File No: LTD/1960

March 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

5-Benzofuranol, 3-methyl-

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/1960	International Flavours and Fragrance (Australia) Pty Ltd	5-Benzofuranol, 3-methyl-	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*
Acute toxicity, oral (Category 4)	H302 – Harmful if swallowed
Acute toxicity, inhalation (Category 4)	H332 – Harmful if inhaled
Eye Irritation (Category 2A)	H319 – Causes serious eye irritation
Skin irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1B)	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*
Acute Category 2	H401 Toxic to aquatic life
Chronic category 2	H411 - Toxic to aquatic life with long lasting effects

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:
  - Acute toxicity, oral (Category 4): H302 – Harmful if swallowed

- Acute toxicity, inhalation (Category 4): H332 – Harmful if inhaled
- Eye Irritation (Category 2A): H319 – Causes serious eye irritation
- Skin irritation (Category 2): H315 – Causes skin irritation
- Skin sensitisation (Category 1B): 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 and the intended use/exposure scenario.

- The Delegate (and/or the Advisory Committee on Chemicals Scheduling) should consider the notified chemical for listing on the SUSMP.

Health Surveillance

- As the notified chemical is a skin sensitiser, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of skin sensitisation.

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, where possible
  - Adequate 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 inhalation of vapours or aerosols

- 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 and goggles
  - 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 (M)SDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System 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 an inert, non-combustible absorbent material 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 concentration of the notified chemical exceeds or is intended to exceed the following concentrations in end use products
  - 0.06% in non-spray deodorants and hand creams
  - 0.10% in hair styling products
  - 0.12% in fine fragrances
  - 0.18% in face creams
  - 1.00% in hairspray, makeup remover, rinse-off cosmetics, air care products and household products
  - 0.20% in other leave-on cosmetics

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.

(Material) Safety Data Sheet
The (M)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 (M)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, dissociation constant and flash point.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT
None

NOTIFICATION IN OTHER COUNTRIES
Canada, China

2. IDENTITY OF CHEMICAL

MARKETING NAME
Saffiano

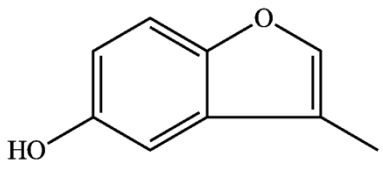
CAS NUMBER
7182-21-0

CHEMICAL NAME
5-Benzofuranol, 3-methyl-

OTHER NAMES
3-Methyl-1-benzofuran-5-ol

MOLECULAR FORMULA
$C_9H_8O_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
148.16

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

3. COMPOSITION

DEGREE OF PURITY
> 99%

IMPURITIES/ADDITIVES/ADJUVANTS
None identified

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	92.5 ± 0.5 °C	Measured
Boiling Point	277 ± 1 °C at 101.6 kPa	Measured
Density	1,320 kg/m^3 at 22 °C	Measured
Vapour Pressure	8.7×10^{-5} kPa at 25 °C	Measured
Surface Tension	60.5 mN/m at 21.6 °C	Measured
Water Solubility	1.42 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionalities
Partition Coefficient (n-octanol/water)	log P_{ow} = 1.65 at 35 °C	Measured
Adsorption/Desorption	log K_{oc} = 1.65 at 35 °C	Measured
Dissociation Constant	Not determined	The majority of the notified chemical is expected to remain undissociated at environmental pH.
Particle Size	Inhalable fraction (< 100 µm): 17.2% Respirable fraction (< 10 µm): ≤ 6.0%	Measured
Solid Flammability	Not highly flammable	Measured
Autoignition Temperature	530 ± 5 °C	Measured
Explosive Properties	Not explosive	Predicted on basis of structure
Oxidising Properties	Not oxidising	Predicted on basis of structure

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 in to Australia in fragrance oils at concentration ranging from 1 to 10%.

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 usually be imported in 208 L polypropylene-lined steel drums by sea. 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. It will be used in various cosmetic, personal care and household products. The final proposed concentration of the notified chemical in end-use products will be as follows:

Body lotion	0.20%	Makeup remover	1.00%
Face cream	0.18%	Hair spray	1.00%
Hand cream	0.06%	Other leave-on cosmetics	1.00%
Deodorant	0.06%	Air care products	1.00%
Fine fragrances	0.12%	Rinse-off cosmetics	1.00%
Hair styling products	0.10%	Household products	1.00%

OPERATION DESCRIPTION
The notified chemical will not be manufactured in Australia. It will be imported at concentrations ≤ 10% in fragrance oils for reformulation into end-use cosmetics and household products at the sites of the notifier's industrial customers. The reformulation process will vary depending on the type of end-use products but is expected to be carried out in closed and highly automated systems with adequate ventilation.

The finished cosmetic and household products containing the notified chemical at up to 1% concentration may be applied by hand, spray or through the use of applicators.

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	4	250
Plant operators – drum handling	1	250
Plant operators – drum cleaning/washing	2	250
Plant operators – equipment cleaning/washing	2	250
Plant operators – quality control	1	250
Professional users (hairdressers, cleaners etc.)	8	250

EXPOSURE DETAILS
Transport and warehouse workers
At the notifier's facility, the primary work activity undertaken by transport and warehouse workers will include the handling, loading and off-loading of drums containing fragrance oils with the notified chemical at up to 10% concentration. Exposure of these workers will be limited to situations involving fragrance oil sampling for quality control, or in the event of a discharge, clean up from a spill or leaking drum. If such an event occurs, a worker may be exposed through dermal or ocular contact. The notifier states that exposure will be minimised through the use of personal protective equipment (PPE) including overalls, hard hats, chemical resistant gloves and safety glasses.

Formulation of end products
Reformulation of the notified chemical containing fragrance oil will only occur at notifier's industrial customer sites. During reformulation dermal, ocular and inhalation exposure of workers to the notified chemical (at ≤ 10% concentration) may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The notifier anticipates that typical practices by cosmetic and consumer product manufacturers will include enclosed mixing vessels and filling areas, local ventilation, PPE such as overalls, safety glasses, impervious gloves and respiratory protection if required, and a high degree of process automation. It is also expected that the workers will be provided the required training and education in proper handling of products containing the notified chemicals.

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products (at up to 1% concentration) may occur in professions where the services provided involve the application of cosmetic and personal care products to clients (e.g. hair

dressers, workers in beauty salons) 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 are expected to follow good hygiene practices and may use some PPE to minimise repeated exposure. 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

There will be widespread and repeated exposure of the public to the notified chemical (at ≤ 1% concentration) through the use of a wide range of cosmetic and household products. The principal route of exposure will be dermal, while ocular exposure and inhalation exposure (e.g., through the use of spray products) is also possible.

