File No: STD/1403

February 2012

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Carbonimidodithioic acid, cyano-, chloromethyl hexyl ester

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 SUBSTANCE	INTRODUCTION VOLUME	USE
STD/1403	Buckman Laboratories Pty Ltd	Carbonimidodithioic acid, cyano-, chloromethyl hexyl ester	Yes	≤ 4 tonnes per annum	Fungicide for leather, used in the preservation of wet blue hides at commercial tanneries.

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] with the following classification:

Xn; R23 Toxic by inhalation
Xi; R38 Irritating to skin
Xi; R41 Risk of serious damage to eyes
Xi; R43 May cause sensitisation by skin contact

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*
Acute toxicity	2	Fatal if inhaled
Skin corrosion/irritation	2	Causes skin irritation
Serious Eye Damage/Eye Irritation	1	Causes serious eye damage
Skin sensitisation	1	May cause an allergic skin reaction
Aquatic Environment	Acute 1	Very toxic to aquatic life
	Chronic 1	Very toxic to aquatic life with long lasting effects

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

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

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical may pose a risk to the environment. If the notified chemical is retained in alkaline settling ponds for at least five days, or otherwise treated such that the concentration in effluent is < 0.036 µg/L, before release to sewer, it is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- Safe Work Australia should consider the following health hazard classification for the notified chemical:
  - Xn; R23 Toxic by inhalation
  - Xi; R38 Irritating to skin
  - Xi; R41 Risk of serious damage to eyes
  - Xi; R43 May cause sensitisation by skin contact

- Use the following risk phrases for products/mixtures containing the notified chemical:

  - Concentration ≥ 25%: R23, R38, R41, R43
  - 20% ≤ Concentration < 25%: R20, R38, R41, R43
  - 10% ≤ Concentration < 20%: R20, R41, R43
  - 5% ≤ Concentration < 10%: R20, R36, R43
  - 3% ≤ Concentration < 5%: R20, R43
  - ≥ 1% Concentration < 3%: R43

- Based on the Acute I and Chronic I classifications for the aquatic environment, the notified chemical should be classified as follows under the Australian Dangerous Goods Code:
  - Class 9 (environmentally hazardous substance)

Health Surveillance

- As the notified chemical presents a skin sensitisation health hazard, employers should carry out health surveillance for any worker who has been identified in the workplace risk assessment as having a significant risk of sensitisation.

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical:
  - Local exhaust ventilation should be in place during all operations involving handling of the notified chemical where aerosols or mists may be generated.
  - Use of closed processes where possible.

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - Avoid contact with eyes and skin.
  - Do not generate aerosols or mists.
  - Clean up any spills or soiled personal protective equipment promptly.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical during handling of the notified chemical:
  - Gloves
  - Safety glasses
  - Protective clothing
  - Respiratory protection for any process where aerosols/mists are generated

  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.

Environment

- The following concentration limits should be implemented by all users of the notified chemical for release of the notified chemical to the environment:
  - the concentration of notified chemical released to sewer from any site of use should not exceed 0.036 µg/L.
  - notified chemical is not to be released directly to surface waters.

- The following control and/or monitoring measures should be implemented by all users to minimise environmental exposure during manufacture, formulation and/or use of the notified chemical:
  - in batchwise waste treatment operations, batches of liquid containing the notified chemical are to be treated in alkaline settling ponds (pH > 9 at ambient temperature) for at least 5 days before release to sewer, unless monitoring shows the concentration of the notified chemical in effluent to be < 0.036 µg/L; and/or
  - in continuous waste treatment operations, the complete batch of liquid containing the notified chemical is to be treated in alkaline settling ponds (pH > 9 at ambient temperature) for at least 5 days, after receiving the final batch of waste water, unless monitoring shows the concentration of notified chemical in effluent to be < 0.036 µg/L.

- The following monitoring should be conducted by the end user to measure environmental release during use of the notified chemical:
  - effluent released from the site of use should be analysed by a reliable and validated method to ensure that the notified chemical in effluent is < 0.036 µg/L in the cases where wastewater treatment operations are < 5 days and/or pH < 9 per batch of wastewater.

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. Release in concentrated form to the aquatic environment should be prevented.

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(2) of the Act; if
  - the function or use of the chemical has changed from a fungicide for leather used in the preservation of wet blue hides at commercial tanneries, or is likely to change significantly;
  - the amount of chemical being introduced has increased from 4 tonne 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 notified chemical is to be used at sites with receiving STPs having an average daily flow rate of less than 300,000 L/day;
- the treatment of effluent containing the notified chemical in alkaline settling ponds will be less than 5 days, and/or the pH of alkaline treatment ponds will be less than 9, unless monitoring indicates the concentration of notified chemical in effluent released from site is < 0.036 µg/L;
- tanning conditions change from those considered in this assessment (based on a maximum of 12 kgs of notified chemical used per tannery per day, and 15% fixation rate);
- notified chemical is to be released directly to surface waters;
- if the concentration of notified chemical released from sites of use is anticipated, or found, to exceed 0.036 µg/L.

