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July 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

TEA-NAA201

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.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

This Public Report is also 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
STD/1518	Idemitsu International (Asia) Pte Ltd	TEA-NAA201	ND*	≤ 10 tonnes per annum	Diesel fuel additive

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the 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.

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 its limited aquatic exposure and assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced (in diesel fuel):
  - Clean up spills promptly.

- 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 for the 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

- The notified chemical in fuel should be disposed of in accordance with local regulations for recycling, re-use or recovery of calorific content.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by 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 chemicals 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(2) of the Act; if
- the function or use of the chemical has changed from diesel fuel additive, 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.

No additional secondary notification conditions are stipulated.

(Material) Safety Data Sheet
The (M)SDS of the product containing the notified chemical provided by the notifier was 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)
Idemitsu International (Asia) Pte Ltd (ABN: 20 960 769 454)
163 Penang Road,
#06-01/05 Winsland House II, 238463
Singapore

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, CAS number, molecular and structural formulae, molecular weight, analytical data, constituents, use details and import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: some physico-chemical properties and toxicity endpoints.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
TEA-NAA201

MOLECULAR WEIGHT
> 500 Da

ANALYTICAL DATA
Reference IR spectra was provided.

3. COMPOSITION

DEGREE OF PURITY
100%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Light brown solid

Property	Value	Data Source/Justification
Melting Point	59 °C	Measured
Boiling Point	Not determined	The notifier stated that decomposition is expected to occur prior to boiling point being reached.
Density	9054 kg/m^3 at 70 °C	Measured
Vapour Pressure	2.76 x 10^{-23} kPa at 25 °C	Calculated
Water Solubility	<0.001 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Contains hydrolysable functionalities. However, the notified chemical is not expected to be significantly hydrolysed in the environmental pH range (4 – 9).
Partition Coefficient	log Pow > 8.8	Measured

(n-octanol/water)		
Adsorption/Desorption	Not determined	Expected to adsorb to soil, sediment and sludge based on its low water solubility and potential cationicity.
Dissociation Constant	Not determined	The notified chemical has potential to be ionised under normal environmental conditions (pH 4 – 9).
Particle Size	Not determined	The notified chemical will be imported as a component of a liquid product.
Flash Point	282 °C at 101 kPa	Measured
Autoignition Temperature	Not determined	Expected to be high, based on flash point of 282 °C.
Explosive Properties	Not determined	The notified chemical is not expected to have explosive properties based on its structure.
Oxidising Properties	Not determined	The notified chemical is not expected to have oxidising properties based on its 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 for the 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 be imported as a component (at 0.008% concentration) of diesel fuel.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤10	≤10	≤10	≤10	≤10

PORT OF ENTRY
Major ports in Australia (Sydney, Melbourne, Brisbane and Perth).

IDENTITY OF MANUFACTURER/RECIPIENTS
Idemitsu International (Asia) Pte Ltd

TRANSPORTATION AND PACKAGING
The imported diesel fuel containing the notified chemical will be shipped in bulk (in isotainers up to 26000 L) by sea. The diesel fuel will be offloaded onto tank trucks or rail cars and transported to the importer's storage facilities, or directly distributed to customer sites/end-users.

USE
The notified chemical will be used as an additive in diesel fuels.

OPERATION DESCRIPTION
The notified chemical will not be manufactured in Australia. It will be imported in isotainers (up to 26000 L) as an additive in diesel fuels. There will be no reformulation or repackaging of the imported product containing the notified chemical. The imported diesel fuels containing the notified chemical will be transported from wharf by road or rail to importer storage facilities or to refuelling stations.

At the refuelling station, the diesel fuel will be pumped and transferred from the isotainer into underground storage tanks. A 10 cm hose with coupling mechanism and air back flush system will be used to reduce any spills or leak during transfer. Service stations are also fitted with fill/dip or spill containment to collect any overfill.

It is expected that diesel fuel containing the notified chemical will be used to refill cars, trucks and other vehicles.

