File No: LTD/1543

September 2012

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Octanamide, N-hydroxy- (INCI NAME: Caprylhydroxamic Acid)

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:

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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/1543	Bronson and Jacobs Pty Ltd	Octanamide, N-hydroxy- (INCI NAME: Caprylhydroxamic Acid)	ND*	≤ 1 tonne per annum	A component of cosmetic products

*ND = not determined

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified chemical cannot be classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

and

The classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2009) is presented below.

	Hazard category	***Hazard statement***
Environment	Acute Category 2	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 workers during transport and storage, reformulation and retail. In addition, the notified chemical is not considered to pose an unreasonable risk of adverse systemic effects to workers in hair and beauty salons if the maximum end use concentration is 0.3%.

When used in the proposed manner, the notified chemical is not considered to pose an unreasonable risk of adverse systemic effects to the public if the maximum end use concentration is 0.3%.

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

REGULATORY CONTROLS

- The notified chemical should be considered for listing on the SUSMP based on the repeated dose toxicity results. The Full Public Report will be provided to the Medicines and Poisoning Scheduling Secretariat.

CONTROL MEASURES
Occupational Health and Safety

- Employers at reformulation plants should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Avoid contact with eyes and skin.

- A copy of the MSDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

- Formulators should consider monitoring products for formation of hydroxylamine, if formulated at pH < 5 or pH > 8, or if formulation intermediates are substantially acid or basic.

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
- the importation volume exceeds one tonne per annum notified chemical;
- the notified chemical is used in cosmetic products at > 0.3%;
- the notified chemical is used in oral care products;
- new information on the inhalation 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 in cosmetic products, 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 MSDS of the product containing the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

Applicant(s)
Bronson and Jacobs Pty Ltd (ABN 81 000 063 249)
70 Marple Avenue VILLAWOOD NSW 2163

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: analytical data

Variation of Data Requirements (Section 24 of the Act)
Variation to the schedule of data requirements is claimed as follows: Boiling Point, Vapour Pressure, Hydrolysis as a Function of pH, Partition Co-Efficient, Adsorption/Desorption, Dissociation Constant, Particle Size, Flammability Limits and Explosive Properties

Previous Notification in Australia by Applicant(s)
New topical excipient substance application was approved by Therapeutic Goods Administration.

Notification in Other Countries
Canada

2. IDENTITY OF CHEMICAL

Marketing Name(s)
Lexgard CHA
Spectrastat (containing 15% notified chemical)

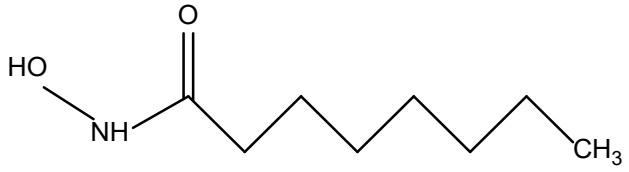
CAS Number
7377-03-9

Chemical Name
Octanamide, N-hydroxy-

Other Name(s)
Caprylhydroxamic Acid (INCI name)
Octanohydroxamic Acid
N-hydroxyoctanamid
N-hidroxioctanamida
N-hydroxy-caprylohydroxamic acid
Caprylohydroxamic acid
Capryloylhydroxamic acid
CHA
Octanoylhydroxamic acid
Oct HA
Taselin

Molecular Formula
$C_8H_{17}NO_2$

Structural Formula



Molecular Weight
159.26 Da

Analytical Data
Reference NMR, IR, HPLC and MS spectra were provided.

3. COMPOSITION

Degree of Purity > 99%

Hazardous Impurities/Residual Monomers None

Non Hazardous Impurities/Residual Monomers (>1% by weight) None

Additives/Adjuvants None

4. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa: white to tan crystalline solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	81ºC	Measured
Boiling Point	343.32ºC	Calculated (Adapted Stein & Brown method)
Density	341.3 kg/m^3 at 25ºC (sample not compressed) 478.9 kg/m^3 at 25ºC (sample tamped down)	Measured
Vapour Pressure	3.33 × 10^{-7} kPa at 25ºC	Calculated (Modified Grain Method)
Water Solubility	1.55 g/L at 23°C	Measured
Hydrolysis as a Function of pH	Not determined	The notified chemical contains hydrolysable functionality but it is not expected to significantly hydrolyse under environmental pH (4 – 9).
Partition Coefficient (n-octanol/water)	log Kow = 1.66	Calculated by KOWWIN (v1.67) (US EPA, 2009)
Adsorption/Desorption	log K_{oc} = 1.84	Calculated by KOCWIN (v2.00) (US EPA, 2009). Although the calculated log K_{oc} value is low, the notified chemical is expected to sorb to soil and sediments due to its chelating ability.
Dissociation Constant	pKa ~ 9	Estimated based on the pKa of hydroxamic acids
Particle Size	Not determined	Imported as a component of a blended liquid or in finished formulations.
Flash Point	113ºC at (pressure unknown)	Measured
Autoignition Temperature	264ºC at 102 kPa	Measured
Explosive Properties	Not determined	The notified chemical does not contain structural groups associated with explosive properties.

Discussion of Properties
For full details of tests on physical and chemical properties, refer to Appendix A.

Reactivity
Stable under normal environmental and usage conditions. The notified chemical forms strong complexes with oxidised transition metals almost instantaneously. May react with oxidisers and acids. Decomposition products at high temperature are ammonia and oxides of carbon and nitrogen.

The chemical may form octanoic acid and hydroxylamine if hydrolysed. This is most likely to occur at high or low pH.

Dangerous Goods classification
Based on the submitted physical-chemical data in the above table the notified chemical is not classified according to the Australian Dangerous Goods Code (NTC, 2007). However the data above do not address all Dangerous Goods endpoints. Therefore consideration of all endpoints should be undertaken before a final decision on the Dangerous Goods classification is made by the introducer of the chemical.