The Director will then decide whether a reassessment (i.e. a secondary notification and assessment) is required.

No additional secondary notification conditions are stipulated.

Material Safety Data Sheet
The MSDS of 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)
Buckman Laboratories Pty Ltd (ABN 53 000 922 118)
212 East Bomen Rd, Wagga Wagga NSW 2650

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: vapour pressure, adsorption/desorption, dissociation constant, flammability limits, explosive properties, eye irritation, ready biodegradation, bioaccumulation

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
CEC (2006)

NOTIFICATION IN OTHER COUNTRIES
New Zealand (2006)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
CHED (notified chemical)
BLX-13715 (product containing 4% notified chemical)

CAS NUMBER
852023-54-2

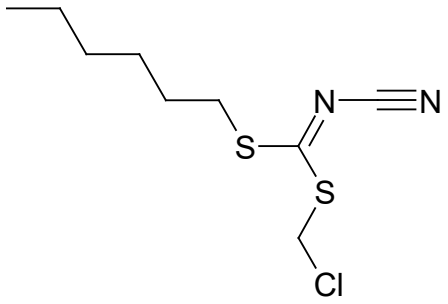
CHEMICAL NAME
Carbonimidodithioic acid, cyano-, chloromethyl hexyl ester

OTHER NAMES
CO36000

CO36001
NC36000

MOLECULAR FORMULA
$C_9H_{15}ClN_2S_2$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
250.816 Da

ANALYTICAL DATA
Reference HPLC spectra were provided.

3. COMPOSITION

DEGREE OF PURITY Approximately 60%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS

Chemical Name	Carbonimidodithioic acid, cyano-, methylene dipropyl ester		
CAS No.	58585-54-9	*Weight %*	9
Hazardous Properties	Irritant (information provided by the notifier)		

Chemical Name	Carbonimidodithioic acid, cyano-, dihexyl ester		
CAS No.	56342-27-9	*Weight %*	16
Hazardous Properties	Irritant (information provided by the notifier)		

Chemical Name	Carbonimidodithioic acid, cyano-, bromomethyl hexyl ester		
CAS No.	Unassigned	*Weight %*	< 6
Hazardous Properties	Unknown		

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight)

Chemical Name	Polymeric by-product		
CAS No.	Unassigned	*Weight %*	15

ADDITIVES/ADJUVANTS None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 ºC AND 101.3 kPa: orange brown liquid

Property	Value	Data Source/Justification
Freezing Point	< -5ºC	Measured
Boiling Point	> 100ºC (pressure unknown)	MSDS for CHED
Density	1100 kg/m^3 at 25ºC	Measured
Vapour Pressure	2.74 × 10^{-6} kPa at 25ºC	Estimated (Modified Grain Method, US EPA)
Water Solubility	5.6 × 10^{-3} g/L at 25ºC	Measured
Hydrolysis as a Function of pH	t ½ = 159 h (pH 5 at ~25ºC) t ½ = 135 h (pH 7 at ~25ºC) t ½ = 6.3 h (pH 9 at ~25ºC)	Measured
Partition Coefficient (n-octanol/water)	log Kow = 4.6	Measured
Adsorption/Desorption	log K_{oc} = 3.50, 3.86	Calculated (KOCWIN v2.00) by the MCI and Kow methods, respectively
Dissociation Constant	Not determined	No dissociable functions
Particle Size	Not determined	Liquid
Flash Point	> 90ºC (pressure unknown)	Measured
Flammability	-	Not determined
Autoignition Temperature	280ºC	Measured
Explosive Properties	Not expected to be explosive	Based on structural information and the lack of structural alerts
Viscosity	29 cps (temperature unknown)	Measured

DISCUSSION OF PROPERTIES
For full details of tests on physical and chemical properties, refer to Appendix A.

Reactivity
Incompatible with strong acids, strong oxidisers and strong bases. Stable under normal conditions of use.

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 be imported as CHED (containing the notified chemical at approximately 60%) in 1200 kg Intermediate bulk containers (IBCs).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	2	2.5	3	3.5	4

PORT OF ENTRY
Melbourne

IDENTITY OF RECIPIENTS
Buckman Laboratories Pty Ltd, Wagga Wagga NSW

TRANSPORTATION AND PACKAGING
The imported 1200 kg IBCs containing CHED (the notified chemical at approximately 60%) will be transported by road to the formulation site. The formulated product (containing the notified chemical at 4%) will be transported in 1000 L IBCs on trucks to customers across Australia.

USE
A leather fungicide used in the preservation of wet blue hides at commercial tanneries.

OPERATION DESCRIPTION
Formulation
The imported CHED containing the notified chemical at 60% will be charged to a sealed process vessel by vacuum with other materials, such as solvents and surfactants and mixed by agitation. After the formulated product (containing the notified chemical at 4%) is sampled for quality control, it will be transferred to 1000 L IBCs. The IBCs will be loaded on a transport truck with a forklift in a fully contained area for transport to the sites of tanning operations.