Data on typical use patterns of various types of consumer products in which the notified chemical may be used are shown in the following tables (SCCS, 2012; Cadby *et al.*, 2002; ACI, 2010; Loretz *et al.,* 2006). For the purposes of exposure assessment via the dermal route, Australian use patterns for various products are assumed to be similar to the consumer use patterns in Europe. In the absence of dermal absorption data and based on the low molecular weight of the notified chemical (148.16 Da), a dermal absorption (DA) of 100% was assumed (European Commission, 2003). For inhalation exposure estimation of spray products, a 2-zone approach was used (Steiling *et al*., 2014; Rothe *et al*., 2011; Earnest, Jr, 2009) with an adult inhalation rate of 20 m^3/day (enHealth, 2012). It was conservatively assumed that the fraction of the notified chemicals inhaled be 50%, with the remainder ending up on the targets as intended. A lifetime average female body weight (BW) of 64 kg (enHealth, 2012) was applied in the calculations.

Cosmetic products (dermal exposure)

Product type	*Amount (mg/day)*	*Chemical concentration (%)*	*Retention Factor (RF)*	*Daily systemic exposure (mg/kg bw/day)*
Body lotion	7820	0.20	1.000	0.2444
Face cream	1540	0.18	1.000	0.0433
Hand cream	2160	0.06	1.000	0.0203
Fine fragrance	750	0.12	1.000	0.0141
Deodorant	1430	0.06	1.000	0.0141
Shampoo	10460	1.00	0.010	0.0163
Conditioner	3920	1.00	0.010	0.0061
Shower gel	18670	1.00	0.010	0.0292
Hand wash soap	20000	1.00	0.010	0.0313
Hair styling products	4000	0.10	0.100	0.0063
Total				**0.4252**

Daily systemic exposure = (Amount × Chemical concentration × RF × DA)/BW
(RF = retention factor; DA = dermal absorption; BW = body weight)

Household Products (Indirect dermal exposure – from wearing clothes)

Product type	*Amount (g/use)*	*C (%)*	*Product Retained (%)*	*Product Transferred (%)*	*Daily systemic exposure (mg/kg bw/day)*
Laundry liquid	230	1.00	0.95	10	0.0341
Fabric softener	90	1.00	0.95	10	0.0134
Total					**0.0475**

Daily systemic exposure = (Amount × C × PR × PT × DA)/BW
(C = chemical concentration; PR = product retained; PT = product transferred; DA = dermal absorption; BW = body weight)

Household products (Direct dermal exposure)

Product type	*Frequency (use/day)*	*C (%)*	*Contact Area (cm^2)*	*Product Usage (g/cm^3)*	*Film Thickness (cm)*	*Time Scale Factor*	*Daily systemic exposure (mg/kg bw/day)*
Laundry liquid	1.43	1.00	1980	0.01	0.01	0.007	0.0003
Dishwashing liquid	3	1.00	1980	0.009	0.01	0.03	0.0025
All-purpose cleaner	1	1.00	1980	1	0.01	0.007	0.0217
Total							**0.0245**

Daily systemic exposure = Frequency × C × Contact Area × Product Usage × Film Thickness × Time Scale Factor × DA/ BW
(C = chemical concentration; DA = dermal absorption; BW = body weight)

Aerosol products (Inhalation exposure)

Product type	*Amount* (g/day)	*C* (%)	*Exposure Duration Zone 1* (min)	*Exposure Duration Zone 2* (min)	*Volume Zone 1* (m^3)	*Volume Zone 2* (m^3)	*Daily systemic exposure* (mg/kg bw/day)
Hairspray	9.89	1.00	1	20	1	10	**0.0322**

Daily systemic exposure = [(Amount × C × 20 m^3/day Inhalation Rate × 50% Fraction Inhaled × 0.1) / BW × 1440)] × (Exposure Duration Zone 1/Volume Zone 1 + Exposure Duration Zone 2/Volume Zone 2)
(C = chemical concentration; BW = body weight)

The worst case scenario estimation using these assumptions is for a person who is a simultaneous user of all products listed in the above tables that contain the notified chemicals. This would result in a combined internal dose of 0.5294 mg/kg bw/day for the notified chemical. It is acknowledged that inhalation exposure to the notified chemical from use of other cosmetic and household products (in addition to hair spray) may occur. However, it is considered that the combination of the conservative (screening level) hair spray inhalation exposure assessment parameters, and the aggregate exposure from use of the dermally applied products, which assumes a conservative 100% absorption rate, is sufficiently protective to cover additional inhalation exposure to the notified chemical from use of other spray cosmetic and household products with lower exposure factors (e.g., air fresheners and deodorants).

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*
Rat, acute oral toxicity	LD_{50} 1000 mg/kg bw; harmful
Rat, acute dermal toxicity	LD_{50} > 2000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC_{50} 4.68 mg/L/4 hour; harmful
Skin corrosion (in vitro RHE test)	non-corrosive
Skin irritation (in vitro RHE test)	irritating
Eye irritation (in vitro BCOP test)	not causing serious eye damage
Rabbit, eye irritation	severely irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Human, skin sensitisation – RIPT (0.25%)	no evidence of irritation or sensitisation
Human, skin sensitisation – RIPT (1.25%)	equivocal
Rat, repeat dose oral (diet) toxicity – 43-44 days	NOAEL 138 mg/kg bw/day males 162.9 mg/kg bw/day females
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro mammalian chromosome aberration test	non genotoxic
Phototoxicity – in vitro 3T3 NRU Test	non-phototoxic
Rat, reproductive and developmental toxicity*	NOEL 162.9 mg/kg bw/day

* – conducted as part of repeated dose oral (diet) toxicity study

Toxicokinetics, metabolism and distribution

No information on toxicokinetics, metabolism and distribution data was provided. Based on the low molecular weight, the notified chemical is expected to cross biological membranes.

Acute toxicity

Acute toxicity tests conducted on the notified chemical found the chemical to be harmful via the oral and inhalation routes and of low toxicity via the dermal route.

Irritation and sensitisation

The notified chemical was found to be irritating to the skin but not corrosive in *in vitro* irritation studies using the reconstituted human epidermis (RHE) model. In an *in vitro* eye irritation study using the bovine corneal opacity and permeability (BCOP) test method, the notified chemical had scores indicating that it did not cause serious eye damage (Cat 1). However it was severely irritating to the eyes (Cat 2A) in an *in vivo* study conducted on rabbits.

The notified chemical was found to be a skin sensitiser in a local lymph node assay with a calculated EC3 value of approximately 5.2. The notified chemical was found to be non-irritating and/or sensitising in a human

repeated insult patch (HRIPT) study carried out at 0.25%. In another HRIPT study conducted using the notified chemical at 1.25% concentration, one test subject showed mild erythema at 72 h and 96 h after challenge. A sensitisation response in this study cannot be ruled out.

Repeated dose toxicity
A combined repeated dose toxicity study with the reproduction/development toxicity screening test was conducted using the notified chemical in rats. The test substance was administered via the oral route in diet at 750ppm (low dose), 2500ppm (mid dose) and 7500ppm (high dose) concentrations. The effective concentrations tested in mg/kg bw/day were 42.4, 138 and 412.8 for male rats; 56.1, 162.9 and 463 for female rats during pre-pairing stage and 56.6, 192.3 and 546 for female rats during the gestation.

