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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Alkyl hydroxamic acids

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 the Environment, Water, Heritage and the Arts.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full 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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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Lynas Corporation Ltd (27 009 066 648)
Level 7, 56 Pitt Street
SYDNEY NSW 2000

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:
Marketing Name, Methods of detection and determination, Purity, Impurities, Import volume, Confidential details of use, Identity of manufacturer/recipient.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:
Melting point, Boiling point, Water solubility, Vapour pressure, Hydrolysis as a function of pH, Partition coefficient, Adsorption/Desorption, Dissociation constant, Flammability limits, Autoignition temperature, Acute oral toxicity, Acute dermal toxicity, Skin irritation, Eye irritation, Skin sensitisation, Repeat dose toxicity, Mutagenicity - bacterial reverse mutation, Genotoxicity – in vitro, Developmental and reproductive effects, Carcinogenicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

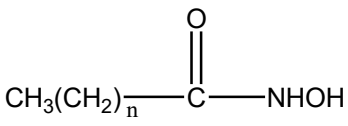
CHEMICAL NAME
Hydroxamic acids, alkyl, C5-9

OTHER NAME(S)
Modified hydroximic acid

CAS NUMBER
Not assigned

MOLECULAR FORMULA
$C_nH_{(2n+1)}NO_2$ where n = 5-9

STRUCTURAL FORMULA



Where n = 3-7

MOLECULAR WEIGHT
117 to 173 Da

ANALYTICAL DATA
Reference IR spectrum was provided.

3. COMPOSITION

DEGREE OF PURITY < 60%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Dark reddish brown, viscous liquid (for product containing < 85% notified chemical).

Property	Value	Data Source/Justification
Melting Point	Not determined	Only imported as a liquid.
Boiling Point	> 300°C at 101.3 kPa	Estimated (EPIWIN v3.20)
Density	930 kg/m^3 at 20°C*	MSDS
Vapour Pressure	≤ 1.39 x 10^{-5} kPa at 25°C	Estimated (EPIWIN v3.20)
Water Solubility	Sparingly soluble (> 0.001 g/L at 20°C)	Estimated
Hydrolysis as a Function of pH	Stable at neutral pH, slow hydrolysis in acidic and alkaline media.	Estimated
Partition Coefficient (n-octanol/water)	Expected to partition to octanol at neutral pH, to water at alkaline pH.	Estimated. Measurement would be compromised by surface activity.
Adsorption/Desorption	Expected to sorb strongly to clays.	The notified chemical contains hydrophilic and hydrophobic moieties and is surface active
Dissociation Constant	pKa ~ 9	Analogue data
Flash Point	74°C*	MSDS
Flammability	Not expected to be highly flammable.	Based on stated flash point in MSDS.
Autoignition Temperature	Not determined	Not expected to autoignite during normal handling and use.
Explosive Properties	Not expected to be explosive.	The structural formula contains no explosophores.

* For product containing < 85% notified chemical.

DISCUSSION OF PROPERTIES
The water solubility, hydrolytic stability, partition coefficient, adsorption/desorption and dissociation constant were not measured but have been inferred from the structure and from analogue data. The notified chemical contains several components with different chain lengths. Hydrophilicity will decline with increasing chain length. The notified chemical is soluble at alkaline pH, but expected to be sparingly soluble at most pH values encountered in the environment. The notified chemical is surface active and has a low vapour pressure.

Based on the measured flash point, the product containing < 85% notified chemical is not classified as flammable but would be considered to be a C1 combustible liquid [NOHSC:1015(2001)].

Reactivity
The notified chemical undergoes some degree of hydrolysis both in acidic and alkali solutions, but has greater stability in the latter. It is reported by the notifier that decomposition occurs during storage. For example, in a study conducted over 8 months, up to 25% of the notified chemical was lost during storage.

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported as a viscous aqueous product at a concentration of < 85%.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 400	< 400	< 700	< 700	< 700

PORT OF ENTRY
Fremantle

TRANSPORTATION AND PACKAGING
The product containing < 85% notified chemical will be imported by ship in shipping containers in 1 tonne collapsible bulk boxes. The containers will be transported by rail to Kalgoorlie, where the bulk boxes will be removed from the sea containers and put onto flatbed trucks for transportation to the mine site. The chemical will be stored in bunded storage sheds with dedicated sump pumps.