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)*
Dockside worker	1-2	12
Transport and storage	1-12	50
Service station attendants	0.5	300

EXPOSURE DETAILS

Dockside workers

Dermal and ocular exposure of workers to the fuel containing the notified chemical at 0.008% is not likely to occur during unloading of the imported isotainers from the ship and onto the trucks or trains using cranes, except in the case of an accident involving damage to the isotainers.

Transport and storage workers

Transport and storage workers are not likely to be exposed to large quantities of the diesel fuel containing the notified chemical except in the case of an accident involving damage to the isotainers. Dermal and ocular exposure may occur during filling underground tanks of the service stations using the transfer pump and lines (connecting and disconnecting the transfer lines). The transfer equipment has controls that would reduce spills and overfill.

Service station attendants

Service station workers may be incidentally exposed to the notified chemical through dermal and ocular routes through refilling vehicles, contact with equipment and during cleaning up of any spills, using spill kits (adsorbent material). Inhalation exposure is not expected during these operations.

Some workers will use personal protective equipment such as goggles, impervious gloves and coveralls during the above operations, to protect against exposure to hazardous components of diesel fuel; however, for operations such as re-filling vehicles use of PPE is not expected.

6.1.2. Public Exposure

The notified chemical will not be made available to the general public. The public may experience accidental dermal and ocular exposure to diesel fuels containing the notified chemical at 0.008% concentration when re-filling vehicles at service stations.

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 >2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 >2000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	non-irritating

Guinea pig, Maximisation test – skin sensitisation	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL 1000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vivo Micronucleus test	non genotoxic

Toxicokinetics, metabolism and distribution.
The potential for dermal absorption is likely to be reduced by the relatively high molecular weight (> 500 Da) and the high lipophilicity of the notified chemical.

Acute toxicity.
The notified chemical is considered to be of low acute toxicity via the oral and dermal routes based on tests conducted in rats. Information on the acute inhalation toxicity was not available.

Irritation and sensitisation.
Based on a test conducted on rabbits, the notified chemical is considered to be non-irritating to the skin and to the eye. The notified chemical was found to be a non-sensitiser in a Maximisation test in guinea pigs.

Repeated dose toxicity.
In a 28-day repeat dose oral toxicity study conducted on rats no test substance related effects were observed at all dose levels tested. Therefore, the No Observed (Adverse) Effect Level (NO(A)EL) was established as > 1000 mg/kg bw/day, based on the highest dose level examined.

Mutagenicity/Genotoxicity.
The notified chemical was found not to be mutagenic in a bacterial reverse mutation test. It was also not genotoxic in an in vivo Mammalian Erythrocyte Micronucleus test; however, in the absence of adverse clinical signs or any toxicity in bone marrow cells, it is not clear whether the test substance reached the target tissue.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the 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 available information, the notified chemical is of low hazard. Workers may have incidental dermal and ocular exposure to diesel fuel containing the notified chemical at low concentration (0.008%) during transfer, dispensing and cleaning processes. Worker exposure would be further reduced by safe work practices. The notified chemical is expected to be combusted as part of the diesel fuel and will then not be available for further exposure.

Based on the available information on toxicity and the occupational use scenarios and controls in place, the notified chemical is not expected to pose an unreasonable risk to workers.

6.3.2. Public Health
The public may be incidentally exposed to the notified chemical in diesel fuel at 0.008% through operations such as refuelling vehicles. Due to the low concentration of the notified chemical in the diesel fuel and the expected low hazard of the notified chemical, the risk to the public from use of diesel fuel containing the notified chemical at 0.008% is not considered to be unreasonable.

It is expected that the notified chemical will be combusted as part of the diesel fuel, and will not be available for further exposure.

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 or reformulated/repacked in Australia. Therefore, release of the notified chemical from these activities is not expected.

RELEASE OF CHEMICAL FROM USE
The notified chemical will be imported as an additive in diesel fuel. No significant release of the notified chemical to aquatic systems is expected when it is used as a diesel fuel additive.