Test substance related effects were observed in the male and female rats from high dose groups. The marked changes observed were in the kidneys of male rats and reduction in body weights in both male and female rats. The reduction in weight gain was attributed to reduction in food consumption due to local irritating effects in the gastrointestinal tract cause by the test substance. This was evident in form of hyperkeratosis in the oesophagus and acanthosis and hyperkeratosis in the stomach. Male rats from the high dose group had significant increase in absolute and relative kidney weights. This was accompanied by hyaline droplets and was considered to be specific to male rats only.

Based on the above findings, a No Observed Adverse Effect (NOAEL) of 138 mg/kg bw/day was established for male rats and a NOAEL of 162.9 mg/kg bw/day female rats.

Mutagenicity/Genotoxicity
The notified chemical was non mutagenic in a bacterial reverse mutation test and non clastogenic when tested *in vitro* using cultured human lymphocytes.

Phototoxicity
The notified chemical was reported to be non phototoxic in an *in vitro* study conducted using 3T3 cell lines.

Toxicity for reproduction
The test was conducted as part of the repeated dose toxicity study reported above. No changes in the reproductive and developmental parameters tested were noted including oestrous cycle, mating, fertility, gestational length, litter size and weights. Marginally reduced litter size and weights were noted for the high dose group (7500ppm). These were attributed to the reduction in body weight gain in maternal animals due to the local irritating effects in the gastrointestinal tracts. In addition one high dose female had total litter loss on Day 3 *post partum*. This was not included in the analyses of litter results, and was considered by the study authors to be likely a result of a slightly longer parturition length, and not related to treatment.

A No Observed Effect Level (NOEL) of 162.9 mg/kg bw/day was established for reproductive / developmental toxicity.

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***
Acute toxicity, oral (Category 4)	H302 – Harmful if swallowed
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Skin irritation (Category 2)	H315 – Causes skin irritation
Skin sensitisation (Category 1B)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation
The notified chemical is harmful via the oral and inhalation routes, is severely irritating to the eyes, irritating to the skin and is a sensitiser via the dermal route. Prolonged and repeated exposure to high concentrations of the notified chemical may also cause adverse systemic effects.

6.3.1. Occupational Health and Safety

Reformulation

Workers may experience dermal, ocular and perhaps inhalation exposure to the notified chemical at up to 10% concentration during reformulation. The use of enclosed, automated processes with exhaust ventilation and PPE such as coveralls, goggles, impervious gloves (and respiratory protection if required) should minimise the potential for exposure and risk. Therefore, provided that adequate control measures are in place to minimise worker exposure, the risk of workers from use of the notified chemicals is not considered to be unreasonable.

Professional end use

Hair and beauty care professionals and cleaners may come into contact with the notified chemical at ≤ 1% concentration during the use of cosmetic and household products. Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. The 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

Irritation

The notified chemical may cause severe eye irritation. Accidental ocular exposure of consumers may occur from use of cosmetic products and spray on household products containing the notified chemical. Given the low proposed use concentration of ≤1%, significant eye irritation effects are not expected. While the notified chemical is also considered to be a skin irritant, skin irritation effects are not expected from use of the notified chemical at the proposed use concentrations.

Skin sensitisation

When tested in an LLNA study, the notified chemical was considered a skin sensitiser with a calculated EC3 value of ~5.2. Proposed methods for the quantitative risk assessment of the dermal sensitisation have been the subject of significant discussion (i.e., Api *et al.,* 2008 and RIVM, 2010). Using face cream as an example product that may contain the notified chemical (at 0.18% concentration), as a worst case scenario, the Consumer Exposure Level (CEL) for the notified chemical is estimated to be 4.91 μg/cm^2/day (Cadby *et al.,* 2002). Consideration of available information and application of appropriate safety factors allowed the derivation of an Acceptable Exposure Level (AEL) of 5.72 μg/cm^2/day. In this instance, the factors employed included an interspecies factor (3), intraspecies factor (10), a matrix factor (3.16), use/time factor (3.16) and database factor (1), giving an overall safety factor of 300.

As the AEL > CEL, the risk to the public of the induction of sensitisation that is associated with the use of face cream (a worst case example of a leave-on cosmetic product) at ≤ 0.18% concentration is not considered to be unreasonable. All other proposed cosmetic products that may contain the notified chemical were calculated to have a lower CEL than face cream. For other leave-on cosmetic products which have not been specifically proposed, the CEL is expected to be less than AEL if the concentration of the notified chemical is ≤ 0.2% in the product(s). Based on the significantly lower expected exposure level from household and fabric care products (≤ 1% notified chemical) the risk of induction of sensitisation associated with the use of these products is also not considered to be unreasonable. It is acknowledged that consumers may be exposed to multiple products containing the notified chemical, and a quantitative assessment based on the aggregate exposure has not been conducted.

Therefore, based on the information available, the risk to the public associated with the use of the abovementioned products containing the notified chemical at these concentrations is not considered to be unreasonable.

Repeat dose toxicity

The potential systemic exposure to the public from the use of the notified chemical in cosmetic and household products was estimated to be 0.5294 mg/kg bw/day (see Section 6.1.2). Using the lowest NOAEL of 138 mg/kg bw/day reported for male rats derived from a combined repeated dose oral dietary toxicity study with reproductive/developmental toxicity screening, the margin of exposure (MOE) was estimated to be 261. A MOE value greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences.
Therefore, based on the information available, the risk to the public associated with the use of the notified chemical at ≤ 1% 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 notified chemical will not be manufactured in Australia. Therefore, there will be no release of the notified chemical to the environment from this activity. The notified chemical will be imported as a component of fragrance formulations, for reformulation into finished cosmetic and household products. There is unlikely to be any significant release to the environment from transport and storage, except in the case of accidental spills and leaks. Accidental leaks and spills of the product containing the notified chemical is expected to be collected by inert absorbent material and disposed of to landfill in accordance with local government regulations.

The reformulation process will involve batch blending operations that are expected to occur within fully enclosed systems. Therefore, significant release of the notified chemical to the environment from this process is not expected. Wastes containing the notified chemical generated from reformulation including equipment wash water, empty import containers and spilt materials are expected to be disposed of to on-site waste water treatment or directly to the sewer system. Empty import containers are expected to be recycled or sent to landfill 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 domestic products, which are washed off the hair and skin of consumers as well as from cleaning activities.

RELEASE OF CHEMICAL FROM DISPOSAL

It is expected that some of the product containing the notified chemical will remain in end-use containers. Wastes and residue of the notified chemical in empty containers are likely to either share the fate of the container and be disposed of to landfill, or be released to the sewer system when containers are rinsed before recycling through an approved waste management facility.

7.1.2. Environmental Fate

Following its use in cosmetic formulations and household products in Australia, the majority of the notified chemical will enter into the sewer system before potential release to surface waters nationwide. The chemical is not readily biodegradable and there is no data available for inherent biodegradability. For details of the environmental fate study, please refer to Appendix C.

