File No: STD/1472

August 2013

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Chemical in E-470M

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (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 Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of Sustainability, Environment, Water, Population and Communities.

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:

Street Address:	Level 7, 260 Elizabeth Street, SURRY HILLS NSW 2010, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

TABLE OF CONTENTS

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/1472	Kao Australia Pty Ltd	Chemical in E-470M	ND*	≤ 150 tonnes per annum	Component of liquid laundry detergent

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
No toxicity data were provided for the notified chemical. As only limited toxicity data were available for the analogue chemicals, the notified chemical cannot be classified 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).

The environmental hazard classification according to the *Globally Harmonised System for the 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

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

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable risk to public health.

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the 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 the laundry detergent:
  - Avoid direct skin/eye contact with the product
  - Rinse off any skin/eye contamination with large quantity of water immediately

- 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 as introduced in the laundry detergent:
  - Impervious gloves
  - Protective clothing

  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 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.

Public Health

- The following measures should be taken by the notifier to minimise public exposure to the notified chemical:
  - Adequately label the products containing the notified chemical to avoid contact with skin and eyes, and keep out of the reach of children
  - Products containing the notified chemical should only be formulated in non-nitrosating systems, to avoid the formation of hazardous nitrosamines.

Disposal

- The notified chemical should be disposed of to landfill.

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
  - additional information on the eye or skin irritation potential of the notified chemical becomes available;
  - additional information on the potential for systemic toxicity of the notified chemical becomes available;

Or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of liquid laundry detergent, 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 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)
Kao Australia Pty Ltd (ABN: 059 054 708 299)
1A The Crescent
KINGSGROVE NSW 2208

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, other names, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, polymer constituents, residual monomers, impurities, additives/adjuvants, specific use details and manufacture/import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: All physico-chemical endpoints, apart from specific gravity/density and all human health endpoints.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
E-470M (≥ 70% notified chemical in aqueous solution, intermediate product not imported into Australia)

OTHER NAME
Laundry Detergent A (product containing < 32% notified chemical, imported into Australia)

MOLECULAR WEIGHT
< 1,000 Da

ANALYTICAL DATA
Reference NMR, IR and LC-MS spectra were provided.

3. COMPOSITION

DEGREE OF PURITY > 90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Liquid (Aqueous solution containing 70% notified chemical)

Property	Value	Data Source/Justification
Melting Point/Freezing Point	Not determined	Introduced only in formulated products
Boiling Point	Not determined	Introduced only in formulated products
Density	1,018 kg/m^3 at 20°C (20% solution)	Measured using in-house test method (study report not provided)
Vapour Pressure	1.46×10^{-9} to 1.04×10^{-8} kPa at 25°C	Calculated (KOWWIN v1.68; US EPA, 2011)

Water Solubility	Not determined	Expected to be low based on its predominantly hydrophobic nature, however, the notified chemical may be dispersible in water based on its surface activity
Hydrolysis as a Function of pH	Not determined	Does not contain hydrolysable functionality and is not expected to hydrolyse under environmental conditions (pH 4-9)
Partition Coefficient (n-octanol/water)	Not determined	Expected to partition to the interface between octanol and water, based on its surfactant properties
Adsorption/Desorption	Not determined	Expected to partition to phase boundaries based on its surfactant properties
Dissociation Constant	pKa = -3.58	The notified chemical is a salt and is expected to ionise in the environment
Flash Point/Flammability	Not determined	Introduced only in formulated products. Not expected to be flammable under conditions of use
Autoignition Temperature	Not determined	Imported only in formulated products. Not expected to autoignite under normal conditions of use
Explosive Properties	Not determined	Contains no functional groups that would imply explosive properties
Oxidising Properties	Not determined	Contains no functional groups that would imply explosive properties

DISCUSSION OF PROPERTIES

Reactivity
The notified chemical is expected to be stable under normal conditions of use.

Physical hazard classification
Based on the limited submitted physico-chemical data depicted in the above table, the notified chemical cannot be classified 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 into Australia as a component of formulated detergent products at < 32% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 150	< 150	< 150	< 150	< 150

PORT OF ENTRY
Melbourne and Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
Kao Australia Pty Ltd

TRANSPORTATION AND PACKAGING
Liquid laundry detergent products containing the notified chemical at < 32% concentration will be imported and transported in 650 ml plastic bottles in cardboard box shippers on pallets which will be shrink-wrapped. The products will be transported by road from the port to storage warehouses and finally distributed to retail stores and commercial laundries.

USE
The notified chemical is a surfactant that will be used as a component of finished liquid laundry detergent products at < 32% concentration.