Environmental release from spills of diesel fuel containing the notified chemical may be expected during the transfer of the diesel fuel. Spills during refilling of the diesel fuel to underground storage tanks from isotainers, and to car fuel tanks at fuel bowsers are expected to be insignificant (<1% of the total import volume). These spills are expected to be contained in on-site interceptor drains at service stations to trap and filter the diesel fuel containing the notified chemical. Hence, the notified chemical will be prevented from entering the sewer via rainwater runoff. Larger spills will be dammed and collected using a suitable adsorbent material within spill kits which are present at service station sites. The collected spills are expected to be disposed of to landfill. Isotainers, containing residues of diesel fuel and the notified chemical, are expected to be reused during transportation of the diesel fuel. Most of the notified chemical will be consumed during the combustion of the fuel in vehicle engines.

RELEASE OF CHEMICAL FROM DISPOSAL
Empty import containers containing residues of the notified chemical are expected to be recycled by accredited waste management companies or disposed of according to local regulations.

7.1.2. Environmental Fate
In a study submitted by the notifier, the notified chemical was shown to be biodegradable. However, the notified chemical cannot be formally classified as readily biodegradable according to the test guidelines. For the details of the environmental fate study, refer to Appendix C. Bioaccumulation and bioavailability of the notified chemical is not expected due to its biodegradability and limited potential for exposure to the aquatic compartment.

Most of the notified polymer in fuel will be consumed and degraded during use. Minor amounts of the notified chemical are expected to be released to landfill as residues in containers or treatment wastes. Release to the aquatic compartment is unlikely based on the reported use pattern. In landfill, the notified chemical is not expected to be mobile due to its moderate to high molecular weight, low water solubility and potential cationicity. The notified chemical is expected to slowly degrade by biotic and abiotic processes in landfill, or by thermal decomposition, to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)
The predicted environmental concentration (PEC) has not been calculated since no significant release of the notified chemical to the aquatic environment is expected from the reported use pattern.

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)	LL50 > 100 mg/L (filtered WAF)	Not harmful to fish
Daphnia Toxicity (48 h)	EL50 > 100 mg/L (filtered WAF)	Not harmful to aquatic invertebrates
Algal Toxicity (72 h)	E_rL50 > 100 mg/L (filtered WAF)	Not harmful to algae

WAF: Water Accommodated Fraction

Based on the above reported endpoints for the notified chemical, it is not considered to be harmful to fish, daphnia and algae. Therefore, the notified chemical is not harmful to aquatic organisms. Consequently, under

the Globally Harmonised System of Classification and Labelling of Chemicals (GHS; United Nations, 2009), the notified chemical has not been formally classified for acute and chronic toxicity.

7.2.1. Predicted No-Effect Concentration

A predicted no-effect concentration (PNEC) has not been calculated as no significant aquatic exposure is expected based on the reported use pattern.

7.3. Environmental Risk Assessment

The risk quotient, Q (= PEC/PNEC), of the notified chemical has not been determined due to its low potential for release to the aquatic compartment. The majority of the notified chemical will be thermally decomposed during its use as an additive in fuels. Exposure of the notified chemical to the aquatic compartment is unlikely based on the reported use pattern. On the basis of its limited aquatic exposure and assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 59 °C

Method	Similar to OECD TG 102 Melting Point/Melting Range.
Remarks	Use of capillary tube in a liquid bath.
Test Facility	NOF Corporation (2013)

Density 9054 kg/m^3 at 70 °C

Method	Japanese Industrial Standard Method JIS K0061.
Remarks	Tested using float type densimeters. The melting point is approximately 60 °C and the density was measured at 70 °C.
Test Facility	NOF Corporation (2013)

Water Solubility <0.001g/L at 20 °C

Method	OECD TG 105 Water Solubility.
Remarks	Column Elution Method. Limit of detection (LOD) for the detector used in the HPLC was not reported.
Test Facility	SCAS (2014)

Partition Coefficient (n-octanol/water) log Pow >8.8

Method	OECD TG 117 Partition Coefficient (n-octanol/water), High Performance Liquid Chromatography (HPLC) Method
Remarks	HPLC Method. The column retention time for the notified chemical was longer than that for the standard (chemical) with the longest retention time.
Test Facility	SCAS (2014)

Flash Point 282 °C at 101 kPa

Method	Japanese Industrial Standard Method JIS K2265.
Remarks	Using Cleveland open cup method (corresponding test method ISO 2592:1973 petroleum products).
Test Facility	NOF Corporation (2013)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure.