Tanning operation
At the end-use site, the formulated product (containing the notified chemical at 4%) will be pumped from the storage drum and weighed into a mixing box and automatically fed into the tanning drum. After the product containing the notified chemical has been added, 10 tonnes of hides and 10 tonnes of liquor will be added and rotated for 10 hours and the hides will be unloaded from the tanning drum. Each hide will be put through the sammyer (wringing process) for 10 seconds, weighed, graded and palleted accordingly. Hide samples will be taken for laboratory analyses (chamber, challenge and active tests). One pallet will be held on site for monthly assessment for 6 months. Pallets will be shrink-wrapped and dispatched for export and further processing.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and warehouse		
Transport workers	1	2
Warehouse staff – forklift driver	1	5
Formulation		
Manufacturing operators	2	5
Quality control chemist	1	5
Forklift driver	1	220
Tanning operation		
General hand	2	240
Sammyer/sorter	4	240
Quality control chemist	1	5

EXPOSURE DETAILS
Transport and warehouse
It is unlikely that transport and warehouse workers come into contact with the notified chemical unless in the event of accident.

Formulation
During formulation, dermal, ocular and inhalation exposure to the notified chemical at < 60% is possible from spills, drips and splashes during the blending of the notified chemical with other materials and during product sampling and drumming. The exposure is expected to be reduced by the use of automated processes. Process workers handling the notified chemical are also expected to wear personal protective equipment (PPE) to minimise exposure.

Tanning operation
During the tanning operation, workers' exposure to the notified chemical at 4% via dermal, ocular and inhalation routes is possible, especially when connecting and disconnecting the pump to the product drum. The exposure during drum tanning is expected to be minimal as this process occurs in an enclosed and automated system. After the drum tanning process, workers carrying out tasks such as manually feeding hides into the

sammyer, sorting hides on pallets and conducting quality control checks would also be exposed to the notified chemical at lower concentrations. Exposure is expected to be reduced by the use of personal protection equipment and if workplace engineering controls such as local exhaust ventilation are in place.

6.1.2. Public Exposure

The final concentration of the notified chemical in the leather article that the public may come in contact with is expected to be < 100 ppm (a retention of 50 ppm is required for fungal protection). There is potential for dermal exposure to the leather articles but it is expected that the notified chemical will be fixed in the leather structure. In addition, finishing treatments for leather add another layer and further reduce the potential for dermal exposure. Therefore the potential for public exposure to the notified chemical is expected to be very low.

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*
Rat, acute oral toxicity	LD50 3269mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute inhalation toxicity	LC50 = 0.478 mg/L/4 hours (male) and 0.51-2.01 mg/L/4 hours (female); toxic
Rabbit, skin irritation	Moderately to severely irritating
Guinea pig, skin sensitisation – non-adjuvant test	evidence of sensitisation
Rat, repeat dose dermal toxicity – 90 days	NOAEL = 250 mg/kg bw/day (female) NOAEL = 125 mg/kg bw/day (male)
Mutagenicity – bacterial reverse mutation	equivocal
Genotoxicity – in vitro <Mammalian Cell Gene Mutation Test>	genotoxic
Genotoxicity – in vitro <Mammalian Chromosome Aberration Test>	non genotoxic
Genotoxicity – in vivo <Mammalian Erythrocyte Micronucleus Test>	non genotoxic

Toxicokinetics, metabolism and distribution

Based on measured water solubility and partition coefficient values, the notified chemical has a reasonably high lipophilicity, and hence percutaneous absorption would be limited. However, the irritating effects of the notified chemical may increase dermal absorption. Oral absorption may occur through micellular solubilisation.

Acute toxicity

The notified chemical is of low acute toxicity *via* the oral and dermal routes.

The notified chemical is toxic via inhalation. However, a mist is not likely to be generated, should leakage of the transport containment for the notified chemical accidentally occur. Therefore classification of the notified chemical as Class 6.1 (Toxic) under the ADG Code is not warranted.

Irritation

Based on effects observed throughout a study in rabbits, the notified chemical is considered to be moderately to severely irritating to the skin.

No study for the eye irritation was available. Based on the available skin irritation study, the notified chemical is considered likely to be severely irritating to eyes. The notifier has also classified the notified chemical as R41: Risk of serious damage to eyes.

Sensitisation

The notified chemical is expected to have the potential to cause skin sensitisation based on a non-adjuvant skin sensitisation study in guinea pigs. Information on the potential for respiratory sensitisation is not available.

Repeated dose toxicity

No data was available on the effects of the notified chemical after repeated oral or inhalation exposure.

A No Observed Adverse Effect Level (NOAEL) could not be established in a 90-day dermal repeated dose study in rats, due to adverse dermal effects at all dose levels. Dermal irritation effects also limited the doses that could be tested via this route.