5. INTRODUCTION AND USE INFORMATION

Mode of Introduction of Notified Chemical (100%) Over Next 5 Years
The notified chemical will not be manufactured in Australia. It will be imported as a blended mixture (< 20% notified chemical) or as a component of finished formulations (cosmetic and personal care products) at < 0.5%.

Maximum Introduction Volume of Notified Chemical (100%) Over Next 5 Years

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.5	0.7	≤ 1	≤ 1	≤ 1

Port of Entry
The notified chemical will be imported through various sea ports.

Identity of Recipients
Importers & distributors of bulk materials/chemicals and/or finished products.

Transportation and Packaging
The bulk material (< 20% notified chemical) will be transported into Australia by ship in 27 L HDPE closed-head pails with tamper-evident closures. It will be transported by road from the wharf to the notifier's site for storage, from where it will be distributed to customers for reformulation. The finished cosmetic and personal care products will be packaged into consumer packaging (e.g. plastic tubes, jars, bottles and sticks) and packed into shippers before being transported by truck or van to various warehousing facilities or directly to retail outlets or salons around Australia.
Where the notified chemical is imported as a component of finished formulations it will be transported into Australia by ship in the consumer packaging, packed in bulk cartons. From the dock it will be transported by road to the distributor's site and from there by truck or van to various warehousing facilities or directly to retail outlets around Australia for retail sale.

Use
A chelating agent for use in topical cosmetic and personal care formulations including hair and skin care and toiletry formulations at up to 0.5%.

Operation description
The notified chemical will not be manufactured in Australia. It will be imported as a blended bulk raw material (< 20% notified chemical) or as a component of finished formulations/cosmetic/personal care products at < 0.5%.

Reformulation
When imported as bulk material for reformulation of cosmetic products, it will be transported from the dock directly to the notifier's warehouse for storage and forwarded to the formulation site on order. The reformulation process will vary with the product and reformulation site. Typically, the formulation process will involve manual weighing, transfer to a mixing vessel, a blending operation which is usually automated and in a closed vessel, followed by quality control testing, transfer to a storage tank and then filling using automatic lines in containers of various types and sizes. Manufacturing equipment is typically cleaned with hot water and rinsed after every batch. The containers will then be sealed and packaged into cardboard transport cartons.

End-use - consumer
The final cosmetic product will be distributed to retail outlets, displayed and sold to the public. Finished cosmetic products containing < 0.5% of the notified chemical will be used by consumers. Products will be applied by hand, applicators and aerosols.

End-use - professional
The final cosmetic product will also be distributed for professional use in beauty salons and by hairdressers. Finished cosmetic products containing < 0.5% of the notified chemical will be used by professionals. Products will be applied by hand, applicators and aerosols.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage			
From dock to warehouse	1 – 2	Incidental exposure only	Intermittent
Warehouse	1 - 2/site	Incidental exposure only	Intermittent
From warehouse to formulators	1 - 2	Incidental exposure only	Intermittent
Reformulation			
Formulation, filling, cleaning maintenance, quality control	1 - 3/site	1 - 2	20 - 50
Retail workers	> 500	Incidental exposure only	Intermittent
Professionals	5000	Up to 8	200

Exposure Details
Transport, distribution and store workers are not expected to be exposed to the notified chemical at up to 20% except in an event of an accident. In case of such accidental exposure, main routes of exposure would be dermal and ocular. However, the likelihood of such an accidental exposure is minimal.

Dermal and ocular exposure of the chemist to the notified chemical at up to 20% may occur during weighing, mixing and formulation processes including sampling and testing of the raw and finished products for QA purposes.

Packers of cosmetic products, during monitoring the line filler and the capper where the finished product will be filled into retail bottles, may also be exposed to the notified chemical at up to 0.5% via dermal and ocular routes.

Potential inhalation exposure may occur during these processes if aerosols are generated.

However exposure is likely to be minimised through the automation of the process and closed systems and the

use of personal protective equipment (PPE) such as safety glasses, safety shoes, impervious gloves and overalls. In addition, appropriately located exhaust is expected to be used. Overall, the exposure of these workers to the notified chemical is expected to be low.

Workers in hair and beauty salons may experience extensive dermal exposure during application of products containing the notified chemical (< 0.5%) by hand. Such professionals may use some personal protective equipment to minimise repeated exposure, and good hygiene practices are expected to be in place. Exposure of such workers is expected to be of either a similar or higher level than that experienced by consumers using products containing the notified chemical.

6.1.2. Public Exposure

End-use products are designed to be sold to consumers. The general public will be repeatedly exposed to levels of the notified chemical up to 0.5% in a range of cosmetic products.

Public exposure from transport, storage, reformulation or disposal is considered to be negligible.

Public exposure to the notified chemical is expected to be widespread and frequent through daily use of personal care products containing the notified chemical. Exposure to the notified chemical will vary depending on individual use patterns. The principal route of exposure will be dermal, and accidental ocular exposure may also occur. Some ingestion may also occur from the use of facial or oral products e.g lip products or toothpaste. Inhalation exposure is not expected as the notified chemical is not planned to be used in products that are applied by spray and the notified chemical has very low vapour pressure.

The notifier has advised that the notified chemical will be used in a wide range of cosmetic products, but not including oral care products. Public exposure to the notified chemical in Australia has been calculated using estimates for preservative exposure in the Scientific Committee on Consumer Safety' (SCCS's) Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation (SCCS, 2010) and applying the following assumptions:

- Bodyweight (BW) of 60 kg for females (SCCS, 2010);
- The maximum concentration of the notified chemical in cosmetic products 0.5%;
- 100% dermal absorption (worst case scenario);
- An individual uses all product types containing the notified chemical;
- Oral care products are not included.