Species/Strain	Rat - Sprague Dawley Crl:CD(SD)
Vehicle	0.5% Methylcellulose
Remarks - Method	No protocol deviation occurred during the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 F	300	0
2	1F	2000	0
3	4 F	2000	0

LD50	>2000 mg/kg bw
Signs of Toxicity	Substance-coloured stool in all animals on day one after dosing 300 or 2000 mg/kg bw. On day two all animals returned to normal appearance.
Effects in Organs	A slight body weight decrease in two animals on day 3 after dosing 2000 mg/kg bw but returned to normal appearance on day 7.
Remarks - Results	No evidence of morphologic abnormalities after necropsy was seen.

CONCLUSION: The notified chemical is of low toxicity via the oral route.

TEST FACILITY: Biotoxtech (2014a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 402 Acute Dermal Toxicity – Limit Test.

Species/Strain	Rat/ Sprague Dawley
Vehicle	Water was used to moisten the pulverised solid
Type of dressing	Occlusive
Remarks - Method	No protocol deviation occurred during the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 M, 5 F	0	0
2	5 M, 5 F	2000	0

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	No cutaneous reactions were observed.
Signs of Toxicity - Systemic	No systemic clinical signs were observed.
Effects in Organs	A statistically significant decrease in body weight gain in female rats dosed at 2000 mg/kg bw of the test substance was observed on day 14, compared to the control group.
Remarks - Results	No remarkable necropsy findings were seen in any animals of the 2000 mg/kg bw dose group.

CONCLUSION: The notified chemical is of low toxicity via the dermal route.

TEST FACILITY Biotoxtech (2014b)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Vehicle	Water was used to moisten the solid.
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	No deviation from protocol was recorded. The notified chemical was ground to powder in a mortar prior to application. The notified chemical was applied at 0.5 g (moistened with water to ensure a good contact with the skin) for 4 hours on one the rabbit's clipped back. The other untreated site of the rabbit served as control. One animal was tested initially, to evaluate the irritation potential.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0	0	0	-	0
Oedema	0	0	0	0	-	0

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

Remarks - Results All animals exhibited normal body weight gains, no abnormal clinical signs or symptoms and no adverse skin reactions throughout the study (72 hours).

CONCLUSION The notified chemical is non-irritating to the skin.

TEST FACILITY Biotoxtech (2014c)

B.4. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 M
Observation Period	72 hours
Remarks - Method	The notified chemical (0.1 g) was instilled in the conjunctival sac of the right eye. The other untreated eye served as the control.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0	0	0	0	-	0
Conjunctiva: chemosis	0	0	0	0	-	0
Conjunctiva: discharge	0	0	0	0	-	0
Corneal opacity	0	0	0	0	-	0

Iridial inflammation	0	0	0	0	72 hours	0

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

Remarks - Results: All animals exhibited normal body weight gains, no abnormal clinical signs or symptoms, no signs of pain or distress and no reactions on the cornea, iris or conjunctivae.

CONCLUSION: The notified chemical is non-irritating to the eye.

TEST FACILITY: Biotoxtech (2014d)

B.5. Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 406 Skin Sensitisation - Maximisation test.

Species/Strain: Guinea pig/ Albino

PRELIMINARY STUDY: Maximum Non-irritating Concentration:
intradermal: 0.5%
topical: 50%

MAIN STUDY

Number of Animals: Test Group: 10 Control Group: 5

INDUCTION PHASE: Induction Concentration:
intradermal: 0.5%
topical: 50%

Signs of Irritation: None

CHALLENGE PHASE

challenge: topical: 50%

Remarks - Method: The vehicle used was corn oil, in which the notified chemical was soluble.
A preliminary test was conducted at concentration of 50%, 20%, 10% and 5% of the test substance.
Main study:
All animals were treated with 10% sodium dodecyl sulfate (SDS) 24 hours before the epidermal induction exposure to enhance reactions.
All animals were challenged with 50% of the substance in vehicle after 14 days of the induction phase.
A periodic check of the test system was carried out with 20% α-hexylcinnamaldehyde as a positive control.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: challenge*	
		24 h	*25 h*
Test Group	50%	0	0
Control Group	50%	0	0

