File No: LTD/1982

August 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Benzoic acid, 2-methyl-, methyl ester

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/1982	International Flavours and Fragrances (Australia) Pty Ltd	Benzoic acid, 2-methyl-, methyl ester	Yes	≤ 1 tonne per annum	Fragrance ingredient

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is recommended for 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 4)	H227 – Combustible liquid
Skin Irritation (Category 2)	H315 – Causes skin irritation

Human health risk assessment
Provided that the recommended controls are being adhered to, 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

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Skin Irritation (Category 2): H315 – Causes skin irritation

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

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, due to the limited hazard information available:
  - Enclosed, automated processes, where possible
  - Good general ventilation, including local exhaust ventilation if possible

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Avoid contact with skin and eyes
  - Avoid inhalation of aerosols or mist

- 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:
  - Impervious gloves, eye protection, coveralls
  - Respiratory protection, if inhalation exposure may occur

  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.

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.

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 concentration of the notified chemical exceeds 0.4% in cosmetic or household products (taking into account the limited information regarding repeated dose toxicity);
  - information on repeated dose or reproductive and developmental toxicity becomes available;

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 SDS of the notified chemical and a product containing the notified chemical provided by the notifier were 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
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 as follows: Hydrolysis as a function of pH, absorption/desorption, dissociation constant, flammability, explosive and oxidising properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT
Previous permits

NOTIFICATION IN OTHER COUNTRIES
Canada, China, Europe, Japan and USA

2. IDENTITY OF CHEMICAL

MARKETING NAME
Ylanganate

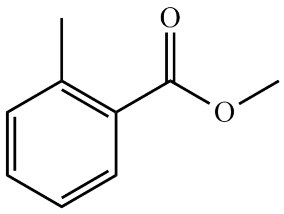
CAS NUMBER
89-71-4

CHEMICAL NAME
Benzoic acid, 2-methyl-, methyl ester

OTHER NAME
Methyl 2-methylbenzoate
o-Toluic acid, methyl ester

MOLECULAR FORMULA
$C_9H_{10}O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
150.17 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 98%

IMPURITIES/ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -20 °C	Measured
Boiling Point	216 °C at 101.3 kPa	Calculated
Density	1069 kg/m^3 at 20 °C	Measured
Viscosity	2.07 cP at 25 °C	Measured
Vapour Pressure	1.29×10^{-2} kPa at 23 °C	Measured
Water Solubility	2.63 g/L at 22 °C	Measured
Hydrolysis as a Function of pH	5.49 years at pH 7	Estimated by HYDROWIN v2.00 model (US EPA, 2012a)
Partition Coefficient (n-octanol/water)	log P_{ow} = 3 at 25 °C	Measured
Adsorption/Desorption	log K_{oc} = 2.52	Estimated by KOCWIN v2.00 model (US EPA, 2012a).
Dissociation Constant	Not determined	The notified chemical is not expected to dissociate at environmental pH (4-9).
Flash Point	87 °C at 101.3 kPa	Measured
Flammability Limits	Not determined	-
Autoignition Temperature	475 °C	Measured
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising 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 recommended for 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 4)	H227 – Combustible liquid

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 in fragrance oils at ≤ 10% concentration for reformulation into end-use cosmetic and household products. The notified chemical may also be imported in end-use products at ≤ 0.4% concentrations.

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 will be imported into Australia in fragrance oils at concentrations ≤ 10%. The fragrance oils will be imported in 208 L polypropylene-lined steel drums. Within Australia the drums will be transported by road to the warehouse for storage and later distributed to the industrial customers by road.

USE
The notified chemical is a fragrance ingredient for use in cosmetic and household products. The proposed final concentration of the notified chemical in end-use cosmetic and household products will be ≤ 0.4%.

OPERATION DESCRIPTION
The notified chemical will be introduced in to Australia in fragrance oils at concentrations ≤ 10%. It will be reformulated by the notifier's industrial customers into end-use cosmetic and household products.