Measured data indicates that the notified chemical is not readily biodegradable (13% in 28 days). Based on its low adsorption coefficient (log K_{OC} = 1.65) and high water solubility (1.42 g/L at 20 ºC) the notified chemical is expected to remain in the water phase, and may be released from sewage treatment plants to surface waters. The low n-octanol/water partition coefficient (log P_{OW} = 1.65) and calculated low bioconcentration factor (log BCF = 1.87, BCFBAF v3.01; US EPA, 2008) suggest that the notified chemical is not expected to bioaccumulate. A small proportion of notified chemical may be applied to land when effluent is used for irrigation, and residues in empty containers are expected to be disposed of to landfill. The notified chemical in landfill, soil and sludge is expected to be mobile and anticipated to eventually degrade through biotic and abiotic processes to form water and oxides of carbon.

The half-life of the notified chemical in air is calculated to be < 1 h, based on reactions with hydroxyl radicals (US EPA, 2011; calculated using AOPWIN v1.92). Therefore, the notified chemical is not expected to persist in the air compartment.

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 sewage treatment plants (STPs) and there is no removal of the notified chemical at STPs. The release is assumed to be nationwide over 365 days per year.

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	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.61	µg/L
PEC - Ocean:	0.06	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.61 µg/L may potentially result in a soil concentration of approximately 4.04 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of the notified chemical in the applied soil in 5 and 10 years may be approximately 20.19 µg/kg and 40.39 µg/kg, respectively.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 8.43 mg/L	Toxic to Fish
Daphnia Toxicity	48 h EC50 = 5.6 mg/L	Toxic to aquatic invertebrates
Algae Toxicity	72 h E_rC50 = 11.0 mg/L NOEC = 3.2 mg/L	Harmful to algae

Based on the above ecotoxicological endpoints for the notified chemical, it is considered to be toxic to fish and invertebrates while harmful to 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". Based on the acute toxicity and non ready biodegradability of the notified chemical, it is formally classified as "Chronic Category 2; Toxic to aquatic life with long lasting effect" under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The most sensitive toxicity endpoint is found to be for algae (NOEC=3.2 mg/L) and hence the predicted no-effects concentration (PNEC) was calculated using this result. An assessment factor of 100 was used given that measured acute endpoints from three trophic levels and one measured NOEC endpoint are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment	
NOEC (algae)	3.20 mg/L
Assessment Factor	100
PNEC:	32.0 µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.61	32	**0.019**
Q - Ocean	0.06	32	**0.002**

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface

waters, based on its maximum use volume and assessed use pattern. The notified chemical is not readily biodegradable. However it is not expected to bioaccumulate in aquatic environment.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 92.5 ± 0.5 °C

Method	OECD TG 102 Melting Point/Melting Range (1995).
Remarks	Determined using differential scanning calorimeter. Two samples were tested.
Test Facility	Harlan (2014a)

Boiling Point 277 ± 1 °C at 101.6 kPa

Method	OECD TG 103 Boiling Point (1995).
Remarks	Determined using differential scanning calorimeter. Three samples were tested. A dark brown residue after testing indicated that some decomposition may have occurred.
Test Facility	Harlan (2014b)

Density 1,320 kg/m^3 at 22 °C

Method	OECD TG 109 Density of Liquids and Solids (2012).
Remarks	Gas comparison pycnometer method. Two samples were tested.
Test Facility	Harlan (2014b)

Vapour Pressure 8.7×10^{-5} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure.
Remarks	Vapour pressure balance method.
Test Facility	Harlan (2014c)

Water Solubility 1.42 g/L at 20 °C

Method	OECD TG 105 Water Solubility. EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks	Flask Method/Slow-stirring flask Method. The concentration of the notified chemical determined by HPLC. Average pH of the solution was found to be 6.03.
Test Facility	Harlan (2014d)

Partition Coefficient (n-octanol/water) log Pow = 1.65 at 35 °C (HPLC method)

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks	Partition Coefficient of the notified chemical was determined by HPLC Method.
Test Facility	Harlan (2014d)

Surface Tension 60.5 mN/m at 21.6 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions (1995).
Remarks	Ring method. Two samples were tested. The test substance was not considered to be surface-active, based on the study.
Test Facility	Harlan (2014b)

Adsorption/Desorption log K_{oc} = 1.65 at 30 °C

Method	OECD TG 121 Adsorption - Desorption Using High Performance Liquid Chromatography (HPLC).
Remarks	The HPLC method using soil-adsorption-reference data was applied for the determination of the adsorption coefficient.
Test Facility	Envigo (2016a)

Particle Size

Method OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions.

Range (μm)	*Mass (%)*
< 100	17.2
< 10	≤ 6.0
< 5.5	≤ 2.1

Remarks Test conducted using sieving and cascade impactor methods. Mass Median Aerodynamic Diameter was not calculated due to very few particles of size less than 10μm in diameter.
Test Facility Envigo (2016b)

Solid Flammability Not highly flammable

Method EC Council Regulation No 440/2008 A.10 Flammability (Solids).
Remarks The test item did not propagate combustion over the 200 mm in preliminary test. Therefore further testing was not conducted.
Test Facility Harlan (2014d)

Autoignition Temperature 530 ± 5 °C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks The test substance was solid at room temperature.
Test Facility Harlan (2014d)

Explosive Properties Not predicted to be explosive

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks No structural alerts in the chemical structure of the test substance.
Test Facility Harlan (2014d)

Oxidizing Properties Not predicted to be oxidising

Method EC Council Regulation No 440/2008 A.17 Oxidizing Properties (Solids).
Remarks No structural alerts in the chemical structure of the test substance.
Test Facility Harlan (2014d)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method (2001).
Species/Strain	Rat/RccHan™:WIST
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant deviations from the OECD guideline.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 F	300	0/3
2	3 F	2,000	2/3
3	3 F	300	0/3

LD50	1000 mg/kg bw (Category 4 - >300 – 2000 mg/kg bw)
Signs of Toxicity	Clinical signs of toxicity including increased salivation, noisy respiration, increased respiratory rate, prostration, occasional body tremors, hunched posture and pilo-erection were noted in group 2 animals. No signs of toxicity were observed from day 4 onwards in one surviving animal from this group. Hunched posture, ataxia and pilo-erection was also observed in group 1 animals. No clinical signs were noted in group 3. Body weight gains in surviving animals were as expected.
Effects in Organs	Brown liquid was present in the stomach and epithelial sloughing and/or haemorrhage of gastric mucosa was noted in the 2 group 2 animals that died prior to scheduled necropsy. No other macroscopic findings were noted in the animals that survived the study.
Remarks - Results	The LD50 value was derived based on the deaths observed at 2,000 mg/kg bw test concentration.
CONCLUSION	The notified chemical is harmful via the oral route.
TEST FACILITY	Harlan (2014e)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity (1987) – Limit Test.
Species/Strain	Rat/ RccHan™:WIST
Vehicle	Moistened with distilled water
Type of dressing	Semi-occlusive.
Remarks - Method	No significant deviations from the OECD guideline. The test substance was moistened with distilled water. At the start of the study three male rats were outside the ±20% body weight limits for mean weight.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 M & 1 F	2,000	0/2
2	4 M &4 F	2,000	0/8

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	No signs of toxicity were observed.
Signs of Toxicity - Systemic	No signs of toxicity were observed.