Type of exposure	Product	g/day	mg/kg bw/day
Rinse-off skin & hair cleansing products	Shower gel	0.19	2.79
	Hand wash soap	0.20	3.33
	Shampoo	0.11	1.51
	Hair conditioner	0.04	0.67
Leave-on skin & hair care products	Body lotion	7.82	123.20
	Face cream	1.54	24.14
	Hand cream	2.16	32.70
	Deo non-spray	1.50	22.08
	Hair styling	0.40	5.74
Make-up products	Liquid foundation	0.51	7.90
	Make-up remover	0.50	8.33
	Eye make-up	0.02	0.33
	Mascara	0.025	0.42
	Lipstick	0.06	0.90
	Eyeliner	0.005	0.08
Total		**15.1**	**234**

Total systemic exposure was calculated as 1.17 mg/kg bw/day for a female of 60 kg bw (SCCS, 2010) using all types of cosmetic products, in the above table, containing 0.5% notified chemical. It is expected that consumers may use multiple products containing the notified chemical as a chelating agent.

In the absence of application specific data, this exposure estimate was calculated assuming 100% dermal absorption of the amount left on the skin following application, as the worst case scenario, and use of multiple cosmetic products simultaneously by an individual.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Skin irritation and sensitisation – repeated insult patch test	non-irritating and non-sensitising at 100%
Eye irritation - bovine corneal opacity and permeability test	Not corrosive or a severe irritant
In vitro eye irritation – EpiOcular test	non-irritating
Rat, repeat dose oral toxicity – 91 days.	NOAEL = 50 mg/kg bw/day
Developmental and reproductive effects	non-teratogenic
Mutagenicity – bacterial reverse mutation	non mutagenic
Mutagenicity – bacterial reverse mutation	evidence of very weak mutagenicity
Genotoxicity – Rec assay	non genotoxic

Toxicokinetics, metabolism and distribution
No toxicokinetic data was submitted for the notified chemical. Based on the physicochemical properties, percutaneous absorption of the notified chemical is likely. Given the low molecular weight (159 Da) absorption across the GI tract is possible by passive diffusion through the aqueous pores or micellular solubilisation.

The toxicokinetics of the simple hydroxamic acid, acetohydroxamic acid (AHA), has been investigated in mice (Fishbein et al, 1973). In this study radioactively labelled AHA was intraperitoneally administered to mice and absorption, distribution and metabolism measured. The test revealed that AHA is rapidly absorbed into the blood and excreted in the urine mostly unchanged (60%), or as the amide (15-20%) or acid (10%). A further 7% is expired from the lungs as CO_2 derived from the acid. It is not significantly bound to any tissue. When acid is formed from the hydroxamate, hydroxylamine is formed as a transient species and is rapidly reduced to ammonia by haemoglobin, which is itself oxidised to methaemoglobin. Given the presence of the same functional group, the metabolism of AHA may be similar to that of the notified chemical.

Acute toxicity
The notified chemical is expected to have a low oral toxicity based on reported rat LD50 values (> 8,820 mg/kg) (RTECS 2011). No data was available on acute dermal or inhalation effects.

Skin irritation and skin sensitisation
Skin irritation or sensitisation studies to OECD protocols were not available. The notified chemical is potentially surface active and has a low molecular weight and therefore is likely to have irritant properties. However it was not irritating or sensitising in a human repeated insult patch test (52 subjects).

Based on the low molecular weight, potential surface activity and irritancy potential, it is likely that the notified chemical will be able to be absorbed into the skin. Hydroxamic acids are known to inhibit certain enzymes such as urease (Bauer & Exner, 1974) and therefore have been shown to have protein reactivity, an important factor in skin sensitisation potential. The skin sensitisation potential of the notified chemical cannot be ruled out.

The potential for skin irritation and sensitisation is expected to be significantly reduced at the low proposed concentration of end-use (up to 0.5%).

Eye irritation
The notified chemical was tested in a Bovine Corneal Opacity and Permeability Test (BCOP), which focuses on corneal injury. This study protocol has been formally validated only for identification of corrosion and severe irritation. Under the conditions of the test, some irritancy was demonstrated, but significantly below the level to consider the chemical a severe eye irritant. The reliability of the study is reduced by the fact that concurrent positive controls were not included. Based on the BCOP results, the chemical is not expected to cause severe irritation if there is accidental ocular exposure, however it is not possible to conclude the notified chemical is a non eye irritant based on the test results.

An *in vitro* eye irritation test was also performed on the notified chemical at 100% using the EpiOcular Tissue Model. This test method is not a validated alternative to the *in vivo* animal test, although efforts towards

validation are underway. The study authors predicted the notified chemical to be non-irritating to the eye based on the results of the study.

Although the eye irritation potential of the notified chemical as introduced (20%) cannot be ruled out based on the data from the *in vitro* studies, dilute solutions (e.g. 0.5%) of the notified chemical are unlikely to cause significant eye irritation.

Repeated dose toxicity (chronic)
A 90-day repeat dose toxicity study conducted on the notified chemical was summarised in a journal article (Sugiyama et al, 1974). In the study, ten rats of each sex were administered 0, 100, 500 or 2500 mg/kg bw/day of taselin (10% notified chemical in lactose) by gavage. In the 2500 mg/kg bw/day group, increases in leucocyte count and spleen weights and significant decreases in erythrocyte, hematocrit and haemoglobin counts were observed. In addition, slight atrophy in the epithelial cells of the glomeruli and deposit of blood pigment in spleen cells in some animals were observed in the 2500 mg/kg bw/day group. The NOAEL was determined to be 500 mg/kg bw/day for taselin under the conditions of the study. Based on taselin containing 10% notified chemical, the notified chemical is expected to have a NOAEL of 50 mg/kg bw/day. The study authors noted that the haematological effects seen in the study were consistent with those expected to occur with hydroxylamine derivatives.