The product containing < 85% notified chemical will also be introduced into Australia in 20T isotainers that will be transported by trunk to the mine site, 35 km SE of Laverton and stored in a reagents handling area. When the isotainers are connected up ready for use in the flotation area, the area immediately adjacent to the isotainers wlll be bunded.

The concentrate after conditioning with the notified chemical will be bagged and loaded on sea containers. The sea containers will be transported by rail and road to the sea port for export overseas.

USE
The notified chemical will be used as a flotation collector for rare earth minerals in the mining industry.

OPERATION DESCRIPTION
At the mining site, the product containing the notified chemical (at < 85%) will be dosed neat to the crushed and finely ground ore in flotation tanks.

Bulk boxes
A common manifold will be provided to allow two bulk boxes to be connected to the pump system at any one time. As one box is emptied, the manifold will be switched to a full box and the empty box disconnected and replaced. No manual handling of the notified chemical will be required. The flotation operator will replace the empty bulk boxes using a forklift and open the appropriate manifold valve.

Isotainers
The isotainer will pump to a header tank situated immediately above the flotation area and the header tank will be replenished once per day. No manual handling of the notified chemical will be required. The flotation operator will replace the empty isotainers using an isotainer forklift.

During the flotation process, the mineral particles become separated as froth and float to the surface while the tailings settle at the bottom of the flotation tank.

The final concentrate will be thickened, filtered and dried to 5-20% moisture in a semi-enclosed system and packaged using a trouser leg chute into 2.2 tonne bags. The bagging operator will manually tie off the full bags and load them into sea containers on site. The sea containers will be transferred to a storage facility using a forklift, before being transported by rail and road to the sea port for export overseas.

Quality control staff will carry out testing when required. Routine cleaning and minor maintenance of the plant is carried out regularly, and shutdowns occur for major maintenance.

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	5	12	240
Milling operations			
Reagent operator	2	12	240
Flotation	3	12	240
Concentrating and bagging	6	12	240
Quality control	3	12	240
Maintenance	10	12	240

EXPOSURE DETAILS

Transport and Storage

Exposure to the notified chemical during the importation, transport and storage is not expected, except in the unlikely event of an accident where the packaging may be breached.

Milling Operations/Maintenance

Exposure may occur to the notified chemical at high concentrations (at up to 85%) during the manual connection and disconnection of the imported bulk boxes and isotainers by the reagent operators to the flotation circuit, during quality control testing of the imported product and during maintenance activities.

Exposure to the notified chemical at low concentrations could occur to splashes from the flotation tanks and when taking test samples of the processed mineral.

Dermal, and eye contact (due to splashing), are likely to be the main routes of exposure.

Inhalation exposure is not expected given the low vapour pressure of the notified chemical and chelation to the mineral ore. In addition most of the control of the process is remote, therefore workers are not expected to be near the mineral during processing for extended periods of time.

The worst case dermal exposure to the notified chemical is expected to be to workers directly handling the imported product containing the notified chemical at concentrations up to 85%, and is estimated to be 0 - 0.085 $mg/cm^2/day$, based on EASE model (assumptions: non-dispersive use, direct-handling, incidental exposure and 85% of notified chemical in imported product). Therefore, assuming a surface area of 420 cm^2 (one hand) for a 70 kg worker and a 100% dermal absorption factor, systemic exposure is estimated to be a maximum of 0.5 mg/kg bw/day. Exposure is likely to be minimised by good personal hygiene practices and use of industrial standard PPE.

To minimise potential exposure, it is expected that flotation operations and maintenance workers will wear long sleeved clothing, safety glasses and chemical resistant gloves as a minimum. Face shields and/or goggles are stated to be used when connecting new bulk boxes and disconnecting empty boxes, and during maintenance of the pumping system and manifold. Organic vapour respirators are stated to be used during clean up of spills.

6.1.2. Public exposure

The public will not be exposed to the notified chemical except in the unlikely event of an accident during transportation.

6.2. Human health effects assessment

No toxicity data were submitted for the notified chemical. However, toxicity data was supplied for structurally related chemicals that were considered acceptable by NICNAS. The results from toxicological investigations conducted on the structurally related chemicals are summarised in the table below. Details of these studies can be found in Appendix B.

The structurally related chemicals used for the toxicological studies were various individual hydroxamic acids, primarily the C8 and C10 homologues, octanohydroxamic acid (CHA; CAS no. 7737-03-9) and decanohydroxamic acid (DHA; CAS no.2259-58-0), and octanoic acid. The latter was chosen based on the expected partial metabolism of the notified chemical to the corresponding carboxylic acids upon absorption. Hydrolysis of the notified chemical also results in the formation of the carboxylic acids.