The method of incorporation of the notified chemical in to end-use products will vary depending on the product use. In general, the notified chemical in fragrance oils at ≤ 10% concentration is expected to be blended with other ingredients in highly automated closed systems with good control measures and adequate ventilation.

The end-use products containing the notified chemical at concentrations ≤ 0.4% are anticipated to be packaged in sizes suitable for retail sales and will be available to consumers for personal use. The method of application of the products will vary depending on the type of use. They may be applied using hand, spray or an applicator. After use the notified chemical is expected to be released into sewer.

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	none	Incidental exposure only
Plant operator – compounder*	4	250
Plant operator – drum handling*	1	250
Plant operator – drum cleaning/washing*	2	250
Plant operator – equipment cleaning/washing*	2	250
Plant operator – quality control*	1	250
Professional user – hairdressers, cleaners etc.	8	250

* – customer site

EXPOSURE DETAILS
Transport and storage
Exposure of transport and storage workers at the notifier's facility will be limited to situations involving product sampling for quality control, in the event of a discharge, clean up from a spill or leaking drums. In such an event, the principal route of exposure will be dermal and ocular. The notifier states that the exposure will be minimised through the use of personal protective equipment (PPE) including impervious gloves, coveralls, hard hats and safety glasses.

Reformulation
Plant operators at the sites of the notifier's industrial customers may come in contact with the notified chemical at up to 10% concentration during weighing and addition of fragrance oils containing the notified chemical to blending equipment for reformulation, while testing for quality control and during equipment cleaning and maintenance. The workers may experience dermal and possible ocular and inhalation exposure during handling and reformulation. According to the notifier, the reformulation sites are expected to comply with good manufacturing practices and implement control measures for workers such as enclosed systems with local exhaust ventilation and use of PPE such as coveralls, impervious gloves, goggles and respiratory protection if required.

Professional end-users
Exposure to the notified chemical in end-use products (at ≤ 0.4% 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 are 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 at concentrations ≤ 0.4%. 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. A combined internal dose of 0.96 mg/kg bw/day was estimated using a dermal absorption rate of 100% and data on typical use patterns of cosmetic product categories in which the notified chemical may be used at 0.4% concentration (SCCS, 2012; Cadby *et al.*, 2002; ACI, 2010; Loretz *et al.,* 2006). This estimation assumed a worst case scenario and is for a person who is a simultaneous user of a selection of cosmetic products that may contain the notified chemical.

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

Endpoint	*Result and Assessment Conclusion*
Skin irritation and corrosion (*in vitro* RHE test)	irritating
Eye irritation (*in vitro* ICE test)	no serious eye damage
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Human, skin sensitisation – RIPT (10%)	no evidence of sensitisation
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – Bluescreen HC	non genotoxic

Toxicokinetics, metabolism and distribution
No information on toxicokinetics, metabolism and distribution was provided. Based on the low molecular weight (150.17 Da) and partition coefficient (log P_{ow} = 3), the notified chemical is likely to cross biological membranes, i.e. has potential for high dermal absorption.

Acute toxicity
No information on the acute toxicity potential of the notified chemical was provided.

Irritation and sensitisation
A combined *in vitro* skin irritation and skin corrosion study was conducted on the notified chemical. The test substance was found to be irritating to the skin based on the irritation scores obtained in the combined study. The results met the criteria for classification under the GHS as Category 2: irritating to skin.

An in-vitro eye irritation test was conducted to evaluate the irritancy potential of the notified chemical using the isolated chicken eye (ICE) test method. The test, conducted according to the OECD test guideline 438, can be used to identify materials causing serious eye damage (Cat 1 of the GHS), and to identify chemicals that do not

require classification for eye irritation or serious eye damage under the GHS. The notified chemical was found to be not corrosive or severely irritating to the eyes in the study. It also did not meet the criteria for "not requiring classification". Some irritation effects were observed (increase in corneal opacity and swelling compared to the control). However under the test guideline for interpretation of the results, a classification cannot be determined. The study authors proposed the test substance to be classified for eye irritation "Category 2B: causes eye irritation", using in-house interpretation and classification criteria.

