilation. During the reformation process, samples of products containing the notified chemical will be taken for quality control purposes.

End use
Cosmetic products
The finished cosmetic products containing the notified chemical at ≤ 0.1% concentration will be used by consumers, and applied by professionals such as beauticians and hairdressers. Depending on the nature of the products, applications may be by hand, spray or through the use of applicators.

Household products
Household products containing the notified chemical at ≤ 0.1% concentration may be used by consumers and professional workers such as cleaners. The products may be used in either closed systems with episodes of controlled procedures, for instance automatic washing machine cycles, or open manual processes including spraying, brushing, dipping, wiping and rinsing.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	Incidental	Incidental
Compounding	4	250
Drum handling	1	250
Drum cleaning	2	200
Maintenance	2	250
Quality control	1	250
Professional users	8	250

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemical as a component of finished fragrance oils (at ≤ 1% concentration), only in the unlikely event of an accidental breach of import containers.

Reformulation
During reformulation, dermal, ocular and inhalation exposure of workers to the notified chemical (at ≤ 1% concentration) may occur during weighing, transfer, blending, quality control analysis, cleaning and maintenance.

The use of engineering controls including local exhaust ventilation and enclosed systems, and the use of personal protective equipment (PPE) such as coveralls, goggles, impervious gloves and appropriate respiratory protection by workers are expected to minimise exposure to the notified chemical.

End-use
Exposure to the notified chemical in end-use products at ≤ 0.1% concentration may occur in professions where the services provided involve the application of cosmetic products to clients (i.e., hair and beauty salons) or where the cleaning products are used in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposures are also possible. Such professionals may use PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If appropriate PPE is used, exposure of such workers to the notified chemical is expected to be similar or to a lesser extent of that experienced by consumers using the same products.

6.1.2. Public Exposure
There will be widespread and repeated exposure of the public to the notified chemical at ≤ 0.1% concentration through the use of a wide range of cosmetic and household products. The main route of exposure will be dermal, while ocular and inhalation exposures (e.g. through the use of spray products) are also possible. Oral exposure may occur from use of oral care products such as toothpaste or mouthwash.

6.2. Human Health Effects Assessment
The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For details of the studies, refer to Appendix B.

Endpoint	***Result and Assessment Conclusion***
Skin sensitisation – HRIPT (2%)	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – *in vitro* mammalian cell micronucleus test	non genotoxic

Toxicokinetics
Given the low molecular weight of the components of the notified chemical (< 500 g/mol), water solubility (5.69×10^{-3} - 1.56 g/L) and partition coefficient of 2.9 - 4.4, there is potential for the chemical to cross biological membranes.

Acute Toxicity
No studies on the acute toxicity of the notified chemical were provided. For an analogue chemical Zanthoxylum, ext. (CAS No. 102242-62-6), which is expected to have similar components to the notified chemical, the LD50 for acute oral toxicity was estimated to be to 416 mg/kg bw with confidence limits from 344 mg/kg bw to 503 mg/kg bw for both male and female rats based on OCD TG 401 (REACH Data 2020a). Based on this, the notified chemical may be harmful if swallowed, however, the reported data is not sufficient to support classification.

Irritation and Sensitisation
No skin or eye irritation studies on the notified chemical were provided.

In a human repeated insult patch test (HRIPT), the notified chemical at 2% in Ethanol:Diethyl Phthalate (1:3 w/w) (induction concentration) did not elicit a positive irritation or sensitisation response during challenge after 9 days induction with the notified chemical at 2% in 110 individuals.

The three components present at the highest concentrations in the notified chemical are 1,6-Octadien-3-ol, 3,7-dimethyl-, 3-acetate (linalyl acetate) at 37.9%, 1,6-Octadien-3-ol, 3,7-dimethyl- (linalool) at 11.28% and Cyclohexene, 1-methyl-4-(1-methylethenyl)- (limonene) at 7.16%, accounting for 56.13% (ranging from 45-80%) of the notified chemical. These three components are all classified for skin irritation (Category 2) and skin sensitisation (Category 1) under the Hazardous Chemical Information System (HCIS), or are recommended for this classification on the basis of a NICNAS IMAP report (NICNAS, 2018). Based on the concentration of these three components, the notified chemical warrants classification for these two endpoints. It is noted that all three of these components of the notified chemical are likely to oxidise to form skin sensitising chemicals.