Endpoint	*Test Substance*	*Result and Assessment Conclusion*
Rat, acute oral toxicity	various alkyl hydroxamic acids (C6, C7, C8 and C9)	LD50 ≥ 3000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	octanoic acid	LD50 > 5000 mg/kg bw; low toxicity
Rabbit, skin irritation	DHA (1%)	moderately to severely irritating
	octanoic acid	moderately irritating
Rabbit, eye irritation	octanoic acid	severely irritating
Rat, repeat dose oral toxicity – 13 weeks	CHA	NOAEL 50 mg/kg/day
Mutagenicity – bacterial reverse mutation	CHA	evidence of very weak mutagenicity
Genotoxicity – Rec assay	CHA	non genotoxic
Developmental and reproductive effects	CHA	non-teratogenic
Carcinogenicity	CHA	non-carcinogenic

Toxicokinetics, metabolism and distribution

There is no toxicokinetic data on the notified chemical. However, 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. It is expected that the notified chemical will undergo similar metabolic conversion as AHA.

Based on the estimated physicochemical properties, percutaneous absorption of the notified chemical is expected to be slow, but penetration into the stratum corneum is likely. As the chemical is surface active this may enhance the dermal uptake (EC, 2003). Given the low molecular weight (< 200 Da), absorption across the GI tract is possible by passive diffusion through the aqueous pores or micellular solubilisation. Given the low water solubility and low vapour pressure systemic toxicity via inhalation is not expected.

Acute toxicity

The notified chemical is expected to have a low oral toxicity based on reported rat LD50 values for various alkyl hydroxamic acids (hexanohydroxamic acid (CAS no.4312-93-0), heptanohydroxamic acid (CAS no. 30406-18-9), CHA and nonanohydroxamic acid (CAS no. 20190-95-8)) (RTECS, 2009 a-d). No acute dermal toxicity data were available for individual hydroxamic acids, however octanoic acid, a potential metabolite, is reported to have low toxicity in rabbits via the dermal route (FFHPVC, 2004).

Irritation

The notified chemical is surface active and has a low molecular weight and is therefore expected to present irritant properties. This is supported by a study conducted on the individual hydroxamic acid DHA on rabbits where an ointment containing 1% of DHA caused moderate to severe irritancy (Kitagawa, 1965). However, the contribution of the vehicle cannot be discounted. Furthermore, although the notified chemical is expected to be absorbed largely unchanged, it can undergo hydrolysis to give the corresponding carboxylic acids that are known structural alerts for irritancy, particularly at carbon chain lengths < 8 (Hulzebos et al, 2005). For example, administration of neat concentrations of octanoic acid to rabbit skin for 24 hours caused moderate irritation

(Cragg, 2001). In addition, administration of a 5% solution of octanoic acid to the eye of rabbits caused severe corneal injury (Cragg, 2001) Based on the reported irritancy of the individual hydroxamic acid DHA and octanoic acid, the notified chemical is expected to present as skin and eye irritant.

Sensitisation

Based on the low molecular weight, surface activity and irritancy potential, it is likely that the notified chemical will be able to be absorbed into the skin. While some metabolism into the carboxylic acids may occur, the notified chemical is expected to be absorbed into the epidermis largely unchanged. 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. Based on the absence of data and the known protein reactivity of hydroxamic acids, the skin sensitisation potential of the notified chemical cannot be ruled out.

Repeated Dose Toxicity (chronic)

A repeat dose toxicity study has been conducted on CHA with male and female Wistar rats (Sugiyama et al, 1974). In the study, ten rats of each sex were administered 0, 100, 500 or 2500 mg/kg of taselin (10% CHA in lactose) by gavage for 13 weeks. In the high-dose 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 high dose group. The NOAEL was determined to be 500 mg/kg for taselin under the conditions of the study. Based on the data for taselin containing 10% CHA, the notified chemical is expected to have a NOAEL of 50 mg/kg assuming lactose has no contribution to toxicity.