The notified chemical was tested for skin sensitisation using the local lymph node assay (LLNA). It was tested at 7.5%, 15% and 30% concentrations with stimulation indices 1.13, 1.59 and 1.22 respectively. An EC3 value was not determined by the study authors. It is not clear whether higher stimulation indices would have been reached if higher concentrations of the notified chemical were tested. However, no dose response relationship was noted in the study.

The notified chemical (10%) was also tested for skin irritation and sensitisation potential in a human repeated insult patch test (HRIPT), in which no information was provided on the patch size and amount of the substance applied. It was reported to be not irritating and not sensitising in 111 tests subjects who completed the study out of 113 test subjects appointed for the study.

Repeated dose toxicity
No repeated dose toxicity data are provided for the notified chemical or for a close analogue.

NICNAS used OECD QSAR Toolbox (Ver. 3.4.0.17) to identify suitable analogues, however, the analogues identified (methyl salicylate, methyl-n-methylanthranilate and methyl anthranilate) had significant structural differences (e.g. presence of functional groups that can become ionised). These may confer unique toxicological properties that may not be displayed by the notified chemical (a small molecule) due to the lack of that functional group. A No Observed Effect Level (NOEL) of 106 mg/kg bw/day (28-day oral exposure in rats) was predicted (read-across) for the notified chemical. The notified chemical was within the applicability domain of the MUNRO non-cancer EFSA database used in the OECD QSAR Toolbox.

Repeated dose toxicity studies conducted in rats on two related chemicals *p*-toluic acid and *m*-toluic acid after 28 days were also evaluated (OECD SIDS 2008, OECD SIDS 2003). The No Observed Adverse Effect Levels (NOAELs) for both chemicals were 100 mg/kg bw/day in females and 300 mg/kg bw/day in males.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation study. It was reported to be non genotoxic in an *in vitro* BlueScreen HC assay. However, the maximum concentration of the notified chemical tested was low (313 µg/mL) in the BlueScreen HC test due to the low solubility of the test substance in aqueous solution.

Toxicity for reproduction
No data on reproductive or developmental toxicity were provided for the notified chemical. Using the DART Scheme v.1.0. profiler in OECD QSAR Toolbox, the notified chemical gave an alert for reproductive toxicity, due to the sub-structure toluene in the notified chemical. Two separate reproductive and developmental toxicity screening studies in rats conducted on closely related chemicals *p*-toluic acid and *m*-toluic acid, reported NOAELs of 100 mg/kg bw/day and 1,000 mg/kg bw/day respectively for reproductive toxicity (OECD SIDS 2008, OECD SIDS 2003).

Health hazard classification
Based on the available information, the notified chemical is recommended for 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***
Skin Irritation (Category 2)	H315 – Causes skin irritation

Based on an *in vitro* study conducted to identify severe eye irritants or non-irritants (OECD Test Guideline 438), the study authors proposed classifying the notified chemical as a Category 2B eye irritant (H320 – Causes eye irritation). According to the OECD TG 438, it is recommended to use this test only for classifying chemicals as Category 1.

6.3. Human Health Risk Characterisation

Limited toxicity information is available on the notified chemical. It is classified as a skin irritant and has some potential for eye irritation. Due to lack of data there is some uncertainty regarding repeated dose and reproductive / developmental effects.

6.3.1. Occupational Health and Safety

Reformulation

Transport, storage and reformulation workers may have dermal contact with the notified chemical at up to 10% concentration, and perhaps accidental ocular exposure. At these concentrations there is the potential for irritation effects. Safe work practices when handling the notified chemical during reformulation processes and use of PPE including impervious gloves, coveralls and eye protection would limit exposure and risk.

Provided that the above mentioned control measures and PPE are employed, the risk to the health of workers during the handling of the notified chemical is not considered to be unreasonable.