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

Based on the information on main components of the notified chemical (accounting for 56.13% of the notified chemical), it is not expected to have high systemic toxicity (NICNAS 2002, 2016 and 2018).

Mutagenicity/Genotoxicity
The notified chemical was found to be negative in a bacterial reverse mutation assay and in an *in vitro* mammalian cell micronucleus test using human lymphocytes.

Observations on Human Exposure
Alkylamide components in Sichuan pepper (from which the notified chemical is extracted) are known to greatly contribute to the pungency of Sichuan pepper upon consumption (Ji *et al.,* 2019), causing tingling and numbing effects in the mouth. One such chemical, 2,6,8,10-Dodecatetraenamide, *N*-(2-hydroxy-2-methylpropyl)-, (2*E*,6*E*,8*E*,10*E*)- (CAS No. 97465-69-5) was measured as present in the notified chemical at 6.01% and is expected to occur in the range 1% to 10%. It is also known as hydroxyl β-sanshool, and is one of several sanshool derivatives that may be present in Sichuan pepper. The identity and concentration of sanshool derivatives is expected to vary with the species, location, types of extracts and method of extraction. Other sanshool derivatives may be present in the notified chemical, which is not fully characterised.

It is not clear what extent of effects would be expected from use of up to 0.1% of the notified chemical in products applied to the mouth (e.g. toothpaste or mouthwash). It was reported that alkylamides from Xanthoxylum species produced a tingling sensation on the tongue at > 100 µg using 1% test concentration (Bryant and Mezine, 1999). In human sensory testing, the threshold value of the pungent effect for hydroxy β-sanshool was in the range of 5.0 -20.0 × 10^{-5} g/mL (0.005 - 0.02%) with an average of 7.8 × 10^{-5} g/mL (0.0078%) (Sugai *et al.,* 2005). There is uncertainty regarding the concentrations reported as there was not a full analysis of the compound tested available in the papers and the composition of plant extracts could vary depending on various environmental factors. Other components with similar effects may also be present in the notified chemical, and some may have higher potency.

Health Hazard Classification
Based on the available information, the notified chemical is a hazardous chemical according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The hazard classification applicable to the notified chemical is presented in the following table.

Hazard Classification	*Hazard Statement*
Skin corrosion/irritation (Category 2):	H315 – Causes skin irritation
Sensitisation, skin (Category 1)	H317 – May cause an allergic skin reaction

The notifier has also classified the notified chemical as follows:

Serious eye damage/eye irritation (Category 2): H319 – Causes serious eye irritation

6.3. Human Health Risk Characterisation
The notified chemical is classified as a skin sensitiser and skin irritant, and was also classified by the notifier as an eye irritant. These effects are expected to be greatly reduced at the concentration of import and use. At 2% concentration the notified chemical showed no evidence of sensitisation or irritation in 110 subjects (in an HRIPT). The notified chemical may also cause pungent effects (tingling and numbing) when used in oral care products.

6.3.1. Occupational Health and Safety
Reformulation
Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemical at ≤ 1% concentration during reformulation. The use of local ventilation, enclosed/automated processes and PPE by workers (i.e., protective clothing, goggles, impervious gloves and respiratory protection, if inhalation exposure may occur) are expected to minimise the potential for exposure.

Therefore, provided control measures are in place to minimise worker exposure, the risk to workers from use of the notified chemical is not considered to be unreasonable.

End-use
Cleaners and beauty care professionals will handle the notified chemical at up to 0.1% concentration, similar to public use. Such professionals may use PPE such as gloves to minimise repeated exposure, and good hygiene practices are expected to be in place. Therefore, the risk to workers who use products containing the notified

chemical is expected to be of a similar or lesser extent than consumers who use such products on a regular basis. For details of the public health risk assessment see section 6.3.2 below.

6.3.2. Public Health

Members of the public may experience repeated exposure to the notified chemical through the use of cosmetic and household products containing the notified chemical at up to 0.1% concentration.