OPERATION DESCRIPTION
The notified chemical will not be manufactured or reformulated in Australia. The notified chemical will be imported as a component (< 32% concentration) of formulated liquid laundry detergent products for sale to the general public and commercial laundries.

End use
End users (members of the public and professional laundry workers) will manually measure (usually by use of container cap or measuring cup) the required volume of liquid laundry detergent (typically 1 cap full – 50 mL, containing the notified chemical at < 32% concentration) before adding the liquid to a washing machine. During the laundry operations, the notified chemical will be diluted by water. When the end-users remove washed clothes from the washing machine, the notified chemical would have been rinsed off from the clothes.

Household consumers may also carry out hand washing and laundry pre-treatment using the laundry detergent containing < 32% notified chemical.

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	2 - 3	24
Retail workers	8	200
Professional laundry workers	8 - 12	200

EXPOSURE DETAILS

Transport and warehouse workers

Transport and warehouse workers are not expected to have potential for exposure to the notified chemical except in the event of an accident. In this case, dermal and ocular exposure may occur; however, standard clean-up procedures would be in place to minimise worker exposure to the notified chemical.

Retail workers

Retail workers are not expected to have potential for exposure to the notified chemical except in the event of an accidental package breach. In this case, dermal and ocular exposure may occur; however, exposure is expected to be minimised by the use of appropriate PPE including gloves and protective clothing during clean-up of any spills.

Professional laundry workers

Laundry workers may have the potential for dermal and ocular exposure to finished products containing less than 32% of the notified chemical. Exposure may occur during measuring and dispensing of the laundry product. It is recommended that workers wear gloves and protective clothing when handling the laundry products. In addition, eye contact should be avoided. During the laundry operations, the notified chemical in the finished products will be diluted by a substantial amount of water and finally rinsed off from the clothes at the end of the washing cycle. Therefore exposure from handling washed clothes would be negligible.

6.1.2. Public Exposure
Since laundry products containing notified chemical will be sold to members of the public for home use, the public may have the potential for accidental dermal and ocular exposure to the notified chemical (< 32%

concentration). Exposure may occur during measuring and dispensing of the laundry products. It is recommended that the household users avoid direct skin and eye contact with the laundry product. During the laundry operations, the notified chemical will be diluted by a substantial amount of water and finally rinsed off from the clothes at the end of the washing cycle. Trace quantities of residual chemical on the clothes may remain, however the levels are expected to be low.

In addition, household consumers carrying out hand washing and laundry pre-treatment using the detergents (containing < 32% of the notified chemical) also have potential for dermal and accidental ocular exposure to the diluted detergent containing low levels of the notified chemical (< 0.4%). The low level dermal exposure may last for several minutes before the chemical is rinsed off. Potential dermal exposure from hand washing and from use of the laundry liquid to pre-treat laundry is estimated below:

Product type	**Frequency** (use/day)	**C** (%)	**Contact Area** (cm^2)	**Product Use Dilution**	**Film Thickness** (cm)	**Time Scale Factor**	**Daily systemic exposure** (mg/kg bw/day)
Laundry liquid – hand washing	1.43	32	1980	0.01	0.01	0.007	0.0105
Laundry liquid – pre-treating	1.43	32	360	1	0.01	0.007	0.192
Total							0.203

Daily systemic exposure = frequency of use × concentration × body surface contact area × product concentration × film thickness on skin × time scaling factor × dermal absorption (%)/body weight

6.2. Human Health Effects Assessment

No toxicity data were submitted for the notified chemical. The results from toxicological investigations conducted on the analogue chemicals are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*	*Test Substance*
Rat, acute oral toxicity	1,000 < LD50 < 2,000 mg/kg bw; harmful	Analogue A
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity	Analogue C (HPV 2010)
Skin irritation	Slightly irritating to corrosive, concentration dependent	Analogues C (HPV 2010), D (IUCLID 2000) and E (CIR 2012)
Eye irritation	Slightly to highly irritating, concentration dependent	Analogues C (HPV 2010) and D (IUCLID 2000)
Guinea pig, skin sensitisation – Maximisation	No evidence of sensitisation	Analogue A
Rat, repeat dose oral toxicity – 14 day screening test	NOEL = 70.4 mg/kg bw/day for males NOEL = 211.2 mg/kg bw/day for females	Analogue A
Rat, repeat dose oral toxicity – 90 days	NOAEL = 112.3 mg/kg bw/day for males NOAEL = 124.8 mg/kg bw/day for females	Analogue B
Mutagenicity – bacterial reverse mutation	Non mutagenic	Analogue A
Genotoxicity – *in vitro* chromosome aberration test	Non genotoxic	Analogue A

Toxicokinetics, metabolism and distribution
The dermal absorption of structurally similar chemicals (represented by Analogue C with various carbon chain lengths) is relatively poor, as expected for an ionic molecule. The notified chemical has surfactant properties, which may enhance its absorption or that of other substances. The percutaneous absorption of the analogue was measured in a rat *in vivo* study and a dermal flux of 0.0163 $\mu g/cm^2/h$ was determined, indicating that the chemical has potential to penetrate the skin and become systemically available.