Professional end-use

Cleaners and beauty care professionals will handle the notified chemical at ≤ 0.4% concentration, similar to the general public. Therefore, the risk to workers who regularly use products containing the notified chemical is expected to be of similar or lesser extent than that experienced by members of the public 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

The public is likely to have repeated exposure to the notified chemical through use of cosmetic products containing it at ≤ 0.4% concentration. At the proposed use concentration, any irritation potential is expected to be greatly reduced.

Using the OECD QSAR Toolbox predicted NOEL value of 106mg/kg bw/day, (which is close to NOAELs reported for the related chemicals *p*-toluic and *m*-toluic acid) and 100% dermal absorption, the potential systemic exposure to the public from the use of the notified chemical in cosmetic and household products was estimated to be 0.96 mg/kg bw/day (see Section 6.1.2). The indicative margin of exposure (MOE) was estimated to be 110. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. Further information on the repeated dose toxicity of the notified chemical would allow a more reliable quantitative risk assessment.

Based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 0.4% concentration in cosmetic and household products, is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The imported fragrance oils containing the notified chemical will be reformulated into cosmetic and household products in highly automated closed systems. Wastewater generated from the reformulation processes will be discharged to on-site wastewater treatment plants or local sewage treatment plants (STPs) in accordance with local regulations. Accidental spills of the notified chemical during import, transport, reformulation or storage are expected to be adsorbed onto a suitable material, and collected for disposal in accordance with local regulations.

RELEASE OF CHEMICAL FROM USE

The notified chemical will be used as a component of cosmetic and household products. Therefore, the release of the chemical from use will primarily be to sewers across Australia, and then to STPs.

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

Based on its use as a component of cosmetic and household products, the majority of the notified chemical is expected to be released to sewers, and then to STPs. Based on its high water solubility, the majority of the notified chemical after STPs is expected to partition to the water column. A very small proportion of the notified chemical may adsorb to sludge in STPs.

Sludge containing the notified chemical will be sent to landfill for disposal or agricultural land for remediation. A minor amount of the notified chemical may also be disposed of to landfill as collected spills and empty container residues. The notified chemical is not expected to significantly bioaccumulate in biota based on its low log K_{ow} (log K_{ow} = 3.0). In landfill, sludge and water, the notified chemical is expected to undergo degradation by biotic and abiotic processes, eventually forming water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has been calculated to assume the worst case scenario with 100% release of the notified chemical into sewer systems nationwide over 365 days per annum. It is also assumed under the worst-case scenario that there is no removal of the notified chemical during sewage treatment processes. The resultant 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	1000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	2.74	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	24.168	million
Removal within STP	0%	
Daily effluent production:	4,834	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.57	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 0.57 µg/L may potentially result in a soil concentration of approximately 3.78 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 18.89 µg /kg and 37.79 µg /kg, respectively.

7.2. Environmental Effects Assessment

No ecotoxicity data were submitted for the notified chemical. The ecotoxicity effects of the notified chemical were predicted using ecological structure activity relationship ECOSAR v1.10 (US EPA, 2012b). The measured physio-chemical data were used in the model to achieve the best estimation results. The estimated toxicity results are summarised in the table below.

Endpoint	*Result (*)*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 5.2 mg/L	Potentially toxic to fish
Daphnia Toxicity	48 h LC50 = 9.8 mg/L	Potentially toxic to aquatic invertebrates
Algal Toxicity	96 h EC50 = 3.6 mg/L	Potentially toxic to algae

** Estimated by ECOSAR v1.10 model (US EPA, 2012b).*

The notified chemical is predicted to be toxic to fish, aquatic invertebrates and algae. The ECOSAR estimation procedure used here is a standard approach, and is considered reliable to provide general indications of the likely environmental effects of the chemical. However, this method is not considered sufficient to formally classify the

hazards of the notified chemical to aquatic life under the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)*.