No repeated dose information was available for exposure routes other than oral.

Toxicity for reproduction
The notified chemical (10%) was tested in a teratological study in rats (Suzuki et al, 1975). Eighteen pregnant female Wistar rats were administered 0, 50, 250 or 500 mg/kg bw/day of taselin (10% notified chemical) by gavage from days 9 to 14 of gestation. Most were killed on day 20 of gestation. Body weight gains and food intakes were slightly reduced in the dams at 250 and 500 mg/kg bw/day. Foetal body weights were reduced and reduction in ossification was observed at 250 and 500 mg/kg bw/day, however no morphological or functional differentiation of the neonates was observed at any dose. It was suggested that growth retardation of the foetuses and neonates observed at 250 and 500 mg/kg bw/day could have been caused by the slight depression of body weight gains and food consumption in the dams. Based on the absence of adverse effects on neonates at non-toxic doses for the dams, the notified chemical was not teratogenic under the conditions of the study.

Mutagenicity
A recently conducted bacterial reverse mutation study in five strains of *Salmonella typhimurium* was submitted for the notification. Significant toxicity was seen at the higher dose levels tested, however no mutagenic effects were observed under the conditions of the study, with or without metabolic activation.

The notified chemical has previously been tested in the *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay and the *Bacillus subtilis* Rec Assay, as reported by Ohta et al (1980). In the reverse mutation study the notified chemical showed very weak mutagenicity in *E.coli* with and without metabolic activation, but was non-mutagenic in all five *S.typhimurium* bacterial strains under the conditions of the test. The notified chemical was negative in the Rec screening assay with *Bacillus subtilis*.

Based on the most recent study, the notified chemical does not show mutagenicity in bacteria. The older study (Ohta et al, 1980) indicated that the chemical may have some mutagenic potential. However, there is limited data overall, and in particular, no studies are available to assess clastogenicity of the chemical. The available data does not raise a strong suspicion of genotoxicity, however this cannot be ruled out.

Other toxicological data
A range of hydroxamic acid derivatives, including the notified chemical, were demonstrated to have effects in human lymphocytes consistent with inhibition of ribonucleotide reductase, an iron-requiring enzyme (Ganeshaguru et al, 1980). The study authors attributed the effects to iron-binding. They did not consider the effect to be related to cytotoxicity, but stated there was evidence that the compounds may be toxic to cells.

Hydrolysis products
The expected break-down products of the notified chemical, if hydrolysed, are octanoic acid and hydroxylamine. Hydroxylamine is classified under the NOHSC *Approved Criteria for Classifying Hazardous Substances* as a Class 3 carcinogen (limited evidence of a carcinogenic effect) and is haematotoxic.

Health hazard classification
Based on the available data the notified chemical cannot be classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on data provided the irritating and sensitising potential of the notified chemical can not be ruled out.

Although reformulation workers will handle the imported notified chemical at concentrations < 20%, exposure is expected to be low given the proposed use of PPE and largely enclosed, automated processes used in reformulation facilities. The risk to the occupational health and safety of reformulation workers is therefore not considered unreasonable, due to the expected low exposure of the notified chemical.

Workers in hair and beauty salons may be exposed to cosmetic products containing the notified chemical (< 0.5%) during application of the products to their clients. They are not expected to use PPE during these processes. The exposure and risk for these workers is considered to be similar to that of consumers (see section 6.3.2 below).

6.3.2. Public Health
The general public will be repeatedly exposed to the notified chemical during the use of cosmetic products containing the notified chemical at up to 0.5% concentration. Dermal exposure is expected to be extensive. Accidental ocular exposure may occur, and oral exposure may also occur through use of facial or oral products. Inhalation exposure is not expected as the notified chemical is not planned for use in spray products.

Local effects
The irritating and sensitising potential of the notified chemical can not be ruled out. However, the notified chemical will be present in cosmetic products at concentrations < 0.5% and therefore the potential effects are expected to be reduced by the low concentration.

Systemic effects
Effects indicative of toxicity were seen in a repeated dose study in rats. The potential combined total systemic exposure to the public from the use of the notified chemical in multiple cosmetic products (excluding oral care products), considering a 60kg female as the representative receptor of concern, was estimated to be 1.17 mg/kg bw/day, based on a use concentration of 0.5%. Using a NOAEL of 50 mg/kg bw/day based on the repeated dose study using the notified chemical, the margin of exposure (MOE) is calculated to be 43. An MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. Therefore at the proposed maximum concentration of use, adverse long-term effects on consumers cannot be ruled out. Reduction of the use concentration to 0.3% would increase the MOE to 71. This MOE is still below 100, however, given that the exposure estimate is based on the conservative assumption of 100% dermal absorption of the amount left on the skin following application, and the simultaneous use of various products containing the maximum concentration of notified chemical, the risk to the public is not considered unreasonable if products contain a maximum of 0.3% of the notified chemical.

Based on the available data, the notified chemical does not show a concern for genotoxicity, noting however that slight mutagenicity was reported in one study, and that clastogenicity studies are not available.

Hydrolysis of the notified chemical may release hydroxylamine, which is a hazardous substance. Although test data is not available on this endpoint, significant hydrolysis is only expected in acidic or alkaline conditions, This assessment considers that most cosmetic products using the notified chemical would be within the neutral range pH 5 – 8.