The No Observed Adverse Effect Level (NOAEL) for systemic effects was established as 250 mg/kg bw/day in female rats and 125 mg/kg bw/day in male rats in this study, based on adverse effects on body weight, daily body weight gain and daily food efficiency observed in 250 mg/kg bw/day group male rats.

Mutagenicity
The notified chemical was tested in three screening level non-GLP *in vitro* tests for genotoxicity. It showed equivocal results in a bacterial reverse mutation test but was not clastogenic to cultured human peripheral blood lymphocytes in an *in vitro* mammalian chromosome aberration test. The notified chemical was mutagenic to mouse lymphoma L5178Y cells in an *in vitro* mammalian cell gene mutation test, following a 4-hour exposure in the absence and presence of metabolic activation.

The notified chemical was not clastogenic in an *in vivo* mammalian erythrocyte micronucleus test carried out to OECD and GLP guidelines, however exposure of the bone marrow could not be confirmed.

Overall, based on the available data, there is no strong evidence of a genotoxic effect but this cannot be ruled out.

Health hazard classification
Based on the available data the notified chemical is classified as hazardous according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004) with the following risk phrase:

Xn; R23 Toxic by inhalation
Xi; R38 Irritating to skin
Xi; R41 Risk of serious damage to eyes
Xi; R43 May cause sensitisation by skin contact

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
The notified chemical is toxic via inhalation. It is moderately to severely irritating to skin, likely to be a severe eye irritant and is a skin sensitiser.

Workers most at risk will be those handling the imported product containing up to 60% of the notified chemical or the end use products and process liquids containing the notified chemical at up to 4%, particularly during manual process in the formulation and tanning operation, such as blending, product sampling and drumming, connecting and disconnecting the pump to the product drum, manually feeding hides into sammyer, sorting hides on pallets and conducting quality control checks.

In order to mitigate the risk of dermal or eye irritation and skin sensitisation, the use of eye protection, impervious gloves and protective clothing would be required during any manual handling processes where dermal or ocular exposure is likely. If any of the processes are likely to generate mists or aerosols local exhaust ventilation or use of respiratory protection would be needed to avoid inhalation exposure to workers.

Where possible, the use of automated equipment or closed processes would also reduce the exposure and risk to workers.

The risk to workers handling finished leather articles is considered to be negligible as the notified chemical will be fixed in the leather structure and will not be bioavailable.

Overall the risk to workers is not considered to be unreasonable if the above controls are in place.

6.3.2. Public Health

Members of the public will only come into contact with finished leather articles containing the notified chemical, hence their exposure will be primarily dermal. In the finished article, the notified chemical is expected to be fixed in the leather structure and covered by other leather treatments and will not be bioavailable. Therefore, the risk to the public is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

No manufacture of the notified chemical will take place locally. Hence, there will be no environmental exposure associated with this process in Australia. Release to the environment may occur in the event of an accident during transport or storage. During reformulation, imported product containing the notified chemical will be charged to a sealed process vessel by vacuum with other materials, such as solvents and surfactants and mixed by agitation. The process vessel will be washed with solvent, which will be recovered and reused in the next manufacturing batch. Any spills during reformulation will be contained by bunding and hence no releases to the environment are expected due to reformulation. Spills of the notified chemical during transport or reformulation are expected to be absorbed into an inert material and disposed of at a waste treatment facility.

RELEASE OF CHEMICAL FROM USE

The formulated product containing the notified chemical will be pumped from the storage drum and weighed into a mixing box and automatically fed into the tanning drum. The maximum and average daily use rates of the notified chemical at each tannery are expected to be 12 kg and 8 kg, respectively. After the product containing the notified chemical (at 4%) has been added, 10 tonnes of hides and 10 tonnes of liquor will be added and rotated for 10 hours and the hides will be unloaded from the tanning drum. The fixation rate of the notified chemical into leather was advised by the notifier to be 15%. Each hide will be put through the sammyer (ringing process) for 10 seconds, weighed, graded and palleted accordingly. Pallets will be shrink-wrapped and dispatched for export and further processing.

Once the hides are removed from the tanning drum, 85% of the liquid is recycled into the next batch with the remaining 15% sent to the tannery's effluent stream. The effluent undergoes alkaline treatment, flocculation, separation and aeration. The alkaline treatment process was advised to be up to 10 days treatment in settling ponds at pH 8.6 – 10.2. Treated waste water that is not returned to the tanning process will be released to sewer.

The tanning drum sites are bunded, hence no releases to the environment are expected from spills during use of the notified chemical.

RELEASE OF CHEMICAL FROM DISPOSAL

The majority of the notified chemical will share the fate of leather products into which it is incorporated. It is expected that these products will be disposed of to landfill at the end of their useful lives. Notified chemical remaining in tannery wastewater is anticipated to degrade abiotically during treatment in alkaline settling ponds prior to reuse or release to sewer. Unused notified chemical is expected to be returned to the notifier who will recycle the chemical or dispose of it at a waste treatment facility.