Effects in Organs	None reported.
Remarks - Results	During the first week two female rats showed slight body weight loss and one female rat showed no gain in body weight. All the female rats gained body weight during the second week.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Envigo (2016c)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 403 Acute Inhalation Toxicity (2009).
Species/Strain	Rat/RccHan^{TM}:WIST
Vehicle	Ethanol
Method of Exposure	Nose only
Exposure Period	4 hours
Physical Form	liquid aerosol
Remarks - Method	No significant deviations from the OECD guideline. Minor deviations which did not affect the integrity of the study were reported. The test substance was mixed with ethanol (50:50 w/w) to generate mixture to improve aerosolization.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <units>*		*Mortality*
		Nominal	*Actual*	
1	5 F & 5 M	5.97	2.02	0/10
2	5 F & 5 M	10.1	3.56	4 (1 M & 3 F)/10
3	5 M	31.1	5.05	2/5
4	5 F	13.0	2.90	1/5

LC50	4.68 mg/L/4 hours (all animals) Male: 5.46 mg/L/4 hours Female: 3.39 mg/L/4 hours
Signs of Toxicity	Decreased respiratory rate, laboured respiration, ataxia, hunched posture, pilo-erection, red/brown staining around the eyes and/or snout and wet fur was observed in test animals
Effects in Organs	Dark patches in lungs were observed in 2 animals from group 1 and 1 animal from group 2 that survived the study until the end of the recovery period. Gaseous distention of the large intestine was also noted in one of the animals from group 1. No other abnormalities were noted in other animals that survived the study. Abnormally red dark/pale patches in lungs, dark liver and gaseous distention of stomach were noted in various test animals that died during the study.
Remarks - Results	Due to the observations noted during the study and at the necropsy it was considered by the study authors that the deaths noted during the study may have been mainly attributable to local toxicity.
CONCLUSION	The notified chemical is harmful via inhalation.
TEST FACILITY	Envigo (2016d)

B.4. Corrosion – skin (in vitro)

TEST SUBSTANCE	Notified chemical

METHOD: OECD TG 431 In vitro Skin Corrosion (2004) - Human Skin Model Test: EpiSkin™ Reconstituted Human Epidermis Model

Vehicle: None. The skin model was moistened with saline solution.

Remarks - Method: No significant deviations from the OECD guideline. The test substance was able to degrade MTT used to quantitate cell viability. To account for the MTT degradation by the test substance, a negative control using water-killed tissue was conducted in parallel. Glacial acetic acid was used as positive control.

RESULTS

Test material	*Exposure period*	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*
Negative control	240 min	0.939	100
Test substance	3 min	1.441	150.8
	60 min	1.316	117.9
	240 min	0.998	79.1
Positive control	240 min	0.035	3.7

OD = optical density

Remarks - Results: The relative mean viability of the test substance treated cells was > 35%, the cut-off value for a corrosive substance, for all incubation periods.

The positive control gave satisfactory results and the optical density of the negative control was within the acceptable range confirming the validity of the assay.

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

TEST FACILITY: Harlan (2014f)

B.5. Irritation – skin (in vitro)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 439 In vitro Skin Irritation (2010) – Reconstructed Human *Epidermis* Test Method: EpiSkin™ Reconstituted Human Epidermis Model

Vehicle: None. The skin model was moistened with sterile water.

Remarks - Method: No significant deviations from the OECD guideline. The test substance was able to degrade MTT used to quantitate cell viability. To account for the MTT degradation by the test substance, a negative control using water-killed tissue was conducted in parallel. 5% Sodium dodecyl sulphate (SDS) was used as positive control. The exposure period was 15 mins and the post-exposure incubation duration was 42 hours.

RESULTS

Test material	*Mean OD_{562} of triplicate tissues*	*Relative mean Viability (%)*	*SD of relative mean viability*
Negative control	0.878	100	7.5
Test substance	0.363	41.4	12.4
Positive control	0.151	17.0	6.5

OD = optical density; SD = standard deviation

Remarks - Results: The relative mean viability of the test substance treated tissue was below the cut-off value (50%) for classification. Small interference (0.2% relative to the negative control) due to direct reduction of MMT occurred by the test substance. Therefore, the study authors decided not correct the values with results of water-killed tissue.

	The positive control gave satisfactory results and the optical density of the negative control was within the acceptable range confirming the validity of the assay.
CONCLUSION	The notified chemical was irritating to the skin under the conditions of the test.
TEST FACILITY	Harlan (2014g)

B.6. Irritation – eye (in vitro)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 437 Bovine Corneal Opacity and Permeability Test Method for Identifying i) Chemicals Inducing Serious Eye Damage and ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage (2013).
Vehicle	Saline (0.9% W/V sodium chloride solution)
Remarks - Method	No significant deviations from the OECD guideline. The notified chemical was tested at a dilution of 20% in saline solution. 20% imidazole prepared in saline was used as positive control. Scores ≤ 3 are indicative that classification under the GHS is not required. Scores ≥ 55 are indicative of classification as Cat 1 under GHS.

RESULTS

Test material	*Mean opacities of triplicate tissues*	*Mean permeabilities of triplicate tissues*	*IVIS*
Vehicle control	0.0	0.041	0.6
*Test substance**	32.3	1.474	54.4
*Positive control**	58.7	1.029	74.1

IVIS = in vitro irritancy score
*Corrected for background values

Remarks - Results	The controls gave satisfactory results confirming the validity of the test system. The IVIS score of 54.4 indicated eye irritation potential, but was below the score indicative of Cat 1 classification.
CONCLUSION	The notified chemical did not cause serious eye damage (Cat 1) under the conditions of the test. The test results did not rule out classification of the chemical as a Cat 2 eye irritant.
TEST FACILITY	Harlan (2014h)

B.7. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion (2012).
Species/Strain	Rabbit/New Zealand White Hsdlf:NZW
Number of Animals	2
Observation Period	21 days
Remarks - Method	No significant deviations from the OECD guideline. The test was carried out sequentially on two test animals. The study authors stated that addition of a third animal for testing would have not changed the study outcome and hence only two test animals were used. Systemic (0.01mg/kg buprenorphine) and local (0.5% tetracaine hydrochloride) analgesics were used in the study. An extra dose of systemic analgesic was repeated 8 hours after exposure.

RESULTS

Lesion	*Mean Score* Animal No.*		*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2			
Conjunctiva: redness	2	2	2	< 21 d	0
Conjunctiva: chemosis	2	2	2	< 21 d	0
Conjunctiva: discharge	2	2	2	< 14 d	0
Corneal opacity	1	1	1	< 14 d	0
Iridial inflammation	1	1	1	< 7 d	0

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

Remarks - Results: The test animals showed significant test substance related effects which were completely reversible by 21 d.

