File No: LTD/1890

August 2016

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Bamboo Ketone

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.

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/1890	Takasago International (Singapore) Pte Ltd	Bamboo Ketone	ND*	≤1 tonne/s per annum	Fragrance Ingredient

*Not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Human health risk assessment
Under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

Based on the available information, when used for the proposed uses and concentrations, 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 assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

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

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

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

- A copy of the (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 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 of the notified chemical exceeds one tonne per annum;
- the concentration of the notified chemical exceeds or is intended to exceed 0.01% in final consumer products.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a fragrance ingredient, or is likely to change 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 products 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(S)
Takasago International (Singapore) Pte Ltd (ABN: 29 099 666 832)
Level 5
815 Pacific Highway
CHATSWOOD NSW 2067

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, use details, manufacture/import volume, site of manufacture/reformulation and identity of manufacturer/recipients.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
US TSCA (2004)
ELINCS (2005)
FEMA GRAS (2003)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Bamboo Ketone

MOLECULAR WEIGHT
<500 Da

3. COMPOSITION

DEGREE OF PURITY
100%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
No known impurities.

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Colourless to yellow liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	Not determined	Attempted but there was no clear change of temperature related to freezing point.
Boiling Point	231.35–243.25 °C at 101.3 kPa	Measured
Density	923.6 kg/m^3 at 20 °C	Measured

Vapour Pressure	1.1 kPa at 20 °C	Measured
Water Solubility	1.4 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Half-life time (25 °C) pH 7: 12,000 hours pH 9: 390 hours	Measured
Partition Coefficient (n-octanol/water)	log Pow = 2.37 at 20 °C	Measured
Adsorption/Desorption	log K_{oc} = 1.10	Calculated (using KOCWIN v2.00; US EPA, 2009)
Dissociation Constant	pKa = 5.13	Measured
Flash Point	99 ± 2 °C at 101.3 kPa	Measured
Flammability	Not determined	Predicted to be non-flammable.
Autoignition Temperature	275 °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.

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. The notified chemical will be imported as a component of either a finished product (≤0.01% concentration) or a fragrance mixture (≤1% concentration).

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
The notified chemical will be imported to various ports around Australia.

IDENTITY OF MANUFACTURER/RECIPIENTS
A number of importers located in Australia.

TRANSPORTATION AND PACKAGING
The notified chemical will be transported by road within Australia in 1 L aluminium cans (fragrance mixture) or different types of end-use containers (usually plastic).

USE
The notified chemical will be imported as a component of either a finished product or a fragrance mixture. The fragrance mixtures will be reformulated in Australia to produce the final cosmetic products (including fine fragrances and personal cleaning), household and laundry products. Typically, end products will contain the notified chemical at ≤0.01% concentration whereas the maximum concentration of the notified chemical in imported fragrance mixture will be 1%.

OPERATION DESCRIPTION
Where reformulation occurs in Australia, at the customer facilities, the procedures for incorporating the imported preparations containing the notified chemical into end-use products will likely vary depending on the type of product formulated, and may involve both automated and manual transfer steps. However, in general, the blending process will likely be highly automated and will occur in a fully enclosed environment. This will be

followed by automatic filling of the finished products into containers of various sizes which will be distributed to retail outlets.

Household products
Household products containing the notified chemical at ≤0.01% concentration may be used by consumers and professional cleaners. The products may be used in either closed systems with episodes of controlled exposure, for example automatic washing machines or open processes, and manually applied by rolling, brushing, spraying and dipping, using a cloth, sponge, mop or brush followed by wiping. The house hold products can be diluted with water prior to application.

Cosmetic products
The finished cosmetic products containing the notified chemical at ≤0.01% concentration will be used by consumers and beauticians. Depending on the nature of the product, application of products could be by hand, sprayed or through the use of an applicator.

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 storage	1–2	50
Mixers	Up to 8	240
QC Samplers	0.5	240
Cleaners/maintenance	Up to 8	240
End users (professionals)	1–8	200

EXPOSURE DETAILS
Transport and storage
Transport and storage workers may come into contact with the notified chemical as a component of the imported fragrance preparations at ≤ 1% concentration or end-use products at ≤0.01% concentration, only in the event of accidental rupture of containers.