Overall, the risk to the public is not considered unreasonable, if the concentration of use is reduced to maximum of 0.3% of the notified chemical, in order to provide an adequate safety margin for repeated and concurrent use of products containing the notified chemical.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

Release of Chemical at Site
The notified chemical will be imported as a component of finished cosmetic products and will also be imported as raw material for reformulation. During reformulation the notified chemical will be blended with other ingredients and packaged into consumer packaging. Release of the notified chemical to the environment may occur as accidental spills during transport or handling. Spills of the notified chemical are expected to be absorbed into an inert material and either reused or disposed of to landfill. Release of the notified chemical to the environment (< 1% of the annual import volume) from cleaning and maintenance operations of the blending and bottling equipment may occur, with rinsings being released to sewer after onsite treatment of the wastewater.

Release of Chemical from Use
As the notified chemical is used in cosmetics and personal care formulations, such as skin care products and shampoos, it is expected that the majority of the annual import volume will be released to sewer through consumer use. A small proportion of the notified chemical (estimated to be ≤ 2%) may remain as residues within the end-use containers.

Release of Chemical from Disposal
It is expected that end-use containers containing residues of the notified chemical will either be recycled or disposed of as domestic garbage and end up in landfill sites.

7.1.2. Environmental Fate

The majority of the notified chemical will be disposed of to the sewer, with minor amounts disposed of to landfill. The notified chemical is expected to be largely removed from sewage treatment plant (STP) influent since the notified chemical is readily biodegradable. As the notified chemical is anticipated to remain in the water column based on its high reported water solubility, there is the potential for some release to surface waters where it is expected to disperse and degrade. However, the notified chemical is likely to sorb to sediments due to its chelating ability. Notified chemical that partitions to sediment and sludge in STPs will share its fate and will likely be landfilled or used for soil remediation.

The literature indicates a partitioning of 16:1 between water and carbon tetrachloride for the notified chemical (Addison and Côté 1973). This tendency to partition to water is supported by the calculated partition coefficient (log Kow) of 1.66. Therefore, the potential for the notified chemical to bioaccumulate is low, based on its low partition coefficient and ready biodegradability.

In soil and landfill, the notified chemical may leach due to its high water solubility. However, the notified chemical has the potential to chelate to metals in soils which will limit its mobility. The notified chemical is expected to degrade through biotic or abiotic processes to form water and oxides of carbon and nitrogen.

For the details of the environmental fate studies, refer to Appendix C.

7.1.3. Predicted Environmental Concentration (PEC)

Since most of the notified chemical will be released to the sewer, the worst case predicted environmental concentrations (PECs) for release to ocean and inland rivers are calculated as follows based on the water consumption of the Australian population. The PECs estimated below are an overestimate as the notified chemical is readily biodegradable and is therefore expected to be substantially biodegraded during sewage treatment.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	1000	kg/year
Proportion expected to be released to sewer	100%	
Annual quantity of chemical released to sewer	1000	kg/year
Days per year where release occurs	365	days/year
Daily chemical release	2.74	kg/day
Water use	200	L/person/day
Population of Australia (Millions)	21.161	million
Removal within STP	0%	
Daily effluent production	4,232	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	0.65	µg/L
PEC - Ocean:	0.065	µg/L

The notified chemical is readily biodegradable and also expected to chelate to components of sludge and sediments, hence significant removal of the notified chemical from influent by sewage treatment plant (STP) processes is expected. However, the worst-case scenario is considered below where the majority of the notified chemical is assumed to be released in effluent.

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 0.647 µg/L may potentially result in a soil concentration of approximately 4.316 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 21.58 µg/kg and 43.16 µg/kg, respectively. Due to the efficient removal of the notified chemical in STPs, these values represent maximum concentrations only.

7.2. Environmental Effects Assessment

A fish ecotoxicity study on the notified chemical was provided in the form of a peer reviewed paper in the literature (Addison & Côté, 1973). A 96 hour LC50 was extrapolated from a regression of LT50s (time to death for 50% of the test group) on concentration of the notified chemical. Since the endpoint has been extrapolated from a regression curve, it should be treated with caution.

Details of the study can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 (96 h)* = 2.6 mg/L	Toxic to fish

*Extrapolated from LT50 data

Under the Globally Harmonised System of Classification and Labelling of Chemicals (United Nations, 2009) the notified chemical is classified as toxic to fish. Based on this toxicity to fish the notified chemical is formally classified as “Acute category 2; Toxic to aquatic life”. However, as the notified chemical is readily biodegradable and has a predicted log Kow of < 4, it is not classified for long term effects.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) was calculated using an extrapolated LC50 (96 h) for fish. A conservative assessment factor of 1000 was used as only a single extrapolated endpoint is available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Extrapolated fish LC50 (96 h)	2.6	mg/L
Assessment Factor	1000	
PNEC:	2.6	µg/L

7.3. Environmental Risk Assessment

The risk quotients (Q = PEC/PNEC) are calculated below:

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	0.65	2.6	0.249
Q - Ocean	0.065	2.6	0.0249

The notified chemical is a chelating agent used in cosmetics. As a result of its use pattern, the majority of the total annual import volume is expected to be disposed of to the sewer. In sewage treatment plants the notified chemical is expected to biodegrade and therefore be efficiently removed from influent. Any notified chemical that is released to surface waters has a low potential to bioaccumulate and is not expected to persist in the environment. As the risk quotient is below 1 for the unmitigated worst case treated effluent discharge scenario, the notified chemical is not expected to pose an unreasonable risk to the environment on the basis of its assessed use pattern and maximum annual importation volume.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point Average 81ºC

Method	Differential scanning calorimetry method
Remarks	The DSC was run using a TA Instruments Q200 DSC with RCS. The temperature program was a 10°C/min ramp from ambient to 100°C, a 5°C/min cooling ramp to -20°C and a heating ramp at 10°C/min to 100°C.
Test Facility	Edison Analytical Laboratories Inc. (2009)

Density 341.3 kg/m^3 at 25ºC (sample not compressed)
478.9 kg/m^3 at 25ºC (sample tamped down)