Following oral exposure, chemicals represented by Analogue C are readily absorbed in the gastrointestinal tract of human and rat, and excreted principally via the urine. Once absorbed, Analogue C is extensively

metabolized by beta- or omega oxidation.

Analogue E, representing the counter ion part of the notified chemical, is naturally occurring in mammals through metabolism and is excreted in the urine. Analogue E is phosphorylated by ATP in the liver, blood, and brain, and converted to acetaldehyde, ammonia, and inorganic phosphate. The acetaldehyde is oxidized to acetate and can further be converted into carbon dioxide.

Acute toxicity
Analogue A administered by gavage at 2,000 mg/kg bw resulted in total mortality in rats. Based on these results, the chemical was determined to be harmful via the oral route.

Analogue C was considered to be of low acute dermal toxicity to rats in a report of High Production Volume Challenge (HPV 2010).

Analogue D was potentially harmful via oral and dermal routes according to the information available in an IUCLID Dataset (IUCLID 2000).

For Analogue E which represents the counter ion part of the notified chemical, the acute oral toxicity showed LD50 of 2,140 – 2,740 mg/kg bw in rats, 700 -15,000 mg/kg bw in mice and 1,000 – 2,900 mg/kg bw in rabbits. The dermal LD50 in rabbits was reported as 1,000 – 2,500 mg/kg bw, indicative of low acute toxicity.

Irritation and sensitisation

Irritation
Based on the information in the HPV report (HPV 2010), the irritation potential of Analogue C is concentration dependent. Materials with concentrations higher than 70% are determined to be irritating to skin according to EU criteria. At concentrations between 10 and 30%, Analogue C solutions exhibit mild to moderate irritancy. Analogue C with concentrations below 1% is virtually non-irritating.

Skin and eye irritation properties of Analogues C and D are summarised in the following table. Analogue C data is considered more relevant for irritation endpoints than Analogue D.

	Skin Irritation	Eye irritation
Analogue C	> 70%, moderately to severely irritating	≥ 28%, moderately to severely irritating
	10 - 30%, mildly to moderately irritating	1 - 10%, slightly to moderately irritating
	< 1%, non-irritating	< 1%, non-irritating
Analogue D	100%, highly irritating	0.5 - 2%, slightly irritating
	10%, slightly irritating	5 - 20%, irritating to highly irritating

Sensitisation
In a study on Analogue A using guinea pigs, no evidence of skin sensitisation was revealed under the conditions of the test.

Repeated Dose Toxicity
Studies conducted on Analogues A and B showed that prolonged oral exposure to the chemicals may cause significant toxicity to stomach and liver respectively, indicative of potential repeated dose toxicity for the notified chemical. For Analogue A, the NOELs were established as 211.2 mg/kg bw/day for male and 70.4 mg/kg bw/day for female rats, based on the observed gastric erosion in necropsy. For Analogue B, the NOAELs were established as 112.3 mg/kg bw/day for male rats and 124.8 mg/kg bw/day for female rats, based on observations on body weight, feed consumption and effects on the female livers.

Mutagenicity/Genotoxicity

In a bacterial reverse mutation study on Analogue A, the chemical was found not to be mutagenic to bacteria under the conditions of the test. In a chromosome aberration study on Analogue A, the chemical was found not to be clastogenic to Chinese hamster CHL/IU cells treated *in vitro* under the conditions of the test.

Impurities
The notified chemical contains a primary amine group, which could give rise to hazardous nitrosamines, if it is formulated in nitrosating systems.

Health hazard classification
No toxicity data were provided for the notified chemical. As only limited information is available on the analogue chemicals, the notified chemical cannot be classified 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
No toxicity data were provided for the notified chemical. According to the data provided for the analogue chemicals, Analogue A is harmful through the oral route, Analogue B has health effects in mammals when exposed repeatedly, and Analogues C and D are slight to extreme skin and eye irritants depending on the concentration tested (ranging from 1 to 100%). Based on above information, the notified chemical is likely to be a skin irritant as well as an eye irritant, and may have systemic effects.