Mutagenicity

The individual hydroxamic acid CHA has been tested in the *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay and the *Bacillus subtilis* Rec Assay (Ohta et al, 1980; Munakata et al, 1980). CHA showed very weak mutagenicity in *E.coli* with and without metabolic activation but was non-genotoxic in *S.typhimurium* and *B.subtilis* bacterial strains under the conditions of the tests. In the study conducted by Munakata, acetohydroxamic acid was found to be weakly mutagenic to TA 98 and TA 100 with or without metabolic activation. In addition, Munakata studied the mutagenicity of N-acylglycinohydroxamic acids ($RCO\text{-}NHCH_2CONHOH$) and found that mutagenicity was dependent upon the nature of the R group, with aryl groups generally displaying a positive mutagenic response in contrast to alkyl groups that largely displayed a negative response under the conditions of the test (although some positive results were observed). Munakata concluded that mutagenicity is not solely dependent upon the presence of the hydroxamic (CONHOH) moiety.

Given mutagenicity was observed with *E.coli*, albeit very weak, and that mutagenicity has been reported for some hydroxamic acids, in the absence of additional data the potential for mutagenicity in vivo by the notified chemical can not be ruled out

Carcinogenicity

There is considerable evidence of a positive correlation between mutagenicity of substances in vivo and their carcinogenicity in long term studies with animals. However it is noted that both CHA and AHA have been demonstrated to be non-carcinogenic (Munkata et al., 1980). CHA has been tested in a carcinogenicity study in mice (Nishio et al, 1972). In this study, mice were administered orally within 24 hours of birth a diet containing 1% of CHA. The mice were switched to basic feed at 2, 4 and 6 months after administration and autopsies were performed at 3 or 6 months. Liver, lungs, spleens and kidneys were histologically analysed. No increase in the rate of occurrence of cancer was observed. The authors concluded that CHA had no tumour causing properties in relation to the organs examined.

Toxicity for reproduction

The individual hydroxamic acid CHA has been tested in a reproductive study in rats (Suzuki et al, 1975). Eighteen pregnant female Wistar rats were administered 0, 50, 250 or 500 mg/kg of taselin (10% CHA) 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. Foetal body weights were reduced and reduction in ossification was observed at 250 and 500 mg/kg, 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 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, CHA was not teratogenic under the conditions of the study. Propionohydroxamic acid is also reported to have no effect on foetuses (Suzuki et al, 1975). Based on data on individual hydroxamic acids, it is expected that the notified chemical will not be teratogenic.

Health hazard classification
Given no toxicity data is available for the notified chemical the hazardous properties are not known and the chemical cannot be classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). However, based on data for structurally related chemicals, the notified chemical is expected to possess at least moderate irritancy to the skin and eyes. The notifier has included a precautionary classification of R36/38 Irritating to skin and eyes on the MSDS. Potential for mutagenicity cannot be ruled out.

6.3. Human health risk characterisation

6.3.1. Occupational health and safety
The highest occupational exposure to the notified chemical is expected when handling the imported product containing the notified chemical at concentrations up to 85%. Workers most at risk are reagent operators, and maintenance and quality control workers during handling of the bulk boxes and isotainers, maintenance of equipment and taking samples. The risk to other workers is considered low given they are only expected to come into contact with low concentrations of the notified chemical in the mineral slurry and processed ore.

Systemic Effects (dermal exposure)
Dermal exposure is expected to be greatest where contact with the imported product containing the notified chemical at concentrations of up to 85% could occur. Based on a NOAEL of 50 mg/kg bw/day in the repeat dose 13 week oral toxicity study on the analogue CHA and an estimated systemic exposure of 0.5 mg/kg bw /day, the MOE (margin of exposure) is estimated to be 100. The MOE is based on conservative assumptions, including no use of PPE and 100% dermal absorption. It may therefore overestimate the risk. An MOE greater than or equal to 100 is considered acceptable to account for intra- and inter-species differences. This MOE therefore indicates that the risk to workers from exposure to the notified chemical would not be considered unacceptable.

Although the genotoxicity profile of the notified chemical has not been fully investigated, the risk to workers is not considered unacceptable due to the engineering controls, work practices and PPE.

Local Effects (skin/eye)
The notified chemical is expected to be at least moderately irritating to skin and severely irritating to the eyes based on data conducted on individual hydroxamic acids, and skin sensitisation potential cannot be ruled out. The risk of adverse effects would be greatest where dermal and ocular exposure to the notified chemical at high concentrations could occur (i.e. during transfer and quality control operations). However, irritancy effects cannot be ruled out (especially in the eye) where contact with the mineral slurry could occur. The risk of irritancy and sensitisation effects would be minimised by the use of PPE (coveralls, gloves and safety glasses).