Irritation and Sensitisation

Irritation or sensitisation effects are not expected from the use of products containing the notified chemical at the proposed low use concentration (up to 0.1%) in cosmetic and household products.

Systemic toxicity

The repeated dose toxicity effects of the notified chemical have not been determined. However, exposure is expected to be limited by the low concentration of the notified chemical (up to 0.1%) in end use products.

Oral care products

The notified chemical is listed on the Flavour Extract Manufacturers Association (FEMA) Flavouring Substances 26 (GRAS Reference 4754) (IFT 2013), indicating that the FEMA Expert Panel considered it as generally recognised as safe (GRAS). The Anticipated Average Maximum Use Level for the notified chemical in the FEMA listing is at up to 0.04% in beverages.

There is uncertainty about the potential for and extent of tingling and numbing effects that may occur when the public is using oral care products containing the notified chemical at up to 0.1% concentration. Therefore, this effect should be considered when formulating oral care products, to ensure that the concentrations used do not have adverse tingling and numbing effects.

Based on the information available, the risk to the public associated with use of the notified chemical at up to 0.1% concentration in cosmetic and household products is not considered to be unreasonable, if precautions are taken in the formulation of oral care products to avoid adverse tingling and numbing effects.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia as a component of fragrance oil formulations for local reformulation into finished cosmetic and household products. In general, the reformulation processes are expected to involve automated blending operations in an enclosed environment, followed by packing of the finished products into end-use containers. Wastewater from reformulation equipment cleaning containing the notified chemical is expected to be disposed of to sewer via on-site wastewater treatment in accordance with local government regulations. Release of the notified chemical in the event of accidental spills or leaks during reformulation, storage and transport is expected to be collected for disposal, in accordance with local government regulations.

RELEASE OF CHEMICAL FROM USE

The majority of the notified chemical is expected to be released to sewers across Australia as a result of its use in cosmetic and household products, which are washed off hair and skin of consumers as well as from cleaning activities.

RELEASE OF CHEMICAL FROM DISPOSAL

Residues of the notified chemical in empty import and end-use 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

The notified chemical is an UVCB substance comprising a complex mixture of discrete organic molecules, including aliphatic short and long chain carboxylic esters, terpineols and aliphatic cyclic compounds. The majority of these constituents (72.77%) have been well characterised. Accordingly, the properties of the UVCB may be

reasonably estimated based on the individual QSARs of the discrete organic molecules, which comprise the majority of the UVCB (EPHC 2009 and ECHA 2012).

Following its use in cosmetic and household products, the majority of the notified chemical will enter the sewers and be treated at sewage treatment plants (STPs) before potential release to surface waters nationwide. A proportion of the notified chemical may volatilise to air. The half-life of a major component of the notified chemical (linalyl acetate) in air is calculated to be 1.1 h based on reactions with hydroxyl radicals (US EPA, 2012; calculated using AOPWIN v1.92). Therefore, the notified chemical is not expected to persist in the air compartment.

The notified chemical is a natural product extract. Generally chemicals of natural origin readily degrade in the environment as microorganisms have evolved to metabolise these chemicals for use as a fuel source (Boethling and Mackay, 2000). The majority of the identified constituents of the notified chemical (72.77%) are expected to highly sorb to sludge at STPs based on their low water solubility and moderate estimated partition coefficient (log Pow 2.9 – 4.4). Therefore, the notified chemical is expected to be removed effectively at STPs through biodegradation and adsorption to sludge, and only a small portion of the notified chemical may be released to surface waters. A proportion of the notified chemical may be applied to land when effluent is used for irrigation or when sewage sludge is used for soil remediation or disposed of to landfill. The majority of the identified residues of the notified chemical are expected to have low mobility in landfill and soils based on their estimated soil adsorption coefficients (log Koc = 1.88 – 2.79).