Remarks - Results: The preliminary irritation study at up 50% concentration epidermal exposure showed no skin reactions at 24 and 48 hours.
No mortality or symptoms of systemic toxicity were observed in the main study.
Body weights and body weight gain of the treated animals remained in the same range as controls throughout the study period.
No skin reactions were observed after the challenge exposure in the test and control animals.
Sensitisation was evident in the periodic check with the positive control α-hexylcinnamaldehyde, confirming the validity of the test system.

CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Wil (2014a)

B.6. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rats/Crl:CD(SD)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: once daily Post-dosing recovery time: 14 days
Vehicle	20% HCO-60 (Ethoxylated hydrogenated Castor Oil) in water
Remarks - Method	No deviation from protocol was recorded. The statistical significance level for comparison with the controls was 5%. Histopathological examination at the end of the administration period was carried out on control and high dose animals. It was not extended to the other dose groups because of the lack of test article related changes at the high dose. Control: Water for injection containing 20% HCO-60 (Ethoxylated hydrogenated Castor Oil).

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	6 M, 6 F	0	0
low dose	6 M, 6 F	100	0
mid dose	6 M, 6 F	300	0
high dose	6 M, 6 F	1000	0
control recovery	6 M, 6 F	0	0
high dose recovery	6 M, 6 F	1000	0

Mortality and Time to Death

There were no deaths noted during the study.

Clinical Observations

No abnormalities in any test group were observed during the treatment or recovery period.

No statistically significant differences in sensory and motor reactivity to stimuli grip strength between test substance and control groups were observed in week 4 administration or week 2 recovery. A significantly higher motor activity was observed in week 4 administration: from 20 to 30 minutes and from 0 to 60 minutes in 100 mg/kg bw male rats group, and from 40 to 50 minutes in 1000 mg/kg female rats group. These changes were not considered test article related as they were in either transient, or not dose-related.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No significant changes of haematological findings in any test substance or control groups of female and male rats were observed at the end of administration.

In the blood biochemical examination, a significantly high inorganic phosphorus and low albumin (both non-dose dependent) were observed in the 300 mg/kg bw male group compared to the control group. No significant changes were observed in female or male of the recovery groups.

In week 4 of administration, a significant low urine volume (non-dose dependent) in 100 mg/kg bw male group compared to the control was observed. In week 2 of recovery, urine volume was significantly lower in the 1000

mg/kg bw female group but was within the range of historical controls.

Effects in Organs

No statistically significant differences in the mean body weight or mean body weight gain or food consumption between test substance or control female or male rat groups were observed during the administration or recovery period.

A significantly higher relative thyroid weight and absolute and relative uterus weight in the 100 mg/kg bw female group and absolute and relative thyroid weight in the 300 mg/kg bw female group were observed at the end of administration compared to the control. As the effects were not dose-dependent, they were not considered to be test article related. No significant organ weight changes were noted in the female or male recovery group.

Histopathological examination showed the a number of findings in the 1000 mg/kg bw test animals: including spicule, focal artery mineralisation and alveolar macrophage in the lung, cyst in the kidney and in the pituitary gland, microgranuloma, focal necrosis, and periportal vacuolation of hepatocytes in the liver, and mild inflammation in the prostate. These findings were considered incidental changes as they were at low incidence and severity and were also observed in the control group or in the historical control data.

Remarks – Results

Based on the results of this study, the notified chemical administered orally (gavage) to Crl:CD(SD) rats for 28 days did not result in toxicity in the evaluated parameters at dosage levels of 0, 100, 300 or 1000 mg/kg/day.

CONCLUSION

The No Observed (Adverse) Effect Level (NO(A)EL) was established as 1000 mg/kg bw/day in this study, the highest dose tested.

TEST FACILITY Safety Research Institute for Chemical Compounds Co., Ltd. (2014)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.

	Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 and *E. coli*: WP2uvrA (pKM101)
Metabolic Activation System	S9-mix from Phenobarbital / 5,6-Benzoflavone - induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 313-5000 µg/plate b) Without metabolic activation: 313-5000 µg/plate
Vehicle	THF
Remarks - Method	Dose levels were determined by a preliminary test, which was reported as Test 1. Two and three plates per dose were used in the preliminary and main tests respectively. Tetrahydrofuran (THF) was used as the negative control. Furylfuramide (AF2) was used as the positive control for *E.coli.* WP2uvrA(pKM101) in the absence of metabolic activation.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	>5000	>5000	≥313	Negative
Test 2	>5000	>5000	≥313	Negative
Present				
Test 1	>5000	>5000	≥78.1	Negative
Test 2	>5000	>5000	≥313	Negative

Remarks - Results	The deposition of the test substance was observed at relatively low levels but did not interfere with counting of colonies. The positive control markedly showed increased number of revertant colonies compared to test and negative control groups. The growth inhibition by the test substance was not evident at any dose levels in all strains in the presence and absence of metabolic activation.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Biotoxtech (2014e)

B.8. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mouse/CrljOri:CDI(ICR), SPF
Route of Administration	Oral – gavage (via gastric intubation)
Vehicle	0.5% Methylcellulose (MC) solution
Remarks - Method	The notified chemical was ground to a powder in a mortar before being suspended in the vehicle. Negative control: 0.5% MC solution Positive control: Mitomycin C (MMC) Dose-finding study range: 125-2000 mg/kg Since there were no sex differences in clinical signs and mortality in the dose range finding study (15 M, 15 F), 35 males were selected for the main study.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	5 M, 5 M	0	24, 48
II (low dose)	5 M	500	24
III (mid dose)	5 M	1000	24
IV (high dose)	5 M, 5 M	2000	24, 48
V (positive control MMC)	5 M	2	24

RESULTS

Doses Producing Toxicity	No mortality or clinical signs were seen at any of the doses tested. There were no significant differences in body weights of the test substance groups compared to negative control groups).
Genotoxic Effects	There was no significant increase in the incidence of micronuleated polychromatic erythrocytes (MNPCE) in polychromatic erythrocytes (PCE) of the test substance groups compared to the negative control groups ($p \geq 0.05$). The incidence of MNPCE in PCE was significantly increased of the positive control group compared to the negative control group ($p < 0.01$).
Remarks - Results	The mean number of MNPCE in 2000 PCE in positive and negative control groups were within the range of historical control data. There were no significant differences in the ratio of PCE to total erythrocytes of the test substance groups compared to the negative controls. Therefore it cannot be confirmed that the test substance reached the bone marrow.
CONCLUSION	The notified chemical was not clastogenic under the conditions of this study.
TEST FACILITY	Biotoxtech (2014f)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

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 reported
Analytical Monitoring	Titration Method
Remarks - Method	The test was conducted according to the guidelines above using good laboratory practice (GLP). No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Reference substance (Sodium acetate)*	
Day	*% Degradation*	*Day*	*% Degradation*
7	3	2	1
14	20	7	43
23	42	9	56
29	58	14	70

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation (70%) of the reference compound, sodium acetate, surpassed the pass levels of 60% by 14 days. Therefore, the test indicates the suitability of the inoculum. The toxicity control exceeded 25% biodegradation within 14 days showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical after 28 days was 58%. Therefore, the test substance cannot be classified as readily biodegradable according to the OECD (301 B) guideline.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	Wil (2014b)

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 Test
Species	Medaka (*Oryzias latipes*)
Exposure Period	96 hours
Auxiliary Solvent	Not reported
Water Hardness	61 mg $CaCO_3$/L
Analytical Monitoring	Liquid chromatography/mass spectrometry (LC/MS) analysis
Remarks – Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported. The fish ecotoxicity test was conducted in a water accommodated fraction (WAF) of the test substance. A WAF of nominal loading of 100 mg/L was prepared in dechlorinated water, and stirred for 48 hours at 24 ºC. The WAF solution was then filtered through a filter paper (5 µm). The clear and colourless filtered WAF was used for the test. The test was conducted as a limit test.