Respiratory effects
The respiratory effects of the notified chemical are not known, however, as the atmospheric concentration of the notified chemical is expected to be low, there is not expected to be a significant risk of adverse respiratory effects. Where the atmospheric concentration of the notified chemical may build up, the risk of adverse respiratory effects cannot be ruled out, especially in maintenance workers where exposure could be for more prolonged periods of time. The risk would be reduced by the presence of adequate ventilation or the use of respiratory protection where adequate ventilation is not available.

6.3.2. Public health
The risk to public health is considered to be negligible based on the negligible exposure expected.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical is manufactured overseas and used directly as the imported product with no further processing.

RELEASE OF CHEMICAL FROM USE
Almost all of the imported quantity of the notified chemical (estimated 98%) will be collected as chelated concentrate during the flotation process. The concentrate will be processed for export, by thickening, filtration and air drying to 5-20% moisture before bagging. The notified chemical will remain in the concentrate following processing and be exported. The 2% that remains in Australia will be directed to tailings dams.

RELEASE OF CHEMICAL FROM DISPOSAL
The notified chemical is expected to be mainly associated with solids in the tailings dams, with very little in the overlying water. Release to the environment is not expected as the tailings dams are engineered to contain extreme storm events (one in a hundred years), while bunding and diversion channels will prevent access of stormwater to the mine site from surrounding areas. Water will be removed from the tailings dams by evaporation, and by reverse osmosis for use on the mine site. The tailings may be reprocessed at some time in the future, but will otherwise be capped and revegetated.

Spills of the notified chemical will be contained to prevent entry to waterways. Soil contaminated with the notified chemical as a result of spillage will be collected for reclamation.

7.1.2 Environmental fate

No environmental fate data were submitted. The notified chemical is expected to remain with the solid fraction in tailings dams, and slowly degrade. Biodegradability has not been tested, but the notified chemical is expected to undergo abiotic hydrolysis in the environment, including tailings dams, and to be susceptible to microbial degradation. No bioaccumulation is expected as there will be no aquatic exposure when the notified chemical is used as intended. Accidental aquatic exposures from spills or tailings overflows could lead to some short-term accumulation in fish, but published data (Darrow and Addison, 1979) indicate that residues would be rapidly depurated once the contamination incident had passed.

7.1.3 Predicted Environmental Concentration (PEC)

It is neither necessary nor meaningful to determine a PEC as there will be no aquatic exposure when the notified chemical is used as intended.

7.2. Environmental effects assessment

The results from ecotoxicological investigations conducted on the product containing < 85% notified chemical are summarised in the table below. Details of these studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	EC50 = 15-20 mg/L	Harmful
Daphnia Toxicity	EC50 = 2.6 mg/L	Toxic
Algal Toxicity	EC50 = 1.2 mg/L	Toxic

The fish toxicity test involved sublethal exposures, but some published data are available for lethal exposures. Results from testing in fish, daphnids and algae indicate that the notified chemical is likely to be toxic to aquatic life.

7.2.1 Predicted No-Effect Concentration

The PNEC for the product containing < 85% notified chemical can be calculated by application of an assessment factor of 100 to the most sensitive endpoint, as data are available for three trophic levels.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Algal toxicity (EC50)	1.2	mg/L
Assessment Factor	100	
PNEC:	12	µg/L

7.3. Environmental risk assessment

A risk quotient (PEC/PNEC) cannot be calculated as no aquatic exposure is expected when the notified chemical is used as intended. The notified chemical is not considered to pose a risk to the environment, based on the reported use pattern.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification

Given no toxicity data is available for the notified chemical the hazardous properties are not known and the chemical cannot be classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). However, based on data for structurally related chemicals, the notified chemical is expected to possess at least moderate irritancy to the skin and eyes. The notifier has included a precautionary classification of R36/38 Irritating to skin and eyes on the MSDS. Potential for mutagenicity cannot be ruled out.

and

As a comparison only, the classification of the notified chemical using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003) is presented below. This system is not mandated in Australia and carries no legal status but is presented for information purposes.

	Hazard category	***Hazard statement***
Environment		
Acute	2	Toxic to aquatic life

Human health risk assessment

Although there is some uncertainty regarding the hazard properties of the notified chemical, under the conditions of the occupational settings described, the notified chemical is not considered to pose an unacceptable risk to the health of workers.