CONCLUSION: The notified chemical is severely irritating to the eye.

TEST FACILITY: Envigo (2016e)

B.8. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 429 Skin Sensitisation: Local Lymph Node Assay (2010).

Species/Strain: Mouse/CBA/CaOlaHsd

Vehicle: Acetone/olive oil 4:1

Preliminary study: Yes

Positive control: Conducted concurrently using α-hexylcinnamaldehyde

Remarks - Method: No significant deviations from the OECD guideline. A preliminary study using 50% test substance was conducted on one test animal. The test substance did not produce any systemic toxicity or excessive local irritation.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/animal)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5 F	4237.84 ± 1114.21	–
10	5 F	21334.34± 5429.23	5.03
25	5 F	33272.72 ± 5890.12	7.85
50	5 F	44736.97 ± 11878.78	10.56
Positive Control			
25	5 F	35924.10 ± 14452.18	8.48

EC3: 5.2 (estimated using NIES method, ICCVAM)

Remarks - Results: No signs of systemic toxicity were noted. Small amount of pale white residual test substance was seen post exposure on ears of test animals exposed to 50% test substance. The positive control gave satisfactory results demonstrating the sensitivity and reliability of the test system.

CONCLUSION: There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY: Harlan (2014i)

B.9. Skin sensitisation – human volunteers (0.25% notified chemical)

TEST SUBSTANCE: Notified chemical (0.25%) – 2 samples tested

METHOD: Repeated insult patch test with challenge (In-house method)

Study Design: Induction Procedure: 3.63 cm^2 patches containing 0.2 mL 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: 14 days Challenge Procedure: A patch was applied to a naïve site. Patches were removed after 24 h. Sites were graded 24, 48 and 72 h post-patch removal.
Study Group	87 F, 18 M; age range 18–70 years
Vehicle	Ethanol/Diethyl Phthalate 1:3
Remarks - Method	Occluded. 0.2 mL of the test substance was spread on a 3.63 cm^2 patch.

RESULTS

Remarks - Results	105/113 subjects completed the study. Eight subjects discontinued study participation for reasons unrelated to the test substance. No adverse responses were noted at induction and challenge phase, except that with the second sample, a slight irritation score was observed in one subject on two consecutive days of the induction period. No reaction was seen on subsequent days of the induction or challenge.

CONCLUSION	The test substance was non-sensitising under the conditions of the test.
TEST FACILITY	CRL (2015)

B.10. Skin sensitisation – human volunteers (1.25% notified chemical)

TEST SUBSTANCE	Notified chemical (1.25%) – 2 samples
METHOD	Repeated insult patch test with challenge
Study Design	Induction Procedure: 3.63 cm^2 patches containing 0.15 mL 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: 10-21 days Challenge Procedure: A patch was applied to a naïve site. Patches were removed after 24 h. Sites were graded 24, 48 and 72 h post-patch removal.
Study Group	88 F, 23 M; age range 18-70 years
Vehicle	Ethanol/Diethyl Phthalate 1:3
Remarks - Method	Occluded. 0.15 mL of the test substance was spread on a 3.63 cm^2 patch.

RESULTS

Remarks - Results	111/113 subjects completed the study. Two subjects discontinued study participation for reasons unrelated to the test substance. No adverse responses were noted in the induction phase. In the challenge phase, both samples induced erythema (one mild and one barely perceptible) in one subject at 96 h after challenge. The results table suggested that slight erythema was also observed at 72 h after challenge. Based on this result in one subject, a sensitisation response cannot be ruled out.

CONCLUSION	The sensitisation potential of the test substance was equivocal under the conditions of the test.
TEST FACILITY	CRL (2016)

B.11. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (1996).
Species/Strain	Rat/RccHan™:WIST

Route of Administration	Oral –diet
Exposure Information	Total exposure days: 43-44 days (males) & day 5 post-partum (females) Dose regimen: 7 days per week
Vehicle	None
Remarks - Method	No significant deviations from the OECD guideline. The test substance was tested for stability and uniformity in distribution in the prepared diet and was found to be stable at room temperature for up to 22 days at 15000 parts per million (ppm) and the mean dietary concentrations within 94 to 100% of the nominal concentrations.

RESULTS

Group	*Number and Sex of Animals*	*Dietary Concentration (ppm)*	*Mean Achieved Dose (mg/kg bw/day)*			*Mortality*
			Male	Female		
				Pre-Pairing	Gestation	
control	12 F & 12M	0	0	0	0	0/24
low dose	12 F & 12M	750	42.4	56.1	56.6	0/24
mid dose	12 F & 12M	2500	138.0	162.9	192.3	0/24
high dose	12 F & 12M	7500	412.8	463.0	546.0	0/24

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

No test substance related clinical signs were reported.

One female rat from control group had a wound on the right side of the neck on days 16 and 17 during the mating period and scab between days 18 and 30. This was considered to be a physical injury that might have occurred during mating.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Male rats from mid and high dose groups showed statistically significant increases in total leukocyte count and neutrophil count and a statistically significant reduction in haemoglobin. Males and females from high dose group also showed a statistically significant increase in activated partial thromboplastin time.

Female rats from high dose group showed statistically significant increase in bilirubin and chloride concentration. Males from the high dose group showed statistically significant reduction in creatinine.

According to the study authors, the majority of the individual values were within the normal background range for the above parameters and in the absence of any associated histopathology correlates or a true dose related response, the intergroup differences were considered of no toxicological importance.

Effects in Organs

One female from control, four females from low dose and one male and two females from high dose had reddened lungs. In the absence of any associated treatment-related histopathological changes and the fact that one control animal showed the effect, the effect was considered to be not treatment related by the study authors.

Male rats from mid and high dose groups showed statistically significant increase in absolute and organ to body (relative) kidney weights. The increased kidney weights correlated with hyaline droplets seen microscopically in the treated animals. The effects were considered to be test substance related by the study authors.

Females from mid and high dose showed a statistically significant increase in absolute and relative uterus weight. Females from mid dose showed a statistically significant reduction in absolute and relative brain weight. Females from low dose showed a statistically significant increase in absolute and relative spleen weight. Males from high dose showed a statistically significant reduction in absolute and relative seminal vesicle weight. Males treated from mid dose showed a statistically significant increase in absolute and relative pituitary weight. According to the authors, the majority of the individual values were within normal ranges for rats of the strain and age used and in the absence of any associated histopathological correlates or a true dose related response, the weight changes were considered not to be of toxicological significance.

Treatment related histopathological changes were noted in test animals from various groups. Hyaline droplets in kidneys were evident in males from all treatment groups. Hyperkeratosis in oesophagus and acanthosis and hyperkeratosis in stomach was seen in rats from high dose group.

Functional Observations

There were no treatment related changes in the behavioural parameters, functional performance and sensory reactivity.