The majority of the identified components of the notified chemical are not expected to bioaccumulate based on their moderate octanol-water partition coefficient value (log Pow = 2.9 – 4. 2) and biodegradability. Although the aliphatic cyclic constituents (log Pow 4.2-4.4) may have the potential to bioaccumulate, as they are of natural origin, they are also expected to degrade. The notified chemical is not expected to be significantly released to surface waters. In the aquatic and soil compartments, the notified chemical is expected to eventually degrade through biotic and abiotic processes to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The use pattern will result in most of the notified chemical being washed into the sewer. The predicted environmental concentration (PEC) has been calculated assuming the realistic worst-case scenario with 100% release of the notified chemical into sewer systems nationwide over 365 days per annum. The extent to which the notified chemical is removed from the effluent in STP processes based on the properties of the notified chemical has not been considered for this scenario, and therefore no removal of the notified chemical during sewage treatment processes, is assumed. The PEC in sewage effluent on a nationwide basis is estimated as follows:

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

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 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 1,500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.56 µg/L may potentially result in a soil concentration of approximately 3.74 µg/kg. Due to the biodegradability of the notified chemical, annual accumulation is not expected.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on an analogue of the notified chemical (Zanthoxylum, ext., CAS No. 102242-62-6) are summarised in the table below.

Endpoint	*Result*	*Assessment Conclusion*
Daphnia Toxicity	48 h EC50 = 4.01 mg/L (REACH Data 2020b)	Toxic to aquatic invertebrates
Algae Toxicity	72 h EC50 = 8.23 mg/L (REACH Data 2020c)	Toxic to algae

Based on the above ecotoxicological endpoints for the notified chemical, it is expected to be toxic to aquatic invertebrates and algae. Therefore, under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009), the notified chemical is formally classified as "Acute Category 2: Toxic to aquatic life". No chronic endpoints were available. Therefore, the aquatic chronic hazard is determined using the acute data. When the chronic hazard is based on the lowest acute endpoint, taking into account that the substance is rapidly degradable but potentially bioaccumulative, the result is 'Chronic Category 2: Toxic to aquatic life with long-lasting effects".

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated based on the endpoint for Daphnia as shown in the table below. A conservative safety factor of 500 was used given the acute endpoints for two trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 for fish	4.01	mg/L
Assessment Factor	500	
Mitigation Factor	1.00	
PNEC:	8.02	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated based on the PEC and PNEC.

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.56	8.02	**0.07**
Q - Ocean	0.06	8.02	**0.01**

The conservative risk quotients (Q = PEC/PNEC) for the worst-case discharge scenario have been calculated to be less than 1 for both riverine and ocean compartments which indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity and use pattern. Therefore, based on the calculated risk quotient, the notified chemical is not considered to pose an unreasonable risk to the aquatic environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Vapour Pressure 0.0249 kPa at 24°C

Method	Equivalent to OECD TG 104 Vapour Pressure (2006)
Remarks	The Transpiration method or Dynamic headspace method used was considered equivalent to the gas saturation method presented in the OECD TG 104.
Test Facility	IFF (2018)

Flash Point 39 ± 1 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point The International Organization for Standardization (ISO), ISO Guide 2719: "Determination of Flash Point – Pensky Martens Closed Cup method", 2002. ASTM International, ASTM D 93: "Standard Test Methods for Flash Point by Pensky-Martens Closed Cup Tester", December 10, 2002.
Remarks	A Grabner Miniflash FLP closed cup method was used.
Test Facility	IFF (2018)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Skin Sensitisation – Human Volunteers

TEST SUBSTANCE	Notified chemical (2% w/w)
METHOD	Repeated insult patch test with challenge
Study Design	Two different samples of the test substance were tested on each volunteer. Induction procedure: the test substance was applied to the same location on the back of each subject three times per week for a total of nine applications. Test sites were examined for dermal irritation at each visit prior to re-application of the test substance. Rest period: 1 days or 2 days (for Friday applications) Challenge procedure: approximately 10 to 21 days after the final visit of the Induction Phase, subjects returned for the Challenge Phase. The test substance was applied to a virgin site on the back and was removed approximately 24 hours later. Test sites were examined for signs of dermal irritation or sensitisation.
Study Group	90 F, 26 M; age range 18-70 years
Vehicle	Ethanol:Diethyl Phthalate =1:3 w/w
Remarks – Method	Occluded. The test substance was spread on a 1.9 cm × 1.9 cm (3.62 cm^2) patch. The study was completed with 110 subjects. Minor protocol deviations were considered not to have compromised the validity or integrity of the study: before the study started, active eczema or psoriasis on the test sites was not checked when screening the subjects.
RESULTS	
Remarks – Results	There were no adverse effects in the study.
CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	Eurofins (2019a and b)