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

Environmental risk assessment

On the basis of the reported use pattern, the notified chemical is not considered to pose a risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - *Ventilation systems where mineral processing occurs inside buildings.*
  - *Automated processes where practical*

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:
  - *Avoid contact with skin and eyes*
  - *Avoid spills and splashing during use*
  - *Minimise time spent near open flotation tanks*
  - *A shower and eyewash station should be available*

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - *Chemical resistant gloves*
  - *Coveralls*
  - *Protective goggles*

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

- 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.

Disposal

- The notified chemical should be disposed of by landfill.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled by containment, collection and subsequent safe disposal.

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified 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 notified chemical is imported in any form other than as an aqueous dispersion.

or

(1) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a flotation collector for rare earth minerals, or is likely to change significantly;
  - the amount of chemical being introduced has increased from 700 tonnes per annum, 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 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.

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Irritation – skin

TEST SUBSTANCE	DHA (1%)
METHOD	
Species/Strain	Rabbit (strain unknown)
Number of Animals	3
Vehicle	Emulsified ointment base (liquid paraffin, purified lanolin, cetanol, bleached beewax, stearic acid, IPM, isopropyl polyoxyethylene sorbitan monostearate, methyl parahydroxybenzoate, sorbitan monostearate, propyl parahydroxybenzoate, triethanolamine, propylene glycol, EDTA 2Na, purified water). Absorptive ointment base (white Vaseline, liquid paraffin, sorbitan sesquioleate, purified water).
Observation Period	6 days
Type of Dressing	None
Remarks - Method	Test substance was applied to the dorsal skin as an ointment at a concentration of 1% in an emulsified or absorptive ointment base. No dressing was used but a plastic collar was fastened to the animals so they could not lick off the test substance. The ointments were applied twice a day. The amount of ointment applied was approximately 0.7 g per application.
RESULTS	On the third day of treatment with 1% DHA emulsified ointment, the skin started to become rough and stripes of small, white spots started to appear. When the ointment was further applied, the whole area started to become red and yellow white scabs were observed in the whole area. The skin generally became hard, red and swollen. These effects were observed in all 3 animals. The effects were reported as moderate to severe. Inflammation, although milder, was also observed in the animals treated with the emulsified base only. In the case of 1% DHA absorptive ointment, a slight skin irritation was observed after 3 days or more of application. The irritation effects were reported to be much milder than that observed with 1% DHA emulsified ointment. Almost no irritation effects were observed with absorptive ointment base alone.
Remarks - Results	Due to the differing results, the contribution of the vehicle to the irritant effects cannot be discounted.
CONCLUSION	The analogue DHA is at least moderately irritating to the skin.
TEST FACILITY	Kitagawa et al (1975)

B.2. Repeat dose toxicity

TEST SUBSTANCE	CHA (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

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10M/10F	0	0
low dose	10M/10F	100	0
mid dose	10M/10F	500	2F
high dose	10M/10F	2500	0

Mortality and Time to Death
Two female animals died in the mid-dose 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 high dose group. A significant decrease in alanine amino transferase, glucose and potassium level was observed in the high dose males.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Increase in leucocyte count and significant decreases in erythrocyte, hematocrit and haemoglobin counts were seen in both high dose males and females. A significant decrease in alanine aminotransferase, glucose and potassium level was observed in the high dose males.

Effects in Organs
Spleen weights were significantly increased in the high-dose group. Adrenal weights were significantly decreased in the high dose 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 high dose group.

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

CONCLUSION
The individual alkyl hydroxamic acid, CHA, is expected to have a NOAEL of 50 mg/kg/day.

TEST FACILITY Sugiyama (1974)

B.3. Genotoxicity – Reverse Mutation Test (1)

TEST SUBSTANCE CHA

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

B.4. Genotoxicity – Reverse Mutation Test (2)

TEST SUBSTANCE	CHA
METHOD	Similar to OECD TG 471 Bacterial Reverse Mutation Test. Pre-incubation procedure
Species/Strain	*S. typhimurium*: TA98, TA100.
Metabolic Activation System	S9 mix from PCB induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 6.36 - 25440 µg/plate b) Without metabolic activation: 6.36 - 25440 µg/plate
Vehicle	DMSO
RESULTS	
Remarks - Results	CHA was reported to give a negative result at the maximum solubility dose. The exact dose was not reported but was in the range 636-3180 µg/plate.
CONCLUSION	The analogue CHA was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Munakata et al (1980)

B.5. Genotoxicity – Rec Assay (1)