Workers may be exposed to the notified chemical (< 32% concentration) when handling laundry detergents. However, the use of PPE such as gloves and protective clothing may reduce the potential of exposure. During the end use, the notified chemical will be diluted by a substantial amount of water and finally rinsed off from the clothes being washed.

On the basis of safe work practices and PPE used, the risk to the health of workers from normal use of the laundry products containing the notified chemical is not considered to be unreasonable.

6.3.2. Public Health
The members of the public may come into contact with the notified chemical (< 32% concentration) while using the finished liquid laundry products and incidental skin and eye irritation may occur. However, it is largely expected that consumers would wash off any spilt material from their skin or eyes. Accidental ingestion by children of the finished laundry products (< 32% notified chemical) may be possible and should be avoided. The notified chemical will be diluted by a substantial amount of water during the washing and finally rinsed off from the clothes at the end of the cycle. Household consumers carrying out hand washing and laundry pre-treatment using the laundry detergent may come into direct skin contact with the notified chemical.

The repeat dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the notified chemical, based on the use of laundry detergent (see section 6.1.2) and the NOAEL of 112.3 mg/kg bw/day for Analogue B. A MoE value of > 100 is considered acceptable to account for intra- and inter-species differences. Using the abovementioned NOAEL, a MoE of 553 was estimated, which is considered acceptable.

Given the relative low frequency of laundry tasks and the amount of the detergent used in the washing, the exposure of the public to the notified chemical is not expected to be high, and the risk to the public health 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 is not manufactured, reformulated or repackaged in Australia; therefore there will be no release to the environment from these activities. Environmental release during importation, transport, storage and distribution may occur as a result of accidental spills (up to 1% of the total import volume). Spills are expected to be cleaned up by using an appropriate sorbent material and disposed of to landfill or washed to sewers.

RELEASE OF CHEMICAL FROM USE
During use as a detergent, the entire volume of the notified chemical in wastewater from washing machines is expected to be released in to sewers on a nationwide basis. Spills are expected to be cleaned up by using an appropriate sorbent material and disposed of to landfill or washed to sewers. Residues of the notified chemical in the empty containers (up to 2% of the total import volume) are likely to be rinsed and used in the laundry or

disposed of to landfill.

RELEASE OF CHEMICAL FROM DISPOSAL
The majority of the notified chemical is expected to be released to sewer. A small amount of the notified chemical is likely to be disposed of to landfill in domestic waste when unused laundry detergents are discarded.

7.1.2. Environmental Fate
For the details of the environmental fate studies please refer to Appendix C. The notified chemical is expected to be hydrolytically stable under environmental conditions based on structural considerations. The notified chemical is expected to be readily biodegradable based on a biodegradation study for a close analogue of the notified chemical.

The majority of the notified chemical is expected to be released to sewage treatment plants (STPs) via domestic wastewater. Based on its ready biodegradability and applying assumptions in the SimpleTreat model (European Commission, 2003), more than 87% of the notified chemical is expected to be removed during STP processes.Notified chemical remaining in treated sewage effluents is likely to be released to surface waters or applied to land when used for irrigation. Notified chemical in sewage sludge is anticipated be disposed of to landfill or applied to land when sludge is used for soil remediation. Based on its surface activity, the notified chemical is not expected to bioaccumulate.

The notified chemical is expected to degrade in STPs, surface waters, soils and landfill due to its ready biodegradability. The metabolites are expected to further degrade in both the aquatic and terrestrial compartments through biotic and abitoic processes to form water, oxides of carbon and inorganic salts.

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 laundry detergents, it is assumed that 100% of the total import volume of the chemical is released to sewer on a nationwide basis over 365 days per year. Based on assumptions applied in the SimpleTreat model, more than 87% of the notified chemical is expected to be removed during STP processes (European Commission, 2003).

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	150,000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	150,000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release:	410.96	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	22.61	million
Removal within STP	87%	Mitigation
Daily effluent production:	4,523	ML
Dilution Factor – River	1	
Dilution Factor – Ocean	10	
PEC - River:	11.81	µg/L
PEC - Ocean:	1.8	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 11.8 µg/L may potentially result in a soil concentration of approximately 78.8 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 393.8 µg/kg and 787.5 µg/kg, respectively.

7.2. Environmental Effects Assessment
No ecotoxicological data were submitted for the notified chemical. The results from ecotoxicological investigations conducted on Analogues A and E are summarised in the table below. Details of the studies of the Analogue A can be found in Appendix C.