7.2.1. Predicted No-Effect Concentration

The most sensitive endpoint from the ecotoxicity calculations on the notified chemical is for algae, and this was selected for the calculation of the predicted no-effect concentration (PNEC). A conservative assessment factor of 1000 is applied in this case as only estimated acute ecotoxicity endpoints are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Algae)	3.55	mg/L
Assessment Factor	1000	
Mitigation Factor	1.00	
PNEC:	3.55	µg/L

7.3. Environmental Risk Assessment

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

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.57	3.55	**0.160**
Q - Ocean	0.06	3.55	**0.016**

The risk quotient for discharge of effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity, use pattern and predicted ecotoxicological endpoints. Based on its low log K_{ow} (log K_{ow} = 3.0), the notified chemical is not expected to significantly accumulate in biota.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -20 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	Differential scanning calorimetric method. Two samples tested.
Test Facility	IFF (2014)

Boiling Point 216.3 °C at 101.3 kPa

Method	Method stated to be similar to OECD TG 103 Boiling Point.
Remarks	In house method estimated on vapour pressure measurements.
Test Facility	IFF (2014)

Density 1069 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	Oscillating densitometry method. Two samples tested.
Test Facility	IFF (2014)

Viscosity 2.07 cP at 25 °C

Method	OECD TG 114 Viscosity of Liquids.
Remarks	Tested using Rotational viscometer. Two samples tested.
Test Facility	IFF (2014)

Vapour Pressure 1.29×10^{-2} kPa at 23 °C

Method	Method similar to OECD TG 104 Vapour Pressure.
Remarks	Dynamic headspace method, similar to gas saturation method. Three samples tested.
Test Facility	IFF (2014)

Water Solubility 2.63 g/L at 22 °C

Method	OECD TG 105 Water Solubility. EEC Directive 92/96, Part A, No L383/1992 A.6 Water Solubility.
Remarks	Flask Method
Test Facility	IFF (2014)

Partition Coefficient (n-octanol/water) log P_{ow} = 3 at 25 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EEC Directive 92/96, Part A, No L383/1992 A.8 Partition Coefficient.
Remarks	HPLC Method
Test Facility	IFF (2014)

Flash Point 87 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Closed cup method. Two samples tested.
Test Facility	IFF (2014)

Autoignition Temperature 475 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	The lowest ignition temperature of 477ºC from the three main tests was rounded down to the nearest multiple of 5ºC.
Test Facility	WIL (2015)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Irritation – skin (*in vitro*)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 431 *In vitro* Skin Corrosion - Human Skin Model Test Method (2014) and OECD TG 439 *In vitro* Skin Irritation: Reconstructed Human *Epidermis* Test Method (2013)

Vehicle: None

Remarks - Method: No significant deviations from the OECD test guidelines. For *in vitro* skin corrosion assay the skin tissue was exposed to the test substance for 3 min and 60 min and cell viability was measured immediately post-exposure. For skin irritation assay the skin tissue was exposed to the test substance for 60 min and the treated skin tissue cell viability was measured 42 hours post-exposure. Cell viability was quantitated using yellow tetrazolium salt (MTT). Immediately after application of the test substance, a nylon mesh was placed on the skin model to facilitate an equal distribution of the test substance over the skin surface.

The skin irritation and skin corrosion tests were conducted on separate days with freshly prepared test samples. Positive and negative controls were included in each test. 8M potassium hydroxide solution and 5% aqueous sodium dodecyl sulphate were used as positive controls for skin corrosion and skin irritation assays respectively. MilliQ water and phosphate buffered saline were used as negative controls for skin corrosion and skin irritation assays respectively.

A preliminary test was conducted to investigate test-substance mediated conversion of MTT to blue formazan and its interaction with the nylon mesh used for even distribution of the test substance on skin.

RESULTS

Skin irritation test

Test material	*Mean OD_{570} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	2.314	100	3
Test substance	0.108	5	0
Positive control	0.074	3	2

OD = optical density; SD = standard deviation

Skin corrosion test

Test material	*Exposure duration*	*Mean OD_{570} of duplicate tissues*	*Relative mean Viability (%)*
Negative control	3 min	1.831	100
Test substance	3 min	1.784	97
Positive control	3 min	0.084	5
Negative control	60 min	1.636	100
Test substance	60 min	0.260	16
Positive control	60 min	0.081	5

Remarks - Results: The mean OD of the blank, the negative controls and the positive controls demonstrated the expected response confirming the validity of the skin sample and the assay.