TEST SUBSTANCE	CHA
METHOD	Bacillus subtilis rec assay test. Method according to Shirasu et al (1976)
Species/Strain	*B. subtilis*: H17 Rec^+, M45 Rec^-
Remarks - Method	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 37ºC, 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	CHA was found to be negative in this assay.
CONCLUSION	The analogue CHA was not a DNA damaging agent under the conditions of the test.
TEST FACILITY	Ohta et al (1980)

B.6. Genotoxicity – Rec Assay (2)

TEST SUBSTANCE	CHA
METHOD	Bacillus subtilis rec assay test. Method according to Kada et al (1972)
Species/Strain	*B. subtilis*: H17 Rec^+, M45 Rec^-
Remarks - Method	*B. subtilis* H17 Rec^+ and M45 Rec were streaked onto a agar plate, and their starting points were covered with a paper disk soaked with 0.15 ml of DMSO solution containing 0.3-250 µmol of the test substance. After 24 hours incubation at 37°C, the length of the growth inhibition zone of each streak was measured. 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	CHA was found to be negative in this assay.
CONCLUSION	The test substance (CHA) was not a DNA damaging agent under the conditions of the test.
TEST FACILITY	Munakata et al (1980)

B.7. Developmental toxicity

TEST SUBSTANCE	CHA (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 dose groups, and all the dams of 500 mg/kg 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 were a little lower than those of the control.

Effects on Foetus

Foetal weights at the dose levels of 250 and 500 mg/kg 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 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% CHA) is not considered to be teratogenic under the conditions of the study.

TEST FACILITY Suzuki et al (1975)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

Based on its structure, the notified chemical is expected to undergo abiotic hydrolysis in the environment, including tailings dams, and to be susceptible to microbial degradation.

C.1.2. Bioaccumulation

Based on its structure, the notified chemical is expected to be absorbed by fish from contaminated water, but to be readily metabolised and depurated in clean water. Published data (Darrow and Addison, 1979) support this conclusion.

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Product containing < 85% notified chemical
METHOD	A sublethal fish imbalance test in Murray River rainbow fish exposed for 96 hours to the notified chemical at nominal concentrations of 0, 4, 6, 8, 10, 15 or 20 mg/L found no effects at 15 mg/L and complete imbalance at 20 mg/L. There is no test report available. Published data (Addison & Côté, 1973) indicate that lethal toxicity to salmon fry is high (24 hour LC50 = 0.53 mg/L) at longer chain lengths and slight (24 hour LC50 = 86 mg/L) at shorter chain lengths. A 7-hour LC100 of 3 mg/L has been determined in brook trout exposed to a higher homologue (Darrow *et al*, 1978).

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Product containing < 85% notified chemical
METHOD	Based on US EPA Test Guideline (static study)
Species	*Ceriodaphnia dubia*
Exposure Period	48 hours
Auxiliary Solvent	Methanol (final concentration 0.5% v/v)
Water Hardness	Not stated
Analytical Monitoring	Not conducted
Remarks - Method	Two controls were tested, one containing methanol. Four replicates of five daphnids were tested at each concentration.

RESULTS

Concentration mg/L		*Number of C. dubia*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0		20	0	0
0		20	0	0
1		20	0	0
2		20	0	0
3		20	3	17
4		20	8	19
5		20	17	20

LC50	2.6 mg/L at 48 hours
NOEC	2 mg/L at 48 hours

CONCLUSION The notified chemical is toxic to *Ceriodaphnia dubia*

TEST FACILITY Ecotox (2004)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Product containing < 85% notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test
Species *Selenastrum capricornutum*
Exposure Period 72 hours
Concentration Range Nominal: 0, 0.034, 0.12, 0.32, 1.16, 2.96 and 10.6 mg/L
Auxiliary Solvent Methanol (final concentration 0.1% v/v)
Water Hardness Not stated
Analytical Monitoring Not conducted
Remarks - Method Only the growth rates were measured

RESULTS

Growth	
EC50	*NOEC*
mg/L at 72 h	*mg/L*
1.2	0.32

Remarks - Results

CONCLUSION The notified chemical is toxic to *Selenastrum capricornutum*

TEST FACILITY CSIRO (2004)

BIBLIOGRAPHY

Addison RF & Côté RP (1973) Variation with Chain Length in Acute Toxicity of Alkylhydroxamic Acids to Salmon (*Salmo salar*) Fry. Lipids, 8: 493-497.

Bauer L & Exner O (1974) The Chemistry of Hydroxamic Acids and N-Hydroxyimides, Angew.Chem.internat, Edit., 13, 376-384.