Test animals from high dose group showed statistically significant increase in forelimb grip strength when compared to control. No other associated changes to suggest neurotoxic effects were noted and thus the differences were considered not to be toxicologically significant.

Food Consumption and Body Weight Changes

Male rat from low and high dose groups showed a statistically significant reduction in body weight gain during the first week of treatment. Body weight gain for males from low dose group was similar to controls thereafter. Initial recovery was evident for males from high dose group however; body weight gains during Week 4 was lower than controls, and attained statistical significance. Overall body weight gain for males from high dose group was lower than controls.

Body weight gain for females from high dose group was lower than controls during the first week of treatment and throughout gestation and lactation. Cumulative body weight gain during gestation was statistically significantly lower than controls at this dietary concentration and statistically significantly lower absolute body weights from Day 7 of gestation through to Day 4 of lactation was evident.
Reduced food consumption was noted both for male and female rats from high dose group at various stages. The reduction did not reach statistical significance. Reduced food conversion efficiency was evident in animals from high dose group when compared to controls.

Reproductive and Developmental Parameters

Oestrous cycle assessment

No treatment related effects on female oestrous cycles was observed. Two females from low dose, one female treated mid dose and one female from high dose showed extended di-oestrus during the pre-pairing phase. All of these females showed positive evidence of mating however one of the low dose group females and the female from mid dose group were non-pregnant. In the absence of a true dose related response or an effect on mating or fertility, the intergroup differences were considered to be incidental by the study author.

Mating, fertility and gestational length

No treatment related effects on mating, fertility and length of gestation were noted in any of the test animal groups.

Litter responses

In total all females from the control group and eleven females from various treated groups gave birth to a live litter and successfully reared young to Day 5 of age. One female from the high dose gave birth to a litter that had one live offspring, but had a total litter loss prior to Day 5 post-partum. In another high dose litter, one of the offspring was found at necropsy (Day 5 post-partum) to be small and weak with no milk in stomach.

No significant differences were detected for corpora lutea, implantation counts or implantation losses for treated animals when compared to controls.

Offspring litter size and weight

A slight reduction in litter size was evident in females from high dose group; however offspring survival to day 5 post-partum was considered unaffected by treatment. A slight reduction in offspring viability was evident at high dose however this was considered to be the result of one litter which lost one offspring between day 1 and day 4 post-partum. This was considered to be not treatment-related by the study author due to it being not uncommon. No such effects were detected in low and mid dose groups.

One female from high dose group had a total litter loss on day 3 post-partum. This female only had one live offspring in the litter and had a slightly longer parturition length of 23 and half days which according to the study author may have compromised offspring post-natal survival. In the absence of an effect on offspring survival in the remaining litters at this dose group, this total litter loss was considered unrelated to treatment by the study authors.

Lower litter weights were noted in females from high dose group which reached statistical significance at day 4. This was considered to be due to the marginally lower litter size by the study authors. Statistical analysis of surface righting reflex data did not reveal any significant differences among different groups. No obvious clinical signs of toxicity were detected for offspring from treated females when compared to controls. Some incidental clinical signs detected consisting of small size, weak, no milk in stomach, missing and found dead were considered to be low incidence findings observed in offspring in studies of this type and were considered unrelated to test item toxicity by the study authors.

Remarks – Results
Test substance related changes in the kidney and body weight were seen in animals from high dose group.

Reduction in the body weight gain and food consumption was attributed to the local irritation effects by the study authors and was supported by the evident changes in the gastro-intestinal tract; hyperkeratosis and acanthosis in stomach and hyperkeratosis in oesophagus.

The presence of hyaline droplets in the kidneys of male rats from all treatment groups was considered to be not toxicologically relevant by the study authors due its unique nature in male rats only and therefor of limited toxicological significance to humans. Therefore uncertainty remains as to whether the changes in kidney weights are related to the occurrence of hyaline droplets.

CONCLUSION
The parental No Observed Adverse Effect Level (NOAEL) was established as 138 mg/kg bw/day for males and 162.9 mg/kg bw/day for females in this study, based on the adverse effects observed in the gastro-intestinal tract in male and female rats at the highest dose.

The No Observed Effect Level (NOEL) for reproductive/developmental toxicity was established as 162.9 mg/kg bw/day in this study, based on the lower litter weights seen at the highest dose.

TEST FACILITY Envigo (2015)

B.12. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test (1997).
Plate incorporation procedure/Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98 and TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9-fraction from Phenobarbitone/β-Naphthoflavone induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 1.5–5,000 µg/plate b) Without metabolic activation: 1.5–5,000 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	No significant deviations from the OECD guideline. Test 1 was plate incorporation and test 2 was pre-incubation test.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	≥ 500	≥ 5000	Negative
Test 2	≥ 500	≥ 5000	Negative
Present			
Test 1	≥ 500	≥ 5000	Negative
Test 2	≥ 500	≥ 5000	Negative

Remarks - Results The positive controls gave satisfactory results confirming the validity and integrity of the test system and S9-mix.

CONCLUSION The notified chemical was not mutagenic to bacteria under the conditions

of the test.

TEST FACILITY Harlan (2014j)

B.13. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain *Human*
Cell Type/Cell Line lymphocytes
Metabolic Activation System S9-fraction from Phenobarbitone/β-Naphthoflavone induced rat liver.
Vehicle Dimethyl sulphoxide
Remarks - Method No significant deviations from the OECD guideline. 2% S9 mix was used in test 1 and 1% S9 mix in test 2. Dosages were chosen on the basis of a preliminary test.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	23.13, 46.25, 92.5*, 185*, 370*, 555	4	24
Test 2	5.78, 11.56*, 23.13*, 46.25*, 92.5*, 185, 370	24	24
Present			
Test 1	11.56, 23.13*, 46.25, 92.5*, 185*, 370	4	24
Test 2	11.56*, 23.13, 46.25*, 92.5, 185*, 370	4	24

*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				
Test 1	> 370	> 370	> 555	Negative
Test 2	> 185	≥ 92.5	> 370	Negative
Present				
Test 1	> 185	≥ 185	> 370	Negative
Test 2	-	≥46.25	> 370	Negative

Remarks - Results The positive controls gave satisfactory results confirming the validity and integrity of the test system and S9-mix.
The test substance induced modest but statistically significant increase in the frequency of cells with chromosome aberrations at the highest concentration tested, in cells exposed to S9-mix and cells exposed to test substance for 24 hours (test 2) without S9-mix. The increase was not considered to be toxicologically significant by the study authors due the large decrease in mitotic index seen at these concentrations under most of the test conditions, suggesting the test substance to be toxic at these concentrations. The incidence of chromosome aberrations was only slightly higher than the historical controls. In addition, the negative control values in this study were at the low end of the historical controls, increasing the likelihood of a statistically significant increase.

CONCLUSION The notified chemical was not clastogenic to cultured human lymphocytes treated *in vitro* under the conditions of the test.

TEST FACILITY Harlan (2014k)

B.14. Phototoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 432 In Vitro 3T3 Neutral Red Uptake Phototoxicity Test (2004).