B.2. Genotoxicity – Bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997) Plate incorporation procedure (Test 1)/Pre incubation procedure (Test 2)
Species/Strain	*Salmonella typhimurium*: TA1535, TA1537, TA98, TA100 *Escherichia coli*: WP2uvrA
Metabolic Activation System	S9 mix from phenobarbital/β-naphthoflavone induced rat liver.
Concentration Range in Main Test	Test 1: with metabolic and without activation: 0, 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate Test 2: with and without metabolic activation (TA1535, TA98 and WP2*uvrA* only): 0, 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate Test 2: without metabolic activation (TA100 and TA1537 only): 0, 0.5, 1.5, 5, 15, 50, 150, 500 and 1500 µg/plate
Vehicle	Acetone
Positive controls	In the absence of S9-mix: 9-Aminoacridine (9AA) and 4-Nitroquinoline-1-oxide (4NQO) In the presence of S9-mix: 2-Aminoanthracene (2AA) and Benzo[a]pyrene (BP)
Remarks – Method	No protocol deviations were reported. There was no preliminary test.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 500	> 5,000	negative
Test 2	≥ 50	> 5,000	negative
Present			
Test 1	≥ 1,500	> 5,000	negative
Test 2	≥ 500	> 5,000	negative

Remarks – Results

There was a greasy test substance film at 5,000 µg/plate in both the presence and absence of metabolic activation in tests 1 and 2. It did not prevent the scoring of revertant colonies.

There were no biologically relevant increases in the frequency of revertant colonies for any of the bacterial strains, either with or without metabolic activation. Two instances of slight increase in revertants, in different tests, were not dose related and were not considered biologically relevant as they fell with the range of historical negative controls.

CONCLUSION

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

TEST FACILITY

Envigo (2019)

B.3. Genotoxicity – *In Vitro* Mammalian Cell Micronucleus Test

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 487 *In vitro* Mammalian Cell Micronucleus Test (2016)

Cell Type/Cell Line: Human lymphocytes

Metabolic Activation System: S9 mix prepared from phenobarbital and 5,6-benzoflavone induced rat liver homogenate

Vehicle: DMSO

Positive Control: Absence of S9-mix: Mitomycin C (MMC) and Demecolcine (DEME-C)
Presence of S9-mix: Cyclophosphamide (CP)

Remarks – Method: No protocol deviations

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 20, 40*, 80*, 160*, 240, 320, 640	4 h	24 h
Test 2	0*, 60, 120, 140, 160*, 180*, 200*, 220, 260	24 h	24 h
Present			
Test 1	0*, 40, 80, 160, 200*, 220*, 240*, 280,320	4 h	24 h

*Cultures selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 78.13			
Test 1		≥ 160*	≥ 640	negative
Test 2		≥ 140*	≥ 200	negative
Present	> 312.5			
Test 1		≥ 80*	≥ 320	negative

* Haemolysis

Remarks – Results

Reduced cell pellet was noted at ≥ 240 µg/mL in the 4-hour exposure groups in the presence and absence of S9, indicating that the test substance

	was affecting the cell population and confirming maximum exposure. There was no reduced cell pellet in the 24-hour continuous exposure group. There was an inhibition of Cytokinesis Block Proliferation Index (CBPI) in all test conditions. In all tests, the maximum concentration chosen for analysis of binucleate cells showed close to the optimum toxicity range (55±5%) specified in the test guideline. In the 24-hour continuous exposure group, the maximum dose level was also the lowest precipitating dose level. The test substance did not induce a statistically or biologically significant increase in the number of micronucleated cells at all test concentrations in each exposure group, with or without metabolic activation. The negative and positive controls performed as expected, confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic or aneugenic to human lymphocytes treated *in vitro* under the conditions of the test.
TEST FACILITY	Covance (2019)

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