At the notifier and importer facility, the primary work activity undertaken by transport and warehouse workers will include the handling, loading and off-loading of 1 L aluminium cans containing the notified chemical at ≤ 1% concentration. Exposures of these workers will be limited to situations where packaging is accidentally breached. If such an event occurs, workers may be exposed through dermal, ocular or perhaps inhalation exposure.

Formulation of end products
During reformulation, dermal, ocular and perhaps inhalation exposure of workers to the notified chemical at ≤ 1% concentration may occur during weighing and transfer stages, blending, quality control analysis and cleaning and maintenance of equipment. The notifier states that exposure is expected to be minimised through the use of mechanical ventilation and/or enclosed systems, and through the use of PPE such as protective clothing, eye protection and suitable gloves.

Beauty care and cleaning professionals
Exposure to the notified chemical in end-use products may occur in professions where the services provided involve the application of cosmetic products (at ≤0.01% concentration) to clients or the use of household products (at ≤0.01% concentration) in the cleaning industry. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible. Such professionals may use some PPE to minimise repeated exposure and good hygiene practices are expected to be in place. If PPE is used, exposure of such workers is expected to be of a similar or less 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 through the use of the cosmetic and household products at ≤0.01% concentration. The principal route of exposure will be dermal, while ocular and inhalation exposure is also possible, particularly if products are applied by spray.

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	LD50 > 2,500 mg/kg bw; low toxicity
Guinea pig, skin irritation	non-irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation (up to 30% concentration)
Guinea pig, phototoxicity test	no evidence of sensitisation (up to 30% concentration)
Mutagenicity – bacterial reverse mutation	non mutagenic
Human, patch test	non-irritating

Toxicokinetics, metabolism and distribution

Based on the low molecular weight (<500 Da), water solubility (1.4 g/L) and measured partition coefficient (log Pow = 2.37) of the notified chemical, dermal absorption and passive diffusion across the gastrointestinal (GI) tract are expected to occur. The notified chemical may also be absorbed across the respiratory tract.

Acute toxicity

The notified chemical is of low acute toxicity by oral and dermal routes.

Irritation and sensitisation

Based on an animal study, the notified chemical is a moderate skin irritant at 10% concentration following a single 24 h exposure (which is significantly longer than the 4 h exposure recommended by the test guideline), but not at 100% or 1% concentration. In a non-OECD guideline cumulative dermal irritation study, the notified chemical was weakly irritating at 100% concentration but not at 10% concentration.

The notified chemical was not phototoxic to the skin in a non-OECD guideline study. The notified chemical was not a skin sensitiser in a Guinea pig maximisation test; however, there was a significant deviation in the study method as only half the recommended number of animals was used.

Genotoxicity

The notified chemical was negative in a bacterial reverse mutation test and not expected to be genotoxic.

Observations on human exposure

The notified chemical did not induce any dermal irritation at 2.5% and 5% concentration in human patch test following a single exposure.

Health hazard classification

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

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the available information, the notified chemical has the potential for skin and eye irritation at 10% concentration following prolonged exposure. At the proposed concentration in the workplace (<1%) the notified chemical is not expected to be a skin irritant or a skin sensitiser.

Workers may experience dermal, ocular and inhalation exposure to the notified chemical (at ≤ 1% concentration) during reformulation processes, including during transfers of the chemical, sampling and quality control processes, cleaning and/or maintenance of the equipment.

Control measures such as the use of enclosed automated processes and PPE (safety glasses with shields, gloves, apron or coverall), and adequate ventilation are expected to be used in place to minimise worker exposure during formulation processes. Therefore, the risk to workers from transport/storage and reformulation of the notified chemical is not considered to be unreasonable.

End-use
Professional cleaners (household cleaning and laundry products) and beauty salon workers (cosmetic and perfumes) may be exposed to the notified chemical.

Such professionals may use PPE to minimise repeated exposure, and good hygiene practices are expected to be in place. The risk to such workers is expected to be of a similar or lesser extent than that experienced by consumers who regularly use the various cosmetic products containing the notified chemical.