Method	PLTL-90
Remarks	Only test summary was supplied.
Test Facility	Petro-Lubricant Testing Laboratories INC. (2010)

Water Solubility 1.55 g/L at 23°C

Method	OECD TG 105 Water Solubility
Remarks	Shake flask method. A preliminary test indicated that the approximate solubility of the test substance (100% notified chemical) was estimated by visual inspection to be 1-2 g/L. In the definitive test solutions were equilibrated, filtered and the test substance concentration was determined by HPLC. The pH of each sample was reported to be recorded, but the values were not detailed in the test report. The water solubility is calculated to be 2.64 g/L (WSKOW v1.41; US EPA 2009). The notified chemical is likely to be soluble at alkaline pH, but sparingly soluble at most pH values encountered in the environment.
Test Facility	Eurofins PSL (2010)

Flash Point 113ºC at (pressure unknown)

Method	ASTM D-93
Remarks	Pensky Martin Closed Cup was used. Only test summary was supplied.
Test Facility	Petro-Lubricant Testing Laboratories INC. (2010)

Autoignition Temperature 264ºC at 102 kPa

Method	ASTM E-659
Remarks	Ignition delay time was 47.5 seconds. Only test summary was supplied.
Test Facility	Petro-Lubricant Testing Laboratories INC. (2010)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Skin irritation and sensitisation – human volunteers (Repeated Insult Patch Test)

TEST SUBSTANCE	Notified chemical
METHOD	
Study Design	Induction Procedure: Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test substance was applied to upper back (between the scapulae) and was allowed to remain in direct contact for a period of 24 hours. Patches were applied to the same site on Monday, Wednesday and Friday for a total of 9 applications with allowable minor modifications to the schedule. The sites were graded by a technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was modified. Rest Period: 14 days Challenge Procedure: The challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reaction during the challenge phase of the study may have been asked to return for a 96-hour reading.
Study Group	Starting with 56 subjects
Vehicle	None
Remarks - Method	The test substance was applied under semi-occlusive dressing
RESULTS	
Remarks - Results	As 4 subjects discontinued study participation for reasons unrelated to the test substance, a total of 52 subjects completed the study.
CONCLUSION	A repeated insult patch test was conducted using test substance at 100%. The notified chemical was non-irritating and non-sensitising under the conditions of the test.
TEST FACILITY	Clinical Research Laboratories, Inc (2008)

B.2. Irritation – eye (Bovine Corneal Opacity and Permeability Test)

TEST SUBSTANCE	Notified chemical (20%)
METHOD	Adaptation of Bovine Corneal Opacity and Permeability (BCOP) test as described by Gautheron, P., et al., (1992) *Fundamentals of Applied Toxicology*, 18, pp. 442-449.
Species/Strain	Corneas from bovine eyes were dissected from the surrounding tissues with a 2-3 mm rim of sclera was left attached to each cornea.
Number of Animals	5 corneas for the test substance and 2 for controls
Test Period	4 hours exposure followed by an incubation period of 180 minutes.
Vehicle	Minimal essential media (MEM)
Remarks - Method	Negative control was MEM solution. No positive control was used. Five corneas were dosed with 0.75 ml of solution. Opacity measurements and sodium fluorescein permeability were determined. The permeability of each cornea was determined by measuring the optical density at 490 nm (OD_{490}) using a spectrophotometer. The OD_{490} value was compared to the OD_{490} value of the negative control to determine the corrected OD_{490} value.

The *In Vitro* Irritancy Score was calculated using the formula:
In Vitro Irritancy Score = Corrected Mean Opacity Score + 15 × Corrected Mean OD_{490} Score

According to OECD TG 437, a substance that induces an *In Vitro* Irritancy Score ≥ 55.1 is defined as a corrosive or severe irritant. Such substances will be labelled within the European Union with the risk phase R41- "Risk of Serious Damage to Eyes".

However, there are limitations for this test method based on false and positive rates for certain chemical and physical classes (e.g. Alcohols, ketones and solids). In some circumstances, the assay may be useful for identification of categories of ocular irritants other than corrosive or severe, but the accuracy and reliability of the assay have not yet been formally evaluated for this purpose.

RESULTS

Lesion	Mean Adjusted Score					Mean Value
	1	2	3	4	5	
Optical Transmission	10	13	10	10	9.5	10.5
Optical Density	0.149	0.080	0.129	0.086	0.096	0.108
Corneal Score	12.24	14.2	11.94	11.29	10.94	12.12

The corrected mean opacity score was 10.5. The corrected mean optical density (permeability) score was 0.108.

The in vitro score was calculated as 12.12.

Remarks - Results Detailed calculations for the scoring were not provided

CONCLUSION The notified chemical is not an ocular corrosive or severe eye irritant under the conditions of the test.

TEST FACILITY MB research Laboratories (2011)

B.3. Irritation – eye (MatTek EpiOcular MTT Viability Assay)

TEST SUBSTANCE	Notified chemical (> 99% purity)
METHOD	MatTek EpiOcular MTT Viability Assay
Exposure Period	16, 64, 256 mins
Vehicle	None
Remarks - Method	As the EpiOcular method has not yet been validated there is no Test Guideline. The method employed in this study was as follows: MatTek EpiOcular tissue samples were treated in duplicate with the test substance and positive control for various exposure times. Negative controls, treated with tissue culture water, were tested at 16 minutes only. Following treatment, the viability of the tissues was determined using Methyl thiazole tetrazolium (MTT) uptake and reduction. The absorbance of each sample was measured at 540 nm using a reference wavelength of 690 nm. The viability was then expressed a percentage of negative control values. The mean percent viability for each time point was used to calculate an ET_{50}, which represent the time at which the EpiOcular tissues viability was reduced to 50% compared to control tissues. The ET_{50} scores were converted to an irritancy classification using a standard method.