The analogue and the notified chemical are considered to be very similar in structure and therefore the endpoints presented below are likely to reflect the ecotoxicity of the notified chemical. The results from ecotoxicological investigations conducted on the counter ion of the notified chemical are available in a reliable international peer reviewed reports by European Chemicals Agency (ECHA) and are summarised below.

Endpoint	*Result*	*Assessment Conclusion*
Measured Acute Toxicity (Analogue)		
Fish (96 h)	LC50 = 8.1 mg/L	Toxic to fish
Daphnia (48 h)	EC50 = 3.9 mg/L	Toxic to aquatic invertebrates
Acute Toxicity(Counter Ion)		
Fish (96 h)	LC50 = 349 mg/L	Not harmful to fish
Daphnia (48 h)	EC50 = 65 mg/L	Harmful to aquatic invertebrates
Algae (72 h)	E_rC50 = 2.5 mg/L	Toxic to algae
Chronic Toxicity (Counter Ion)		
Fish (30 d)	NOEC = 1.2 mg/L	Not harmful to fish
Daphnia (21d)	NOEC = 0.85 mg/L	Harmful to aquatic invertebrates with long lasting effects

On the basis of the acute toxicity data of Analogue E, it is not harmful to fish, however, it is harmful to aquatic invertebrates and toxic to algae.

On the basis of the acute toxicity data of Analogue A, the notified chemical is toxic to fish and aquatic invertebrates. 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 ready biodegradability of Analogue A, and the notified chemical's surfactant properties, the notified chemical has not been formally classified for a chronic hazard under the GHS.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) for the notified chemical has been calculated and is presented in the table below. The PNEC is calculated based on the endpoint for the most sensitive species (daphnia, EC50). Surfactants similar to the notified chemical are also reported to have ecotoxicites similar to those reported for the notified chemical. Therefore, sufficient data are available to indicate that the endpoint values reported are in fact representative of the notified chemical. Therefore, an assessment factor of 100 has been used.

Predicted No-Effect Concentration (PNEC)of the Notified Chemical for the Aquatic Compartment		
EC50 (Invertebrates).	3.9	mg/L
Assessment Factor	100	
PNEC:	39	µg/L

As the notified chemical is expected to ionise under environmental conditions, the predicted no-effect concentration (PNEC) for the counter ion has been calculated and is presented in the table below. The PNEC is calculated based on the endpoint for the most sensitive species (daphnia, NOEC) and an assessment factor of 50. A conservative assessment factor is appropriate, in this case, as only two chronic (NOEC) endpoints for two trophic levels are available.

Predicted No-Effect Concentration (PNEC) of the Counter Ion for the Aquatic Compartment		
NOEC (Invertebrates).	0.85	mg/L
Assessment Factor	50	
PNEC:	17	µg/L

7.3. Environmental Risk Assessment

The risk quotients for the notified chemical are presented in the table below.

Risk Assessment (Notified chemical)	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	11.81	39	0.303
Q - Ocean:	1.18	39	0.030

The counter ion consists of less than 10% by weight of the notified chemical. Therefore, the PEC of both river and ocean compartments for the counter ion is < 10% of the PEC for the notified chemical. Based on this, the risk quotients for the counter ion are presented in the table below.

Risk Assessment (Counter ion)	*PEC µg/L*	*PNEC µg/L*	*Q*
Q - River:	1.18	17	0.069
Q - Ocean:	0.118	17	0.007

The Risk Quotients (Q = PEC/PNEC) for the notified chemical and the counter ion have been calculated to be < 1 for the river and ocean compartments. Therefore, the notified chemical is unlikely to result in ecotoxicologically significant concentrations in the aquatic environment from the assessed use pattern. The notified chemical is expected to be readily biodegradable, thus it is unlikely to persist in surface waters or soils and is expected to degrade to form low molecular weight metabolites. Both the notified chemical and its low molecular weight metabolites are considered to have low potential for bioaccumulation. Hence, they are expected to be of low hazard to aquatic organisms. Therefore, the notified chemical is not expected to pose an unreasonable risk to the aquatic environment from the assessed use pattern.