6.3.2. Public Health
Cosmetic and household cleaning products containing the notified chemical at ≤ 0.01% concentration will be available to the public. The main route of exposure is expected to be dermal with some potential for accidental ocular or oral exposure. At the proposed concentration in final consumer products (<0.01%) the notified chemical is not expected to be a skin irritant or a skin sensitiser.

Based on the assessed use pattern and available data, the notified chemical is not considered to pose an unreasonable risk to public health.

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, so there will be no environmental release associated with this activity. The notified chemical will be imported into Australia at 1% concentration, in the form of fragrance preparations for further reformulation into end-use cosmetic and household products or as a component of end-use products (at ≤0.1% concentration). Environmental release of the notified chemical during transportation and storage will be limited to accidental spills or leaks of drums, which is expected to be minimal.

A typical blending operation will be highly automated in a fully enclosed/contained environment. Potential sources of release include spills, equipment washing, and container residues. A total of 0.1% of waste may be generated as a result of spills. It is expected that equipment will be cleaned using water that will be reused for subsequent operations. The average amount of residue in empty containers is estimated to be up to 0.5%. Therefore a total of 0.5% waste will be generated each year from reformulation processes.

RELEASE OF CHEMICAL FROM USE
The notified chemical will enter the aquatic compartment during use of the various products into which it will be incorporated. Cosmetic products are expected to be washed off the hair and skin and will enter the aquatic environment diluted in water. Cleaning products will also be diluted in water and will enter the aquatic environment. It is anticipated that the majority of the notified chemical released will enter into sewer systems.

It is estimated that a maximum of 0.3% of the consumer products may remain in the consumer containers that will be sent for disposal.

RELEASE OF CHEMICAL FROM DISPOSAL
Empty containers containing the notified chemical at blending facilities will be recycled or disposed of through an approved waste management facility. Empty product containers are expected to be disposed of to landfill.

7.1.2. Environmental Fate
Following its use in Australia, the majority of the notified chemical is expected to enter the sewer system before potential release to surface waters on a nationwide basis. Biodegradability, persistence and bioaccumulation of the notified chemical were estimated using QSAR (2014). The notified chemical is expected to be readily biodegradable based on the calculated data. The notified chemical is not expected to undergo hydrolysis. Based on its low adsorption coefficient value (log K_{oc} = 1.10), only limited partitioning to sludge is expected. The notified chemical has low potential to bioaccumulate based on its low partition coefficient (log P_{ow} = 2.37). In

surface waters, the notified chemical is expected to disperse and 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 13.104 hours based on reactions with hydroxyl radicals (AOPWIN v1.92; US EPA, 2011). Therefore, in the event of release to atmosphere, the notified chemical is not expected to persist in the atmospheric compartment.

A proportion of notified chemical may be applied to land when effluent is used for irrigation, or disposed of to landfill as waste. Notified chemical residues in landfill and soils are expected to have low mobility based on its low soil adsorption coefficient. In the aquatic and soil compartments, the notified chemical is expected to slowly degrade through biotic and abiotic processes to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

The calculation for the predicted environmental concentration (PEC) is summarised in the table below assuming that 100% of the notified chemical will be released to sewer on a nationwide basis over 365 days per year. The measured log Kow value of 2.37 was used which resulted in 97% mitigation during STP process.

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	97%	**Mitigation**
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.02	µg/L
PEC - Ocean:	0.00	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 0.024 µg/L may potentially result in a soil concentration of approximately 0.1615 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 0.12 µg/kg and 1.615 µg/kg, respectively.

7.2. Environmental Effects Assessment

No ecotoxicity data were submitted. As there is the potential for high aquatic exposure from the use and disposal of the notified chemical, modelled estimates for ecotoxicological endpoints for the notified chemical were calculated using ECOSAR using neutral organic QSAR. The endpoints are tabulated below.