RESULTS

Test substance						
Exposure time (min)	OD 1	OD 2	Mean (OD)	SD	Viability %	Error %
16.0	1.331	1.413	1.372	0.058	99.0	4.2
64.0	1.208	1.380	1.294	0.122	93.4	8.8
256.0	0.115	0.143	0.129	0.020	9.3	1.4
ET_{50} (mins) = 130.8, irritancy classification: non-irritating, minimal						
Positive control (0.3% Triton X-100)						
Exposure time (min)	OD 1	OD 2	Mean (OD)	SD	Viability %	Error %
15.0	1.232	1.263	1.248	0.022	90.0	1.6
45.0	0.440	0.410	0.425	0.021	30.7	1.5
ET_{50} (mins) = 31.5, irritancy classification: within range (12.2-37.5)						
Negative control (water)	1.370	1.402	1.386	0.023	100.0	1.6

OD: optical density; SD: standard deviation

CONCLUSION	Under the conditions of this test, the notified chemical is predicted to be non-irritating to the eye.
TEST FACILITY	MB research Laboratories (2010)

B.4. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical (10% in lactose)
METHOD	Similar to OECD TG 408 Repeated Dose 90-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 91 days Dose regimen: 7 days per week
Vehicle	5% aqueous gum arabic
Remarks - Method	The following parameters were not measured: platelet count, measure of blood clotting potential, creatinine, uterus and ovary weights.

RESULTS

Dose (mg/kg bw/day)	*Number and Sex of Animals*	*Mortality*
0	10 per sex	0
100	10 per sex	0
500	10 per sex	2 F
2500	10 per sex	0

Mortality and Time to Death

Two female animals died in the 500 mg/kg bw/day group that was concluded to be caused by administration error and not by the test substance. No other mortalities were observed.

Clinical Observations

Slowness in activity was observed in the 2500 mg/kg bw/day group. A significant decrease in alanine amino transferase, glucose and potassium level was observed in the 2500 mg/kg bw/day males.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Increase in leucocyte count and significant decreases in erythrocyte, hematocrit and haemoglobin counts were seen in both 2500 mg/kg bw/day males and females. A significant decrease in alanine aminotransferase, glucose and potassium level was observed in the 2500 mg/kg bw/day males.

Effects in Organs

Spleen weights were significantly increased in the 2500 mg/kg bw/day group. Adrenal weights were significantly decreased in the 2500 mg/kg bw/day males. Mild atrophy of the epidermal cell of the loop lining of the glomus and deposit of blood pigment in the spleen was observed in the 2500 mg/kg bw/day group.

Remarks – Results

The No Observed Adverse Effect Level (NOAEL) was established as 500 mg/kg bw/day in this study for 10% of notified chemical in lactose, based on the abnormalities seen in blood cell counts and in the liver, spleen and kidney in the 2500 mg/kg bw/day group. Given lactose is unlikely to contribute to these observed effects, the NOAEL for the notified chemical is estimated to be 50 mg/kg bw/day.

CONCLUSION

The notified chemical is expected to have a NOAEL of 50 mg/kg bw/day.

TEST FACILITY Sugiyama (1974)

B.5. Developmental toxicity

TEST SUBSTANCE Notified chemical (10%)

METHOD

Species/Strain	Rat/Wistar
Route of Administration	Oral – gavage
Exposure Information	Exposure days: Day 9 to Day 14 of gestation
Vehicle	5% Gum Arabic solution
Remarks - Method	Twelve of the control and the 50 and 250 mg/kg bw/day dose groups, and all the dams of 500 mg/kg bw/day group were sacrificed on Day 20. The remaining dams were allowed to litter naturally and lactation, neonatal viability and postnatal development of the young were observed.

RESULTS

Group	*Number of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	18	0	0
1	18	50	0
2	18	250	0
3	18	500	0

Mortality and Time to Death

No mortalities were observed for the dams. Foetal mortality such as resorption and dead foetuses were not observed.

Effects on Dams

No marked changes in behaviour and appearance were observed. However, body weight gains and food intakes at the levels of 250 and 500 mg/kg bw/day were a little lower than those of the control.

Effects on Foetus

Foetal weights at the dose levels of 250 and 500 mg/kg bw/day were lower than that of the control. The retardation of ossifications was observed along with foetal weight decrease. No skeletal abnormalities or functional differences were observed.

Effects on neonates

The body weight of the neonates from the dams at the dose of 250 mg/kg bw/day was significantly lower at birth and weaning.

Remarks - Results

Growth retardation of foetuses and neonates observed at higher doses are considered to be resulted from slight suppression of body weight gains and food consumptions in their dams.

CONCLUSION

The test substance (10% notified chemical) is not considered to be teratogenic under the conditions of the study.

TEST FACILITY Suzuki et al (1975)

B.6. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	USFDA (21 CFR Part 48) (similar to OECD TG 471 Bacterial Reverse Mutation Test). Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA98, TA100, TA102, TA97a
Metabolic Activation System	Rat liver s-9 homogenate (induction system not reported)
Concentration Range in Main Test	a) With metabolic activation: 0, 16, 50, 160, 500, 1600, 5000 µg/plate b) Without metabolic activation: 0, 16, 50, 160, 500, 1600, 5000 µg/plate
Vehicle	Dimethyl Sulfoxide (DMSO)
Remarks - Method	Although E. Coli was not included, the strains used were consistent with the recommendations of OECD TG471. In addition to the usual protocol, spot tests were conducted on the highest sample concentration. No preliminary test was conducted. The test samples were analysed on two separate test days in all strains except for TA97a for which all six concentrations were tested on the same test day.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*		
	Cytotoxicity in Main Test	*Precipitation*	*Genotoxic Effect*
Absent			
Test	> 500	> 5000	negative
Present			
Test	> 500	> 5000	negative