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Analogue A (70.4% purity)
METHOD	Similar to OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure.
Species/Strain	Rat/SD IGS [Crl: CD (SD) IGS]
Vehicle	Water
Remarks - Method	No statement regarding GLP was made. Doses were calculated based on the raw test material. High dose (2,000 mg/kg bw) was first tested and caused total mortality. Therefore a lower dose (1,000 mg/kg bw) was then selected for further test.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 (F)	2,000	3/3
2	5 (F)	1,000	0/3

LD50	1,000 mg/kg bw < LD50 < 2,000 mg/kg bw
Signs of Toxicity	In high dose (2,000 mg/kg bw) group, all animals died on Day 1 after administration. Bradykinesia, crouching and diarrhoea were observed. Contamination of perianal area was seen on necropsy. No animal mortality and abnormal clinical signs were observed in low dose (1,000 mg/kg bw) group.
Effects in Organs	Gastrointestinal tract
Remarks - Results	LD50 for the pure Analogue A should be greater than 704 mg/kg bw but less than 1408 mg/ kg bw adjusted by the purity of the test substance.
CONCLUSION	The analogue chemical is harmful via the oral route.
TEST FACILITY	Saitama (2007a)

B.2. Skin sensitisation

TEST SUBSTANCE	Analogue A (70.4% purity)
METHOD	Similar to OECD TG 406 Skin Sensitisation – Guinea Pig Maximisation Test. No statement was made regarding GLP. Samples were prepared on the basis of the concentration of the pure Analogue A.
Species/Strain	Guinea pig/Hartley White, female
PRELIMINARY STUDY	Maximum Non-irritating Concentration: Intradermal: 0.03% in 24 h, 0.05% in 48 and 72 h Topical: 0.3%
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 5
INDUCTION PHASE	Induction Concentration: intradermal: 0.1% in saline or emulsion of saline/FCA topical: 1% in water
Signs of Irritation	None recorded
CHALLENGE PHASE	
1st challenge	Topical: 0.5, 0.3, 0.1, 0.05, 0.03 and 0.01%
Remarks - Method	Only one challenge with various concentrations of the analogue in separate skin spots was conducted on the test animals.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge*		
		3 h	*24 h*	*48 h*
Test Group	0.01 – 0.5%	0	0	0
Control Group	0.01 – 0.5%	0	0	0

Remarks - Results

CONCLUSION There was no evidence of reactions indicative of skin sensitisation to the analogue chemical under the conditions of the test.

TEST FACILITY Saitama (2007b)

B.3. Repeat dose toxicity - 14-day

TEST SUBSTANCE Analogue A (70.4% purity)

METHOD Similar to OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.

Species/Strain Rat/SD [Crl: CD (SD) IGS], SPF

Route of Administration Oral – gavage

Exposure Information Total exposure days: 14 days
Dose regimen: 7 days per week, once daily
Post-exposure observation period: 14 days

Vehicle Water

Remarks - Method No statement was made regarding GLP. Samples were prepared based on the raw test substance (70.4% purity).

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
Control	8 (4 M /4 F)	0	0/8
Low dose	8 (4 M /4 F)	30	0/8
Mid dose 1	8 (4 M /4 F)	100	0/8
Mid dose 2	8 (4 M /4 F)	300	0/8
High dose	8 (4 M /4 F)	1,000	2/8 (1/4 M + 1/4 F)

Mortality and Time to Death
In the study, 1 male (on Day 3) and 1 female (on Day 4) in the high dose (1,000 mg/kg bw/day) groups died. The male rat died after exhibiting bradykinesia, crouching position, paralysis of forelimbs, weight loss, prone position and bradypnea. The female rat died after exhibiting the same symptoms without prone position and bradypnea. On necropsy, gastric bleeding was seen in the male.

Clinical Observations
In the high dose (1,000 mg/kg bw/day) groups, among survival animals, bradykinesia, crouching position and salivation were seen. Supressed weight gain or weight loss were also observed in groups at early stage of the study but recovered after Day 7. One female in mid dose 2 (300 mg/kg bw/day) group showed weight loss on Day 13.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
GPT level was detected high in the males of the high dose (1,000 mg/kg bw/day) group and tended to be high in the females. As associated changes, hypertrophy of the liver was observed on necropsy and weight increase of the liver was noted, suggesting effects of the tested chemical.

Effects in Organs
All animals of the high dose (1,000 mg/kg bw/day) groups were seen with gastric erosions and ulcers on the necropsy. One female of the mid dose (300 mg/kg bw/day) group was seen with gastric erosion, indicative of the effects of the tested chemical.

Remarks – Results
The No Observed Effect Levels (NOELs) were established separately for male and female rats based on the organ effects on stomachs.

CONCLUSION
The NOELs were established as 300 mg/kg bw/day (equivalent to 211.2 mg/kg bw/day pure analogue chemical) for males and 100 mg/kg bw/day (equivalent to 70.4 mg/kg bw/day pure analogue chemical) for females in this study, based on the observed gastric erosion in necropsy.