Endpoint	Result	Assessment Conclusion
Fish (96 h)	LC50 = 10.66 mg/L	Harmful to fish
Daphnia (48 h)	EC50 = 4.26 mg/L	Toxic to aquatic invertebrates
	ChV = 0.16 mg/L	Harmful to aquatic invertebrates with long lasting effects
Algal (96 h)	ChV = 0.26 mg/L	Harmful to algae with long lasting effects

The modelled endpoints used here were derived from the ECOSAR, using a class that was the best fit for the notified chemical, and are considered useful to provide a general indication of potential environmental effects for the notified chemical. However, modelled endpoints are not considered sufficient to formally classify the acute hazard of the notified chemical under the Globally Harmonised System for the Classification and Labelling of Chemicals (United Nations, 2009).

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) has been calculated from the chronic daphnia toxicity of the notified chemical. A more conservative assessment factor of 1,000 is used, as these endpoints are modelled estimates from QSAR.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
NOEC (Invertebrates)	0.17	mg/L
Assessment Factor	1,000	
PNEC:	0.17	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) has been calculated for a worst case discharge scenario based on the predicted PEC and PNEC.

Risk Assessment	***PEC µg/L***	***PNEC µg/L***	***Q***
Q - River:	0.02	0.166	0.146
Q - Ocean:	0.00	0.166	0.015

The risk quotient for discharge of treated effluents containing the notified chemical to the aquatic environment (Q < 1) indicates that the notified chemical is unlikely to reach ecotoxicologically significant concentrations in surface waters based on its maximum annual importation quantity. The notified chemical is calculated to be biodegradable and due to its solubility in water and low partition coefficient the notified chemical is expected to have a low potential for bioaccumulation. On the basis of the PEC/PNEC ratio, low import volume and assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the aquatic environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Boiling Point 231.35 °C at 101.3 kPa

Method OECD TG 103 Boiling Point.
Remarks The distillation method was used. The test result is mean value of initial boiling point from 2 independent tests. Initial boiling point and Dry point was measured and results are expressed as a range (230.88 °C to 243.6 °C).
Test Facility SCAS (2014c)

Density 923.6 kg/m^3 at 20.0 °C

Remarks The density was determined using a gas comparison pycnometer. The test result is mean value of 2 independent tests.
Test Facility SCAS (2014c)

Vapour Pressure 1.1 Pa at 25 °C (or 20 °C)

Method OECD TG 104 Vapour Pressure.
Remarks Static Method
Test Facility SCAS (2014a)

Water Solubility 1.4 g/L at 20 °C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Flask Method
Test Facility SCAS (2014a)

Hydrolysis as a Function of pH Half-life time (25 °C) pH 7: 12,000 hours pH 9: 390 hours

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*Temperature (°C)*	*$t_{½}$ hours*
7	25	12,000
9	25	390

Remarks Test was done for Tier I and Tier II for preliminary test and hydrolysis of unstable substances respectively.
Test Facility SCAS (2014b)

Partition Coefficient (n-octanol/water) log Pow = 2.37 at 20 °C

Method OECD TG 117 Partition Coefficient (n-octanol/water).
EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks HPLC Method. The test samples were dissolved in 70% methanol at nominal concentration of 0.1 w/v %.
Test Facility Takasago (2014)

Dissociation Constant pKa = 5.13

Method OECD TG 112 Dissociation Constants in Water.
Remarks The titration method was used because the material was soluble in water at 1 g/L. The dissociation constant of the test substance was determined to be pKa = 5.13 by titration with 0.1N NaOH at 20 °C.
Test Facility Takasago (2015)

Flash Point 99 ± 2 °C at 101.3 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Closed cup equilibrium
Test Facility	SafePharm Laboratories (2003a)

Autoignition Temperature 275 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility	WIL Research (2014)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
- Species/Strain: Rat/Sprague-Dawley CD (Crl: CD® (SD) IGS BR)
- Vehicle: None
- Remarks - Method: A total of six test animals divided into two groups were administered a single 2,000 mg/kg oral dose of test substance and were observed for acute toxicity for 14 days. Dosing was performed through gavage. At the end of the observation period all animals were sacrificed by cervical dislocation and subjected to macroscopic necroscopy examination.
  GLP Certificate.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3F	2,000	none
2	3F	2,000	none

- LD50: >2,000 mg/kg bw
- Signs of Toxicity: No evidence
- Effects in Organs: No effect
- Remarks - Results: No deaths were observed during the study period. The following signs of systemic toxicity were observed in all animals: hunched posture, ataxia, lethargy, decreased respiratory rate and laboured respiration. Piloerection was noted in three animals. Loss of righting reflex was noted in one animal. The animals recovered one day after the dosing. All animals showed expected gains in the bodyweight over the study period and no abnormalities were noted at necroscopy.