Cell Line BALB/c 3T3 C3

Vehicle Dimethyl sulphoxide

Positive control Chlorpromazine

Range finding test A range finding test was performed to determine the acceptable concentrations for the confirmatory test. The highest test concentration was 1000 µg/mL with serial dilution with factor of 2 up to lowest test concentration of 7.813 µg/mL.

Confirmatory test Based on the results of the range finding test, a confirmatory test was conducted using the following test substance concentrations:

Without irradiation: 6.25, 12.5, 25, 37.5, 50, 75, 100, 200 µg/mL

With irradiation: 0.125, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0 µg/mL

The test substance was irradiated with artificial sunlight for 50 minutes with 1.5 to 1.65 mW/cm^2 UVA, resulting in an irradiation dose of ~ 5 J/cm^2 UVA. The test substance without irradiation was kept in dark.

Remarks - Method No significant deviations from the OECD guideline.

RESULTS

Test type	*Test material*	*ED_{50} (+UV) µg/mL*	*ED_{50} (-UV) µg/mL*	*Photo Irritant Factor*	*Mean Phototoxic Effect*	*%Viability**
Preliminary	Test substance	369.3	493.8	1.34	-0.007	97.5
	Positive control	0.15	10.69	70.67	0.723	93.1
Confirmatory	Test substance	407.6	680.9	1.67	0.008	100.6
	Positive control	0.17	22.11	133.8	0.764	101.5

ED_{50} = effective dose where only 50% of cells survived

'*' = viability of solvent control of irradiated versus non irradiated plate

Remarks - Results The photo irritant factor was 1.34 and 1.67 in preliminary and confirmatory test respectively. The results suggest the test substance did not have phototoxic effects under the test conditions.

The mean of solvent control values of the irradiated group versus the non irradiated group met the acceptance criteria.

The positive control induced phototoxicity in the expected range after irradiation with artificial sunlight.

The above results confirmed the validity and integrity of the test system.

CONCLUSION The test substance is not considered to have phototoxic potential in In Vitro 3T3 Neutral Red Uptake Phototoxicity Test.

TEST FACILITY Harlan CCR (2014)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.

Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Amount of Carbon dioxide ($ThCO_2$)
Remarks - Method	Conducted in accordance with the test guidelines above, and in compliance with GLP standards and principles. Nominal concentration of the test solution was 13.7 mg/L based on the calculation of 10 mg Carbon/L. The Actual concentration of the test solution was found to be 8.66 mg Carbon/L.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
8	0	8	62
14	1	14	78
21	10	21	79
28	13	28	79
29	10	29	88

Remarks - Results: Validity criteria for the test are satisfied.

Toxicity control was conducted in parallel and found to be 41% biodegradable after 14 days and 49% biodegradable after 28 days which indicates non-inhibitory nature of the test substance (greater than 25%, OECD).

The percentage degradation of the reference compound (sodium benzoate) surpassed the threshold level of 60% after 8 days (62%). Therefore, the tests indicate the suitability of the inoculum. After 28 days the test substance was degraded only by 13%. Therefore, the test substance is not considered to be readily biodegradable according to the OECD (301 B) guideline.

According to the OECD Test guideline on 29th day an additional CO_2 measurement was carried out after acidification of the 28 days sample to further account presence of any dissolved CO_2.

CONCLUSION: The notified chemical is not readily biodegradable

TEST FACILITY: Harlan (2014l)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD OECD TG 203 Fish, Acute Toxicity Test –semi static.
Species Zebrafish (*Brachydanio rerio*)
Exposure Period 96 hours
Auxiliary Solvent None
Water Hardness 80 mg $CaCO_3$/L
Analytical Monitoring GC-MS
Remarks – Method The test was conducted according to the above test guideline without significant deviation from the protocol.

RESULTS

Concentration mg/L					*Number of Fish*	*Mortality*			
Nominal	*Actual*					*24 h*	*48 h*	*72 h*	*96 h*
	24 h	*48 h*	*72 h*	*96 h*					
Blank-Control					10	0	0	0	0
6.0	ND	5.69	ND	4.93	10	0	0	0	1
7.2	ND	6.95	ND	6.08	10	0	0	1	1
8.6	ND	8.03	ND	7.26	10	0	0	4	7
10.3	ND	8.91	ND	9.02	10	1	1	5	7
12.4	ND	11.05	ND	10.82	10	8	9	10	10
14.9	ND	12.47	ND	ND	10	10	10	10	10

LC50 8.43 mg/L at 96 hours (95% confidence limit: 7.59 – 9.31 mg/L)
NOEC NA
Remarks – Results All the validity criteria were satisfied.

No fish showed any abnormal behaviour (including mortality) in the control group.

Initial 10.0% mortality was observed at 96h with nominal concentration of 6.0 mg/L and 100% mortality was observed with nominal concentration of 12.4 mg/L at 72 h.

The deviation from nominal to actual test concentration is within the limit of ±20%. Therefore, results are reported based on Nominal concentration.

CONCLUSION The notified chemical is toxic to fish

TEST FACILITY SXZD (2014)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test –Static.
Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent None
Water Hardness 250 mg $CaCO_3$/L
Analytical Monitoring HPLC/UV
Remarks - Method The test was conducted according to the above test guideline without significant deviation from the protocol.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Blank-Control	-	20	0	0
1.0	ND	20	0	0

1.8	ND	20	0	0
3.2	2.82	20	0	0
5.6	5.18	20	9	10
10.0	9.09	20	14	20

EC50	5.6 mg/L at 48 hours (95% confidence limit: 5.0 – 6.4 mg/L)
NOEC	3.2 mg/L
Remarks - Results	All validity criteria were satisfied. As the measured concentration of the test solution at 0 and 48 h satisfactorily maintained within ± 20%, final results were calculated based on nominal concentration. Up to the nominal concentration of 3.2 mg/L no mortality was observed, while 100% mortality was observed at 48 h with 10 mg/L of nominal concentration.
CONCLUSION	The notified chemical is toxic to aquatic invertebrate
TEST FACILITY	Harlan (2014m)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Freshwater Alga and Cyanobacteria, Growth Inhibition Test- static.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 1.0, 3.2, 10.0, 32.0 and 100 mg/L Actual (72h): 0.92, 2.93, 9.88, 32.4 and 98.9 mg/L
Auxiliary Solvent	None
Water Hardness	Not available
Analytical Monitoring	HPLC/UV
Remarks - Method	The test was conducted according to the above test guideline without significant deviation from the protocol.

RESULTS

Biomass		*Growth*	
EC50 *mg/L at 72 h*	*NOEC* *mg/L*	*EC50* *mg/L at 72 h*	*NOEC* *mg/L*
4.90	1.0	11	3.2

Remarks - Results	All validity criteria were satisfied. The deviation from nominal to actual test concentration is below ±20% (range from 91-104%). Therefore, final result was calculated using the nominal concentration.
CONCLUSION	The notified chemicals is toxic to algae
TEST FACILITY	Harlan (2014n)

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