Remarks - Results	The test sample did not produce a two-fold increase in the number of revertants or a clear dose related response in any of the five tester strains. The spot plates showed a clear zone at the inoculation site indicating the sample was toxic to the bacteria but was not surrounded by a ring of increased reversion. This result indicates that the sample was not mutagenic in the spot test.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Nelson Laboratories, Inc. (2007)

B.7. Genotoxicity – Reverse Mutation Test

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100. *E. coli*: WP2 *hcr trp*
Metabolic Activation System	S9 mix from Aroclor 1254 induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 0 - 2000 µg/plate b) Without metabolic activation: 0 - 2000 µg/plate
Vehicle	DMSO

RESULTS

Remarks - Results	The methodology and results were reported briefly in a journal article. The notified chemical showed a very weak but clear dose-dependent mutagenic activity for *E. coli* WP2 *hcr* (induced revertants/mmol 0.0065) but not for any of the 5 S.*typhimurium* strains.

CONCLUSION	The notified chemical showed very weak mutagenic activity to one strain only under the conditions of the test.
TEST FACILITY	Ohta et al (1980)

B.8. Genotoxicity – Rec Assay

TEST SUBSTANCE	Notified chemical
METHOD	Bacillus subtilis rec assay test. Method according to Shirasu et al (1976)
Species/Strain	*B. subtilis*: H17 Rec^+, M45 Rec^-
Remarks - Method	The methodology and results were reported briefly in a journal article. The overnight cultures of *B. subtilis* H17 Rec^+ and M45 Rec were streaked on a B2 agar plate, and a paper disk soaked with 0.02 ml of a solution of the test compound was placed on the starting parts of the bacterial streaks. After 1 or 2 days incubation at 37°C, the length of the growth inhibition zone of each streak was measured. Differences of more than 3 mm were defined as positive. The rec-assay is widely used for the detection of DNA damaging agents. It is not a mutation assay but is used in conjunction with mutation assays for initial screening of mutagens.
RESULTS	
Remarks - Results	The notified chemical was found to be negative in this assay.
CONCLUSION	The notified chemical was not a DNA damaging agent under the conditions of the test.
TEST FACILITY	Ohta et al (1980)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 A Ready Biodegradability: DOC Die-Away Test.
Inoculum	Aerobic activated sludge from a domestic wastewater treatment plant
Exposure Period	28 days
Auxiliary Solvent	None reported
Analytical Monitoring	Dissolved organic carbon (DOC)
Remarks - Method	The ready biodegradability was tested according to guidelines above at a DOC concentration of 9.57 mg/L. A reference (sodium benzoate) control, toxicity control and adsorption control were run in parallel. Test conditions: 21.0 – 21.3°C, pH 6.8 -7.2.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
0	0	0	0
3	90.0	3	99.7
7	99.4	7	97.5
14	97.6	14	99.5
28	98.2	28	100.2

Remarks - Results	No deviations from protocol were reported. All validity criteria for the test were satisfied. Biodegradation amounted to 98% with 14 days of exposure in the toxicity control, thus the notified chemical is not considered toxic to microbial respiration. The net DOC in the adsorption control ranged from 9.5 mg/L on Day 0 to 8.4 mg/L on Day 10 demonstrating no significant adsorption of the test substance to the inoculum during the time of biodegradation was occurring in the test vessels. The abiotic control showed little biodegradation by day 28 (12.7%).
CONCLUSION	The notified chemical is readily biodegradable
TEST FACILITY	Springborn Smithers (2009)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	Protocol not specified
Species	Salmon (*Salmo salar*)
Exposure Period	< 100 hours
Auxiliary Solvent	Isopropanol (0.1% w/w)
Water Hardness	Not reported
Analytical Monitoring	Colorimetric
Remarks – Method	The toxicity of the notified chemical was determined as part of a study investigating the acute toxicity of several alkylhydroxamic acids of different aliphatic carbon chain lengths to salmon fry. Fish (5 – 7 cm) were placed in random groups of 5 in tanks containing 10 L of continuously aerated fresh water at 10°C and allowed to adjust for some hours before exposure to the test substance. The test substance

	was added in 10 mL isopropanol to give final concentrations in the range 1 – 100 ppm. An isopropanol control was run. Fish were not fed during the test and were inspected at intervals of 15 min during first few hours of exposure and then at gradually increasing intervals. Dead fish were removed and the time to death recorded. LT50s (time to death for 50% of the test group) were calculated by probit analysis. A regression curve was constructed relating LT50 to test substance concentration and the 24 hr LC50 was interpolated from this equation. Throughout the test, dissolved oxygen levels were close to saturation and pH was in the range 6.8 – 7.2.
RESULTS	
LC50	13.3 mg/L at 24 h (interpolated from regression curve)
LC50	2.6 mg/L at 96 h (extrapolated from regression curve)
NOEC	Not reported
Remarks – Results	There were no mortalities in the isopropanol control. All fish that died due to exposure to the test substance did so in the same manner. Following a brief period of excitability, they seemed to lose balance, gill movements slowed, and they died with the opercula open as if death were attributable to asphyxiation. Hydroxamic acid concentrations did not vary appreciably in the first 48 hours of the test but by 96 hours were generally 15-20% below starting concentrations. The discrepancy could not be attributed to decomposition of the hydroxylamine or nitrite as these did not increase above control or blank values. The relationship between LT50 and concentration was determined, and utilised to calculate the 24 h LC50 (13.3 mg/L). An estimate for the endpoint of regulatory interest, the 96 h LC 50, could therefore be calculated to give 2.6 mg/L. However, as this endpoint is an extrapolation and not measured data, this endpoint is indicative of potential toxicity only and should be treated with caution.
CONCLUSION	The notified chemical is toxic to fish
TEST FACILITY	Addison & Côté (1973)

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