CONCLUSION: The notified chemical if of low acute toxicity by the oral route.

TEST FACILITY: SafePharm Laboratories (2003)

B.2. Irritation – skin (acute)

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 404 Acute Dermal Irritation/Corrosion
- Species/Strain: White guinea pig (Hartley strain/albino)
- Number of Animals: 3F/group (4 groups)
- Vehicle: Petrolatum
- Observation Period: 48 hours
- Type of Dressing: Semi-occlusive
- Remarks - Method: The study use guinea pig instead of white rabbit (the preferred test species), which is a deviation from OECD guidelines. No justification for the guideline deviation was provided in the report. The 48 hours exposure period was significantly longer than the recommended 4 hours contact period with the chemical.

  A single dose of the notified chemical (at 100%, 10%, 1% and 0%) was applied to closely-clipped skin of one flank of the guinea pig and then the treatment area was covered with semi-occlusive patch for 48 hours. Each application site was examined for evidence of primary irritation and scored at 48 and 72 hours after application. Animals were observed for erythema, oedema formation and desquamation.

RESULTS	The notified chemical at 10% concentration was found to be a moderate irritant. At 100% and 1% concentration the chemical induced mild irritation. The negative control (petrolatum) also produced mild irritation.
Remarks - Results	At 10% concentration, well-defined erythema was noted to one treated skin site and slight erythema was noted in two skin sites one hour after patch removal (i.e. 49 hour). Slight erythema was noted in 2/3 treated skin at 72 hour. At 10% and 1% concentration, very slight erythema was noted in all animals at 49 hour and in one animal at 72 hour.
CONCLUSION	The notified chemical is moderately irritating to the guinea pig skin at 10% concentration.
TEST FACILITY	Takasago (2006a)

B.3. Irritation – skin (cumulative)

TEST SUBSTANCE	Notified chemical
Method	Guide to Quasi-drug and Cosmetic Regulations in Japan (2001)
SPECIES/STRAIN	White guinea pig (Hartley strain/albino)
Number of Animals	3F/group (2 groups)
Vehicle	Ethanol
Observation Period	48 hours
Type of Dressing	Topical application (open)
Remarks - Method	Cumulative skin irritation refers to dermal reactions induced by repeated contact of a test substance with skin. The protocol for this experiment is similar to acute skin irritation test. Instead of a single dose, the test animals are exposed to the notified chemical at 100% and 10% concentration, topically (open) once a day for two weeks (5 days a week). The animals are observed and scored during the treatment period for erythema, oedema and desquamation. The score of erythema, oedema and desquamation was added up and divided by 3 to give the value of irritancy. This irritancy value was divided by the number of observation days to give the index of irritancy. The test item was classified into non/weak, moderate or strong irritant according to the irritancy index.
Remarks - Results	At 100% concentration, all animals in the treatment group showed slight erythema sporadically from day-3 to -14. At day-14 slight erythema and desquamation were noted in 1/3 animal and well-defined desquamation was noted in 1/3 animal. Cumulative irritancy index of this treatment group was 0.7 which was classified as weak irritant. No skin irritation was observed in any test animal of 10% concentration treatment group.
CONCLUSION	The notified chemical is a weak irritant to guinea pig skin at 100% concentration.
TEST FACILITY	Takasago (2006a)

B.4. Phototoxicity

TEST SUBSTANCE	Notified chemical
METHOD	Guide to Quasi-drug and Cosmetic Regulations in Japan (2001)
Species/Strain	White guinea pig (Hartley strain/albino)