Cragg T (2001) Aliphatic Carboxylic Acids, Saturated. In Patty' Toxicology 5th Edition. John Wiley and Sons.

CSIRO (2004) Chronic Algal Growth Test. CSIRO Centre for Advanced Analytic Chemistry, Lucas Heights, NSW, Australia. (Unpublished data provided by the notifier).

Darrow DC, Addison RF & Bayne BL (1978) Induction of Hypoxemia in Brook Trout (*Salvelinus fontinalis*) Following Their Exposure to *n*-Decanohydroxamic Acid, a Component of an Experimental Iron Ore Flotation Agent. Comp Biochem Physiol, 60C: 83-87.

Darrow DC & Addison RF (1979) Uptake, Tissue Distribution, Metabolism and Elimination *n*-Octano-1-^{14}C-Hydroxamic Acid by Brook Trout. Bull Environm Contam Toxicol, 22: 265-270.

Ecotox (2004) Acute Toxicity of [*product containing notified chemical (at < 85%)*] to *Ceriodaphnia dubia*. Ecotox Services Australasia. (Unpublished data provided by the notifier).

FFHPVC (2004) Revised Robust Summaries for C_7-C_9 Aliphatic Aldehydes and Carboxylic Acids. The Flavor and Fragrance High Production Volume Consortia, Washington, USA.

Fishbein W, Streeter CL & Daly J (1973) Physiologic Disposition of Short Chain Aliphatic Hydroxamates in the Mouse. II. Absorption, Distribution, Metabolism and Excretion of 1-^{14}C-Acetohydroxamic Acid. J.Pharmacol. Exp. Ther., 186, 173-182.

Kada T, Tutikawa K & Sadaie Y In vitro and host-mediated "rec-assay" procedures for screening chemical mutagens and ploxine, a mutagenic red dye detected. Mutation Res., 16, 165-174.

Kitagawa H, Yoshida S, Abe M & Ohno F (1965) Pharmacological Studies on Decanohydroxamic Acid. III. General Pharmacological Action. (2). Yakugaku Zasshi, 85(10), 912-916.

Munakata K, Mochida H, Kondo S & Suzuki Y (1980) Mutagenicity of N-Acylglycinohydroxamic acids and related compounds. J.Pharm.Dyn., 3, 557-561.

Nishio O, Yamada F, Sakuma F, Kimura I, & Ito Y (1972) Experiments to Determine the Tumor-Causing Properties of Caprylohydroxamic Acid (CHA). Jap. J. of Vet. Sci., 34, Supplement, 227-228.

NOHSC (1994) National Code of Practice for the Labelling of Workplace Substances [NOHSC:2012(1994)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2003) National Code of Practice for the Preparation of Material Safety Data Sheets, 2nd edition [NOHSC:2011(2003)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances, 3rd edition [NOHSC:1008(2004)]. National Occupational Health and Safety Commission, Canberra, AusInfo.

Ohta T, Moriya M, Kaneda Y, Watanabe K, Miyazawa T, Sugiyama F & Shirasu Y (1980) Mutagenicity Screening of Feed Additives in the Microbial System, Mutation Research, 77, 21-30.

RTECS (2009a) Registry of Toxic Effects of Chemical Substances – Heptanamide, N-hydroxy-. National Institute for Occupational Safety and Health, Cincinnati, Ohio.

RTECS (2009b) Registry of Toxic Effects of Chemical Substances – Hexanamide, N-hydroxy-. National Institute for Occupational Safety and Health, Cincinnati, Ohio.

RTECS (2009c) Registry of Toxic Effects of Chemical Substances – Nonanamide, N-hydroxy-. National Institute for Occupational Safety and Health, Cincinnati, Ohio.

RTECS (2009d) Registry of Toxic Effects of Chemical Substances – Octanohydroxamic acid. National Institute for Occupational Safety and Health, Cincinnati, Ohio.

Sugiyama K, Sagami F & Chiba T (1974) Chronic Toxicity Test of Taselin in Rats. Jap. J. Vet. Sci., 36, 525-538.

Suzuki Y, Okada F & Chiba, T (1975) Negative Result of Teratological Study on Caprylo-Hydroxamic Acid in Rats. Jap. J. Vet. Sci., 37, 307-309.

United Nations (2003) Globally Harmonised System of Classification and Labelling of Chemicals (GHS). United Nations Economic Commission for Europe (UN/ECE), New York and Geneva.