7.1.2. Environmental Fate

A submitted BOD/COD study conducted on a product containing the notified chemical (concentration 10%) indicated the product is likely to be rapidly biodegradable. A hydrolysis study on the notified chemical indicated that it is expected to rapidly hydrolyse in water, with $t_{1/2}$ = 6.3 h at pH 9, which reflects the conditions expected in on-site alkaline treatment ponds. Effluent containing the notified chemical that undergoes this alkaline treatment is expected reused in the tanning process, or released to sewer. Notified chemical in effluent released to sewer is likely to be partially removed during sewage treatment plant (STP) processes by partitioning to sludge, based on its expected high soil adsorption coefficient (log Koc = 3.50 – 3.86). Based on the notified chemical's low water solubility, low molecular weight and measured Kow, it has the potential to bioaccumulate. However, hydrolysis and degradation studies indicate that the notified chemical is expected to rapidly degrade in the environment by abiotic and biotic processes. The notified chemical incorporated into leather is expected to share the fate of the leather products in which it will be incorporated and is likely to eventually be sent to landfill. In landfill or water, the notified chemical is expected to degrade abiotically and biotically to form water, oxides of carbon, nitrogen and sulfur and chlorine compounds.

For details of the fate studies refer to Appendix C.

7.1.3. Predicted Environmental Concentration (PEC)

A Predicted Environmental Concentration (PEC_{max}) has been determined based on worst case assumptions for the operational procedures at tanneries. Based on the notifier's information, it was assumed that a maximum of 12 kg of notified chemical would be used per tannery per day and 15% would be fixed into leather. The notified chemical is expected to be used in up to four tanneries which will each release effluent to four different sewage treatment plants (STPs). The worst case notified chemical concentration (i.e. maximum mass of unfixed notified chemical released to sewer per day ÷ STP daily flow rate) was calculated based on the tannery which has the receiving STP with the lowest daily flow rate. Removal of the notified chemical during STP processes was estimated by Simple Treat (EC, 2003) which resulted in a removal rate of 82% due to partitioning to sludge (51%) and ready biodegradation (31%). The calculations and resulting PEC_{max} are summarised in the table below.

Calculation Factor	Value
Maximum daily use of notified chemical	12 kg
Maximum amount of chemical in wastewater (fixation rate 15%)	10.2 kg
Lowest daily STP flow rate	300,000 L
Maximum concentration of notified chemical in STP effluent	34 mg/L
PEC_{max} = concentration of notified chemical in STP effluent (after 82% removal in STPs estimated by Simple Treat (EC, 2003))	6.12 mg/L

The above calculation of the notified chemical concentration in STP effluent (PEC_{max}) is a conservative upper limit. This is because the notified chemical concentration in tannery effluent is expected to be < 6.12 mg/L due to the continual treatment and recycling of water during tanning operations. During its use in tanning operations, the main removal of the notified chemical is expected to be due to hydrolysis in alkaline settling ponds (pH 8.6 – 10.2, at ambient temperature) before release to the STP. The proportion of notified chemical that will hydrolyse depends on the retention time, which the notifier indicated could be up to 10 days. The PEC_{river} is the riverine Predicted Environmental Concentration for the notified chemical which takes into account both the hydrolysis of the notified chemical in alkaline treatment ponds and its removal during processes in STPs. The PEC_{river} has been calculated for different retention times of the notified chemical in an alkaline pond before release to sewer. The results are summarised in the table below and are based on the notified chemical hydrolysing with a half life of 6.3 hours at pH 9. The PEC_{river} was calculated according to formula $PEC_{river} = 0.5^n \times PEC_{max,}$ where n is the number of half lives (6.3 h) elapsed in the alkaline treatment pond.

Retention time	Number of Half Lives (n)	PEC_{river} / µg/L
None	0	6120
1 day (24 hours)	3.8	436
3 days (72 hours)	11.4	2.22
5 days (120 hours)	19.0	0.0113
10 days (240 hours)	38.1	2.08×10^{-8}

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity (96 h; rainbow trout)	LC50 = 0.010 mg/L	Very toxic
Fish Toxicity (96 h; bluegill sunfish)	LC50 = 0.0036 mg/L	Very toxic
Daphnia Toxicity (48 h)	EC50 = 0.0044 mg/L	Very toxic
Algal Toxicity (72 h)	E_rC50 = 0.30 mg/L	Very toxic
Bacterial Toxicity (5 min)	EC50 = 0.222 mg/L	–

Under the Globally Harmonised System of Classification and Labelling of Chemicals (United Nations, 2009) the notified chemical is considered to be very toxic to fish, aquatic invertebrates and algae. Based on the toxicity to fish the notified chemical is formally classified under the GHS as "Acute category 1; Very toxic to aquatic life". Based on the acute toxicity of the notified chemical, expected rapid biodegradability and measured log Kow (in the absence of measured BCF data), it is formally classified under the GHS as "Chronic category 1; Very toxic to aquatic life with long lasting effects".