Number of Animals	3
Vehicle	Ethanol
Dose Concentration	30%, 10% and 3%
UV Source	320–400 nm UV with five lamps.
Irradiation Dose	UV energy: 14.1 Joule/cm^2 on the skin; 10 cm from the radiation source and irradiated for 60 minutes.
Remarks - Method	Skin phototoxicity refers to reactions such as erythema, oedema and desquamation induced by an activated (by photo-excision) chemical. This test is conducted to predict the severity of skin reactions caused by Ultra-Violet (UV) irradiation (sunlight) after single application of a test item to skin. A single dose of the notified chemical at 30%, 10% and 3% concentration was applied to closely-clipped dorsal skin of one flank of the guinea pig and then the treatment area was exposed to UV light source. Each application site was examined for evidence of erythema and oedema; and scored at 24, 48 and 72 hours after application.
RESULTS	No skin reaction was observed in any test animal.
Remarks - Results	The positive control for this experiment (8-methoxypsoralen) induced severe skin reaction which validates the test result.
CONCLUSION	The notified chemical is not phototoxic to guinea pig skin under the conditions of the test.
TEST FACILITY	Takasago (2006a)

B.5. Skin sensitisation

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 406 Skin Sensitisation - Guinea Pig Maximisation Test
Species/Strain	White guinea pig (Hartley strain/albino)
MAIN STUDY	
Number of Animals	Test Group: 5 Control Group: 5
Positive control	In parallel with the test substance.
INDUCTION PHASE	Induction Concentration: intradermal: notified chemical 30% w/v in paraffin oil topical: sodium lauryl sulfate 10% in petrolatum
Signs of Irritation	The test sites were clipped free of hair 24 hours prior to each dose application. No erythema was observed in test or control animals.
CHALLENGE PHASE	
Topical:	30%, 10%, 5%, 3%, 1% and 0.1% in ethanol
Remarks - Method	There was a significant deviation to the test guideline recommends at least 10 animals in the treatment group, whereas in this experiment only 5 were used.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*	
		24 h	*48 h*
Test Group			
5F	30%, 10%, 5%, 3%, 1% and 0.1%	1	1
Control Group			
5F	0	-	-

Remarks - Results	Very slight erythema was noted at one of the 30% concentration site of the treatment group. No other dermal reaction was noted.

CONCLUSION There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test; however the number of test animals did not meet the recommended minimum as stated in the test guideline.

TEST FACILITY Takasago (2006a)

B.6. Skin Irritation – human volunteers

TEST SUBSTANCE Notified Chemical

METHOD Human patch test with single exposure

Study Group	14 F, 29 M; age range 26–58 years
Vehicle	Petrolatum
Remarks - Method	The notified chemical was absorbed in TORII test plaster at 2.5% and 5% concentration and then the plaster was occlusively fixed to upper arms of test subject. The patch remained affixed for 48 hours clinical observation was made 2 and 26 hours post removal of plaster.

RESULTS

Remarks - Results	No dermal reaction was observed in any test subject.

CONCLUSION The notified chemical was not irritating under the conditions of the test.

TEST FACILITY Takasago (2006b)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified Chemical

METHOD Standards for Mutagenicity Tests using Microorganisms (Notification No. 77, 1988, the Japanese Ministry of the Labour) (stated to be in accordance with OECD TG 471 Bacterial Reverse Mutation Test).
Pre incubation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98 and TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9, Phenobarbitone (PB)/ β-napthoflavone (NF) induced
Concentration Range in Main Test	a) With metabolic activation: 39.1–1,250 µg/plate b) Without metabolic activation: 39.1–1,250 µg/plate
Vehicle	DMSO
Remarks - Method	No significant deviations from the OECD guidelines. A total of four positive control material was used but it was not mentioned which material was used for which strain of bacteria. These controls are: AF-2, NaN_3, 9-aminoacridine and 2-aminoanthracene.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	>1,250	-	negative
Present				
Test 1	-	>1,250	-	negative

Remarks - Results No precipitate or signs of toxicity were noted at any dose level. The number of revertant colonies in the vehicle-treated control was within the normal range, and the positive controls were all mutagenic in their appropriate tester strain, confirming the validity of the test.

CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Takasago (2006c)

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