RESULTS

Concentration ((mg/L;WAF)		*Number of Fish*	*Cumulative Mortality (%)*				
Nominal	*Measured (0 h)*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	-	10	0	0	0	0	0
100	0.36	10	0	0	0	0	0

LL50	> 100 mg/L at 96-h (nominal loading rate)
NOEL	100 mg/L at 96-h (nominal loading rate)
Remarks – Results	All validity criteria for the test were satisfied. The actual concentrations of the test substance in WAFs were measured periodically at 0, 24, 48, and 96 hours. The test solutions were renewed every 24 hours during the 96-h test period. The LL50 determined based on the time weighted mean of measured concentrations was > 0.19 mg/L. However, the end points were determined based on the nominal loading rates as the toxicity cannot be attributed to a single component or mixture of components but to the test substance as a whole.
CONCLUSION	The notified chemical is not harmful to fish at the loading rate of 100 mg/L
TEST FACILITY	Mitsubishi (2014a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static Test
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Not reported
Water Hardness	≤ 250 mg $CaCO_3$/L
Analytical Monitoring	Liquid chromatography/mass spectrometry (LC/MS) analysis
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported. The daphnia ecotoxicity test was conducted in a water accommodated fraction (WAF) of the test substance. A WAF of nominal loading of 100 mg/L was prepared in dechlorinated water, and stirred for 48 hours at 24 ºC. The WAF solution was then filtered through a filter paper (5 µm). The clear and colourless filtered WAF was used for the test. The test was conducted as a limit test.

RESULTS

Concentration (filtered WAF; mg/L)		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Measured (0-h)*		*24 h*	*48 h*
Control	Control	20	0	0
100	0.124	20	0	0

EL50	> 100 mg/L at 48 hours (nominal loading rate)
NOEL	100 mg/L at 48 hours (nominal loading rate)
Remarks - Results	All validity criteria for the test were satisfied. The actual concentrations of the test substance in WAFs were measured periodically at 0, 24 and 48 hours within the 48-h test period. The test solutions were renewed every 24 hours during the 48-h test period. The LL50 determined based on the time weighted mean of measured concentrations was > 0.09 mg/L. However, the end points were determined based on the nominal loading rates as the toxicity cannot be attributed to a single component or mixture of components but to the test substance as a whole.
CONCLUSION	The notified chemical is not harmful to aquatic invertebrates at the loading rate of 100 mg/L
TEST FACILITY	Mitsubishi (2014b)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemicals
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L (loading rate) Measured: 0.378 mg/L (at 0-h)
Auxiliary Solvent	Not reported
Water Hardness	Not reported
Analytical Monitoring	Liquid chromatography/mass spectrometry (LC/MS) analysis
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported. The algae ecotoxicity test was conducted in a water accommodated fraction (WAF) of the test substance. A WAF of nominal loading of 100 mg/L was prepared in dechlorinated water, and stirred for 48 hours at 24 ºC. The WAF solution was then filtered through a filter paper (5 µm). The clear and colourless filtered WAF was used for the test. The test was conducted as a limit test. The treatment WAF solution was prepared in algal test medium.

RESULTS

Biomass (72 h) (filtered WAF; mg/L)		*Growth (72 h) (filtered WAF; mg/L)*	
E_yL50 (mg/L)	*NOE_yL (mg/L)*	*E_rL50 (mg/L)*	*NOE_rL (mg/L)*
> 100 mg/L	100 mg/L	> 100 mg/L	100 mg/L

Remarks - Results	All validity criteria for the test were satisfied. Chemical analyses of the test substance in WAFs were conducted at 0, 24, 48 and 72 hours of the test. Statistically significant reduction of growth rate was not found at the highest treatment, which was at the loading rate of 100 mg/L (time weighted mean of measured concentration of 0.05 mg/L). However, the end points were calculated based on the nominal loading rates as the toxicity cannot be attributed to a single component or mixture of components but to the test substance as a whole. The Analysis of Variance (ANOVA) was used to calculate the end points.
CONCLUSION	The notified chemical is not harmful to algae at the loading rate of 100 mg/L
TEST FACILITY	Mitsubishi (2014c)

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