7.2.1. Predicted No-Effect Concentration

The lowest endpoint from ecotoxicological studies on the notified chemical was used to calculate the Predicted No-Effect Concentration (PNEC). An assessment factor of 100 was used as acute toxicity endpoints are available for the effects of the notified chemical on aquatic species from three trophic levels.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (fish)	0.0036	mg/L
Assessment Factor	100	
PNEC:	0.036	µg/L

7.3. Environmental Risk Assessment

The Risk Quotients (Q = PEC/PNEC) for three discharge scenarios have been calculated below for the river compartment. The PECs correspond to retention of the notified chemical in an alkaline settling pond for 1, 3 and 5 days.

Risk Assessment	Retention time in alkaline pond / days	PEC µg/L	PNEC µg/L	Q
Q - River	1	436	0.036	12111
	3	2.22	0.036	61.67
	5	0.0113	0.036	0.314

Based on the assessed use pattern, there is potentially an unreasonable risk to the aquatic environment (Risk Quotient ≥ 1). If a site is used where release will be to a sewage treatment plant with a flow rate less than 300,000 L/day and/or the pH of alkaline treatment ponds will be less than 9, and/or the time in alkaline ponds will be less than 5 days, the notified chemical will require reassessment unless monitoring indicates the concentration of the notified chemical in waste water released to sewer is less than 0.036 µg/L.

A copy of this report will be referred to relevant Environmental State and Territory Regulatory Agencies for their information.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < -5°C

Method AUS29 Freezing Point Determination (OECD TG 102 Melting Point/Melting Range.)
Remarks The analysis was performed using a glycol bath at -5°C. Only summary was provided.
Test Facility Buckman Laboratories Pty Ltd (2011a)

Density 1100 kg/m^3 at 25°C

Method AUS07 Density Determination (OECD TG 109 Density of Liquids and Solids.)
Remarks The analysis was performed using a calibrated picnometer at 25°C. Only summary was provided.
Test Facility Buckman Laboratories Pty Ltd (2011a)

Water Solubility 5.6×10^{-3} g/L at 25°C

Method US EPA OPPTS 830.7840 Water Solubility: Column Elution Method; Shake Flask Method
Remarks Shake Flask Method. Notified chemical (0.5 g) was added to HPLC grade water (500 mL) and shaken at 30°C for 3 days. After 1, 2 and 3 days an aliquot of the test solution was centrifuged for 5 min at 5000 rpm at 25°C and analysed for the notified chemical by HPLC.
Test Facility Buckman Laboratories International, Inc. (2011a)

Hydrolysis as a Function of pH $t_{½}$ = 159 h (pH 5 at ~25°C)
$t_{½}$ = 135 h (pH 7 at ~25°C)
$t_{½}$ = 6.3 h (pH 9 at ~25°C)

Method US EPA OPPTS 835.2130 Hydrolysis as a Function of pH and Temperature

pH	*T (°C)*	*$t_{½}$ / hours*
5	~ 25	159
7	~ 25	135
9	~ 25	6.3

Remarks Test substance (notified chemical; 0.1052 g, 97% purity) was added to 100 mL of acetonitrile. Three aliquots were diluted in acetonitrile to yield 0.125 ppm dilutions with final pH adjusted to 5, 7 and 9 (with three different buffers), and each within a range of ± 0.03 pH units. Aliquots of each solution were sampled over time, extracted with dichloromethane (3 mL), evaporated by blowing with N_2 gas and reconstituted with mobile phase (2 mL). The samples were then filtered with a 0.45 µm filter for analysis by HPLC. The test was conducted at room temperature (approximately 25°C).
Test Facility Buckman Laboratories International, Inc. (2003)

Partition Coefficient (n-octanol/water) log Kow = 4.6 at 25°C

Method US EPA OPPTS 830.7570 Partition Coefficient (n-Octanol/Water) Estimation by Liquid Chromatography
Remarks HPLC method. The elution time of the notified chemical was measured. By comparison to elution times of reference compounds with known log Kow values, the log Kow of the notified chemical was determined by interpolation. No significant deviations from the test guidelines were reported.
Test Facility Buckman Laboratories Pty Ltd (2011b)

Flash Point > 90°C (pressure unknown)

Method Pensky-Martens (ASTM D93 Proc.A) method
Remarks Only summary was provided.