TEST FACILITY Saitama (2007c)

B.4. Repeat dose toxicity - 90-day

TEST SUBSTANCE Analogue B (62.4% purity)

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
Species/Strain Rat/SD [Crl: CD (SD)]
Route of Administration Oral – diet
Exposure Information Total exposure days: 91 days
Dose regimen: 7 days per week continuously
Post-exposure observation period: 14 days
Vehicle Mixed in the feed
Remarks - Method Sample preparation was based on the raw test substance with a purity of 62.4%. The stability of the test substance in the feed was confirmed.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration*		*Mortality*
		Nominal (%)	*Actual (mg/kg bw/day)*	
Control	20 (10 M/10 F)	0	0	0/20
Low dose	20 (10 M/10 F)	0.125	89 (male), 100 (female)	0/20
Mid dose I	20 (10 M/10 F)	0.25	180 (male), 200 (female)	0/20
Mid dose II	20 (10 M/10 F)	0.5	370 (male), 410 (female)	0/20
High dose	20 (10 M/10 F)	1	720 (male), 830 (female)	0/20
Control recovery	10 (5 M/5 F)	0	0	0/10
High dose recovery	10 (5 M/5 F)	1	720 (male), 830 (female)	0/10

Mortality and Time to Death
No mortality was observed.

Clinical Observations
No dose-dependent significant clinical signs were noted throughout the study. The motor activity of the female rats in the high dose (1%) recovery group was significantly higher than that of the control recovery group at the end of the recovery period (14 days after the termination of the administration). Body weight of the males in mid dose II (0.5%) and high dose (1%) groups tended to be lower than that of the males in other groups towards the second half of the study period, possibly corresponding to the lower level of food intake by the animals. Weight gain of the females in mid dose (0.5%) group was significantly higher than that of the females in the control group, possibly corresponding to the higher level of food intake by the animals.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
In female rats, the percentage of monocytes in animals treated with dose 0.125% was significantly lower than that of the control group but no dose-response was observed.

In male rats, significant lower prothrombin time in the groups treated with doses 0.125% and above was noted, however the significance of this effect is not clear. Significant lower levels of urea nitrogen were also recorded with dose groups of 0.125 and 0.25% but no dose-response was noted. Significant lower blood levels of sodium were recorded in dose groups of 0.25 and 1%. Higher A/G ratios not associated with changes in total protein and albumin was also observed in dose group of 0.5%. Significant lower MCHC, haemoglobin level and haematocrit was noted in the dose group of 1%. Higher blood level of potassium was also recorded in the

dose group of 1%.

Effects in Organs
Increase of liver weight in female rats treated with mid dose II (0.5%) and high dose (1%) of the test substance was noted, possibly due to centrilobular hypertrophy of the hepatocytes.

Remarks – Results
The No Observed Adverse Effect Levels (NOAELs) were established based on the effects on body weight and feed consumption in the male rats, and on the livers of the female rats.

CONCLUSION
The NOAELs were established as 180 mg/kg bw/day (equivalent to 112.3 mg/kg bw/day pure chemical) for males and 200 mg/kg bw/day (equivalent to 124.8 mg/kg bw/day pure chemical) for females in this study, based on the observations on body weight, feed consumption and effects on the female livers.

TEST FACILITY Research Institute for Animal Science in Biochemistry & Toxicology (2012)

B.5. Genotoxicity – bacteria

TEST SUBSTANCE Analogue A (70.4% purity)

METHOD Similar to OECD TG 471 Bacterial Reverse Mutation Test

Species/Strain	*S. typhimurium*: TA98 and TA100
Metabolic Activation System	S9
Concentration Range in Main Test	a) With metabolic activation: TA98: 39, 78, 156, 313, 625 and 1,250 µg/plate TA100: 10, 20, 39, 78, 156 and 313 µg/plate b) Without metabolic activation: 2.4, 4.9, 10, 20, 39 and 78 µg/plate
Vehicle	Water
Remarks - Method	No detailed study descriptions were provided and no statement was made regarding GLP. Samples were prepared based on the pure analogue chemical.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 78	≥ 39	Not observed	Negative
Test 2		≥ 39	Not observed	Negative
Present				
Test 1	≥ 1,250 (TA98) ≥ 313 (TA100)	≥ 625 (TA98) ≥ 313 (TA100)	Not observed	Negative
Test 2		≥ 625 (TA98) ≥ 313 (TA100)	Not observed	Negative

Remarks - Results

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

TEST FACILITY BML (2007)

B.6. Genotoxicity – *in vitro*

TEST SUBSTANCE Analogue A (70.4% purity)

METHOD Similar to OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test.