The viability of test substance exposed cells was reduced at 60 min time

point which suggests the test substance is irritating to the skin. To classify the test substance as corrosive, the cell viability should be less than 50% after 3 min incubation and/or less than 15% after 60 min incubation in skin corrosion assay. The criteria for skin corrosion classification were not met.

To classify as an irritant, the cell viability of the test substance exposed cells should be less than 50% in skin irritation assay. This criterion was met and hence the test substance is considered as irritating to the skin.

CONCLUSION The notified chemical was non-corrosive to the skin under the conditions of the skin corrosion test.

The notified chemical was irritating to the skin under the conditions of the skin irritation test.

TEST FACILITY TNO (2015a)

B.2. Irritation – eye (*in vitro*)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 438 Isolated Chicken Eye Test Method for Identifying Ocular Corrosives and Severe Irritants (2013)

Vehicle None

Remarks - Method No significant deviations from the OECD test guideline. Benzalkonium chloride (BAC) and physiological saline were used as positive and negative controls respectively. Corneal thickness, opacity and fluorescein retention were measured to evaluate the irritation potential of the test substance.

RESULTS

Test material	*Maximum mean score*			*Irritation index*
	Swelling	*opacity*	*Fluorescein retention*	
Test substance	5	2.5	0.8	71
Positive control	32	3.0	3.0	152

Irritation index = maximum mean corneal swelling + maximum mean opacity (×20) + mean fluorescein score (×20)

Remarks - Results The positive and negative controls gave satisfactory results confirming the validity of the test. The irritation index of test substance exposed eyes did not meet the criteria for classification as category 1 according to the OECD test guideline. However, the study authors recommended the test substance to be classified as category 2B eye irritant based on in-house irritation index cut-offs. Increase in corneal opacity and swelling suggest the test substance may have some irritation effects.

CONCLUSION The test substance did not meet the criteria for classification as category 1 eye irritant or not requiring classification for eye irritation or serious eye damage. No prediction can be made under the conditions of the test

TEST FACILITY TNO (2015b)

B.3. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2002)

Species/Strain Mouse/CBA/J

Vehicle Diethyl phthalate/ethanol (3:1)

Preliminary study	No
Positive control	Conducted in parallel with the test substance using 35% Hexylcinnamaldehyde.
Remarks - Method	No significant deviations from the OECD test guideline. The maximum concentration tested was based on estimated concentration of human exposure.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (Mean DPM ± SEM)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5 F	172 ± 16	-
7.5	5 F	195 ± 19	1.13
15	5 F	273 ± 17	1.59
30	5 F	209 ± 26	1.22
Positive Control			
Hexylcinnamaldehyde	5 F	866 ± 73	5.03

EC3	Not determined
Remarks - Results	Ear thickness was also measured after exposure and no significant changes were noted. No clinical signs of toxicity were observed.

CONCLUSION There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY Calvert (2004)

B.4. Skin sensitisation – human volunteers

TEST SUBSTANCE Notified chemical (10% in vehicle)

METHOD Repeated insult patch test with challenge

Study Design	Induction Procedure: Patches containing test substance were applied 3 times per week (Monday, Wednesday and Friday) for a total of 9 applications. Patches were removed by the applicants after 24 h and graded after an additional 24 h (or 48 h for patches applied on Friday). Rest Period: approximately 14 days Challenge Procedure: A patch was applied to a naïve site. Patches were removed by the technician after 24 h. Sites were graded 24 and 48 h post-application.
Study Group	97 F, 16 M; age range 18-69 years
Vehicle	Diethyl phthalate/ethanol (1:3)
Remarks - Method	Occluded. The test substance was spread on a patch and allowed to volatilize for 30 to 90 minutes. The application volume of test substance and the patch size were not mentioned in the test report.