Test Facility Oilcheck Pty Ltd (2011)

Autoignition Temperature 280ºC

Method OL1089 method
Remarks The sample failed to ignite at 260 ºC, however, it ignited at 280ºC. Only summary was provided.
Test Facility Oilcheck Pty Ltd (2011)

Viscosity 29 cps (temperature unknown)

Method AUS25 Viscosity determination referencing OECD TG 114 Viscosity of Liquids.
Remarks The analysis was performed using a Brookfield Viscometer DVI Prime using standard glassware at 25ºC. Only summary was provided.
Test Facility Buckman Laboratories Pty Ltd (2011a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (69.2% purity)
METHOD	U.S. EPA Health Effects Test Guidelines, OPPTS 870.1100 (2002): Up-and-Down Procedure.
Species/Strain	Rat/Sprague-Dawley derived, albino
Vehicle	None
Remarks - Method	A minor deviation in recording was considered to have no impact on the outcome of this study. Acute Oral Toxicity (Guideline 425) Statistical Program (Weststat, version 1.0, May 2001) was used for all data analyses including: dose progression selections, stoping criteria determinations and/or LD50 and confidence limit calculations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	1 F	190	0
2	1 F	600	0
3	3 F	1900	0
4	3 F	5000	3

LD50	3269 mg/kg bw with approximately 95% confidence limits of 5000 mg/kg (upper) and 1900 mg/kg (lower)
Signs of Toxicity	For 190 and 600 mg/kg dose levels, both animals gained body weight and appeared active and healthy. There were no signs of toxicity, adverse pharmacological effects or abnormal behaviour. For 1900 mg/kg dose level, all animals gained body weight. Following administration, clinical signs noted included anogenital staining, diarrhea and reduced fecal volume. However, these animals recovered by day 5 and appeared active and health for the reminder of the 14-day observation period. For 5000 mg/kg dose level, toxic signs noted prior to death included ano-genital staining and diarrhea.
Effects in Organs	For 190, 600 and 1900 mg/kg dose levels, no gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period. For 5000 mg/kg dose level, gross necropsy of the decedents revealed discoloration of the intestines.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Product Safety Laboratories (2004a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical (69.2% purity)
METHOD	U.S. EPA Health Effects Test Guidelines, OPPTS 870.1200 (1998) – Limit Test.
Species/Strain	Rat/Sprague-Dawley derived, albino
Vehicle	None
Type of dressing	Occlusive
Remarks - Method	No protocol deviations.

RESULTS

Number and Sex of Animals	*Dose mg/kg bw*	*Mortality*
5 per sex	2000	0

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	There were no signs of gross dermal irritation.
Signs of Toxicity - Systemic	There were no signs of gross toxicity, adverse pharmacological effects or abnormal behaviour. All animals gained body weight and appeared active and health.
Effects in Organs	No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period.

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

TEST FACILITY Product Safety Laboratories (2004b)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified chemical (69.2% purity)

METHOD U.S. EPA Health Effects Test Guidelines, OPPTS 870.1300 (1998) – Defined LC_{50}.

Species/Strain	Rat/Sprague-Dawley derived, albino
Vehicle	None
Method of Exposure	Oro-nasal exposure.
Exposure Period	241 minutes
Physical Form	Liquid aerosol
Particle Size	Mass median aerodynamic diameter: 2.4 µm (0.106 mg/L exposure level) 2.5 µm (0.51 mg/L exposure level) 2.9 µm (2.01 mg/L exposure level)
Remarks - Method	No protocol deviations. The LC50 was calculated by the Moving Angle Average Method.

RESULTS

Group	*Number and Sex of Animals*	*Concentration <mg/L>*		*Mortality*
		Nominal	*Actual*	
1	5 M	0.1	0.106	0
2	5 per sex	0.5	0.51	3
5	5 per sex	2.0	2.01	10

LC50	0.478 mg/L/4 hours (male) and 0.51-2.01 mg/L/4 hours (female)
Signs of Toxicity	*0.106 mg/L exposure level (males only)* All animals gained body weight and appeared active and health for the entire 14-day observation period. There were no signs of gross toxicity, adverse pharmacological effects or abnormal behaviour. *0.51 mg/L exposure level* Two males were found dead at the end of exposure period. A third male animal died on day 3 of the study. Toxic signs noted prior to death included ocular discharge (red), abnormal respiration, hunched posture, hypoactivity and reduced fecal volume. The surviving animals exhibited similar clinical signs and many developed facial staining. However, these animals recovered by day 8 and appeared active and healthy for the reminder of the study, gaining body weight over the entire 14-day observation period. *2.01 mg/L exposure level* Four males and four females were found dead at the end of exposure period. The final two animals died within three days of the exposure.

Effects in Organs	Toxic signs noted prior to death included abnormal respiration, hunched posture, hypoactivity, facial staining, and reduced fecal volume. *0.106 mg/L exposure level (males only)* No gross abnormalities were noted for any of the animals when necropsied at the conclusion of the 14-day observation period. *0.51 mg/L exposure level* Gross necropsy of the animals that died after treatment revealed discoloration of the lungs (oedematous) and/or intestines, and/or gaseous distention of the intestines. No gross abnormalities were noted for any of the surviving animals when necropsied at the conclusion of the 14-day observation period. *2.02 mg/L exposure level* Gross necropsy of the animals that died after treatment revealed discolouration of the lungs (oedematous) and/or intestines and/or distention of the stomach or intestines.
CONCLUSION	The notified chemical is toxic via inhalation.
TEST FACILITY	Product Safety Laboratories (2004c)

B.4. Irritation – skin

TEST SUBSTANCE	Notified chemical (69.2% purity)
METHOD	U.S. EPA Health Effects Test Guidelines, OPPTS 870.2500 (1998) Similar to OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand albino
Number of Animals	3 F
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive.
Remarks - Method	No protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	2	2	2	2	> 14 days	2
Oedema	2	2	2.3	3	> 14 days	1[1]

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.
[1]Desquamation noted.