Species/Strain	
Cell Type/Cell Line	CHL/IU (Chinese hamster)
Metabolic Activation System	S9
Vehicle	Saline
Remarks - Method	

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0, 78.1, 156, 313, 625, 1250, 2500 and 5000	48 h	48 h
Test 2	0, 32.8, 39.1, 46.5, 55.2, 65.7 and 78.1	48 h	48 h
Present			
Test 1	0, 156, 313, 625, 1250, 2500 and 5000	6 h	24 h

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 156	≥ 65.7	Not observed	Negative
Test 2	≥ 65.7			
Present				
Test 1	≥ 313	≥ 186	Not observed	Ambiguous
Test 2		≥ 203	Not observed	Negative

Remarks - Results Test with metabolic activation at concentration of 186 μg/ml of the analogue resulted in chromosome aberration rate of 5.0%. This observation was not reproduced in a second test and no dose-dependent observation was noted.

CONCLUSION The analogue chemical was not clastogenic to Chinese hamster CHL/IU cells treated *in vitro* under the conditions of the test.

TEST FACILITY UBE (2007)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Analogue A
METHOD	Preliminary study of the extent of degradation of the test substance: Closed System Test. The test was conducted in Japan according to the "Tests of the extent of degradation of chemical substances by microorganisms, etc." stipulated in the "Circular on Test Methods of New Chemical Substances" (November 21, 2003, Yakushokuhatsu No. 1121002; November 13, 2003, Seikyoku No. 2, Kanhokihatsu No. 031121002).
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None reported
Analytical Monitoring	Measurement of biochemical oxygen demand (BOD) using a device for measuring oxygen demand in a closed system
Remarks - Method	No significant deviations from the test guidelines were reported, however, it was noticed that a reference substance was not used in the test.

RESULTS

Extent of degradation from BOD (%)			
Test substance		*Reference substance*	
Day	*% Degradation*	*Day*	*% Degradation*
7	65	7	Not reported
14	77	14	Not reported
28	77	28	Not reported

Remarks - Results	Since the result of a reference compound was not reported, the test did not satisfy the validity criteria. However, 65% degradation of the notified chemical was achieved within the 10-d window. Therefore, based on the significant observed degradation, the test substance is expected to be readily biodegradable.
CONCLUSION	The analogue and, by inference, the notified chemical are readily biodegradable
TEST FACILITY	UBE (2006)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Analogue A
METHOD	Semi-static- Fish, Acute Toxicity Test OECD TG 203
Species	*Oryzias latipes*
Exposure Period	96 hours
Auxiliary Solvent	None reported
Water Hardness	None reported
Analytical Monitoring	None reported
Remarks – Method	The test was conducted according to the guidelines above. No significant deviations from the test guidelines were reported.

RESULTS

Nominal Concentration (mg/L)	*Number of Fish*	*Mortality(%)(96 h)*
Control	8	0
0.469	8	0
0.938	8	0
1.88	8	0
3.75	8	0
7.5	8	37.5
15.0	8	100

EC50	8.1 (5.7 – 120.0) mg/L at 96 hours mg/L
NOEC (or LOEC)	None reported
Remarks – Results	All validity criteria for the test were satisfied. All the exposure solutions containing the test substance were observed to be clear and colourless. The 96-hour LC_{50} was calculated by Probit method

CONCLUSION The analogue and, by inference, the notified chemical are toxic to fish

TEST FACILITY Yamane and Kurihara (2006)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Analogue A

METHOD Static- Daphnia sp., Acute Toxicity Test- OECD TG 202

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None reported
Water Hardness	None reported
Analytical Monitoring	None reported
Remarks - Method	The test was conducted according to the guidelines above. No significant deviations from the test guidelines were reported.

RESULTS

Nominal Concentration (mg/L)	*Number of D. magna*	*Cumulative % Immobilised 48 h*
Control	20	0
0.625	20	0
1.25	20	0
2.5	20	0
5.0	20	90
10.0	20	100

EC50	3.9 (3.4 – 4.2) mg/L at 48 hours
NOEC (or LOEC)	None reported
Remarks - Results	All validity criteria for the test were satisfied. All the exposure solutions containing the test substance were observed to be clear and colourless. The 96-hour LC_{50} was calculated by Probit method.

CONCLUSION The analogue and, by inference, the notified chemical are toxic to aquatic invertebrates

TEST FACILITY Yamane and Kurihara (2006)

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