RESULTS

Remarks - Results	111/113 subjects completed the study. The reason for discontinuation of the study by the 2 test subjects was not reported. No adverse responses were noted during the induction and challenge phases in any of the test subjects who successfully completed the study.

CONCLUSION The test substance was non-sensitising under the conditions of the test.

TEST FACILITY CRL (2004)

B.5. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test (1997). Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 21-5000 µg/plate b) Without metabolic activation: 21-5000 µg/plate
Vehicle	Dimethyl sulphoxide (DMSO)
Remarks - Method	No significant deviations from the OECD test guideline. No preliminary test was performed. The test substance was prepared fresh at 50 mg/mL concentration in DMSO. Some tests were repeated due to the negative were outside the acceptable and/or historical range.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:* *Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 1667	≥ 1667	Negative
Test 2	≥ 800	≥ 2000	Negative
Present			
Test 1	≥ 1667	≥ 1667	Negative
Test 2	≥ 2000	≥ 2000	Negative

Remarks - Results	No remarkable increases in the number of revertant colonies were observed. The positive controls gave satisfactory results confirming the validity of S9-mix and the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	TNO (2015c)

B.6. Genotoxicity – *in vitro*

TEST SUBSTANCE	Notified chemical
METHOD	BlueScreen HC Assay
Cell Type/Cell Line	Genetically modified strain of cultured human lymphoblastoid TK6 cells (GLuc-T01; GLuc reporter system is reported to exploit the proper regulation of the GADD45a gene, which mediates the adaptive response to genotoxic stress)
Metabolic Activation System	S9 fraction from Aroclor-1254 induced rat liver.
Concentration Range in Test	a) With metabolic activation: 2.44-313 µg/mL b) Without metabolic activation: 2.44-313 µg/mL
Vehicle	DMSO and water
Remarks - Method	Eight dilutions of the notified chemical along with positive and negative controls were tested in a 96-well microplate. BlueScreen HC assay (without metabolic activation): The microplates containing the test substance and medium were covered with a breathable membrane and incubated at 37 °C with 5% CO_2 and 95% humidity for 48 hours. The plates are then assessed using fluorescence measurements to determine cell density, then using flash luminescence to determine genotoxicity. BlueScreen HC S9 assay (with metabolic activation): wells containing the

test substance, S9 fraction and medium were incubated (as above) for 3 hours, then washed, harvested and allowed to recover in medium for 45 hours at 37 °C with 5% CO2 and 95% humidity. The plates were then assessed similar to that above.

Reduced (≤ 80%) cell density compared to untreated cells (vehicle control) was used to provide a measure of cytotoxicity of the test substance. Increased (1.8 fold without metabolic activation; 1.5 fold with metabolic activation) induction of GLuc expression relative to the vehicle control was used to provide a measure of genotoxicity of the test substance. Where a positive result was obtained, the Lowest Effective Concentration (LEC; µM) was determined.

Vehicle and positive (without metabolic activation: 4-nitroquinoline-1-oxide (4-NQO) at 0.125 and 0.5 µg/mL; with metabolic activation: cyclophosphamide at 5 and 25 µg/mL) controls were used in parallel with the test substance.

RESULTS

Metabolic Activation	*Highest test substance concentration µg/mL*	*Cytotoxicity*	*LEC (µM)*	*Genotoxic Effect*	*LEC (µM)*
Absent	313	negative	-	negative	-
Present	313	negative	-	negative	-

*LEC = Lowest Effective Concentration for a positive result

Remarks - Results

In the presence and absence of metabolic activation, the test substance was negative for genotoxicity at up to 313 µg/mL in the standard BlueScreen HC assay. Intra-assay quality control checks passed test criteria following the standard protocol. No cytotoxicity was observed up to the high test concentration of 313 µg/mL.

CONCLUSION

The notified chemical was considered by the study authors to be not genotoxic under the conditions of the test.

TEST FACILITY

Gentronix (2013)

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