Remarks - Results	All animals appeared active and healthy. Apart from the dermal irritation, there were no other signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour. On hour after patch removal, all three treated sites exhibited well-defined erythema and moderate oedema. Although an overall decrease in irritation was noted thereafter, desquamation was noted at all sites between days 7 and 14, and erythema and oedema persisted in all animals through the end of study. The primary dermal irritation index is 4.33.
CONCLUSION	The notified chemical is moderately irritating to the skin.
TEST FACILITY	Product Safety Laboratories (2004d)

B.5. Skin sensitisation

TEST SUBSTANCE	Notified chemical (69.2% purity)

METHOD	U.S. EPA Health Effects Test Guidelines, OPPTS 870.2600 (2003) – Buehler Method.
Species/Strain	Guinea pig/Hartley albino
PRELIMINARY STUDY	Maximum Non-irritating Concentration: 25% topical: 25, 50, 75 and 100%
MAIN STUDY	
Number of Animals	Test Group: 20 Control Group: 10
INDUCTION PHASE	Induction Concentration: topical: 100%
Signs of Irritation	For test animals, very faint to severe erythema (0.5-3) was observed at all test sites during the induction phase. For historical positive control animals (α-hexylcinnamaldehyde), very faint to faint erythema (0.5-1) was noted for most positive control sites during the induction phase. Moderate erythema (2) was noted for one site following the third induction.
CHALLENGE PHASE	Induction Concentration: topical: 25%
Remarks - Method	No protocol deviations. Erythema scores > 0.5 were considered to be positive responses.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: challenge*	
		24 h	*48 h*
Test Group	25%	17/20	17/20
Control Group	25%	0/10	0/10

Remarks - Results	The positive response observed in the historical positive control validation study validates the test system used in this study.
CONCLUSION	There was evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Product Safety Laboratories (2004e)

B.6. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical (85.3% purity)
METHOD	U.S. EPA Health Effects Test Guidelines, OPPTS 870.3250 (1998)
Species/Strain	Rat/Crl:CD(SD) IGS BR VAF/Plus
Route of Administration	Dermal –semi-occluded
Exposure Information	Total exposure days: 90 days Dose regimen: 5 days per week Duration of exposure (dermal): 6 hours/day
Vehicle	Corn oil
Remarks - Method	Based on two range finding studies, the dermal concentrations selected for the main study were 0-250 mg/kg/day. The highest dose level was limited by the dermal irritation seen in the range finding studies. During the main study, dislodged wrappings and exposure patches were found on many occasions, especially as the study progressed. Additional checks were made from day 60, and it is not considered that these deviations compromised the efficacy of the study.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10 per sex	0	0
low dose	10 per sex	25	0
mid dose	10 per sex	125	0
high dose	10 per sex	250	0

Mortality and Time to Death

There were no test substance related mortalities during this study. One male rat from the 25 mg/kg bw/day group was found dead on test day 90. This was not considered treatment related.

Clinical Observations

No treatment related cage-side or detailed clinical signs of toxicity were observed. Any increase in incidence was isolated, not dose related, or similar to controls.

One male rat (125 mg/kg bw/day group) was observed on day 87 with focal retinopathy ventral to the optic disc. This posterior ocular segment lesion is common in properly maintained rats and is not considered to be test substance related.

Overall mean body weight, mean daily body weight gain, daily food consumption and mean daily food efficiency for male rats at 25 and 125 mg/kg bw/day and female rats at all dose levels were comparable with control values. Statistically significant decreases were noted in male rats (250 mg/kg bw/day group) during several weekly intervals and overall for mean body weight, mean daily body weight gain, daily food consumption and mean daily food efficiency. These findings are considered test substance related and adverse.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

There were no treatment related or statistically significant effects in haematology, coagulation, clinical chemistry parameters or tests for pathogens.

Effects in Organs

Gross necropsy

Gross necropsy of one male rat found dead on day 90 (25 mg/kg bw/day group) revealed discolouration of the majority of organs and tissues and several other gross abnormalities. However, this animal's death was isolated and considered not to be test substance related. The few gross observations noted in animals from various groups were considered incidental and unrelated to test substance application.

Organ weights, organ to body weight and organ to brain weight ratios

For 250 mg/kg bw/day male group, there were statistically significant decreases ($p < 0.05$ or $p < 0.01$) in absolute liver, kidney, thymus, heart and epididymides weight and kidney and epididymides to brain weight ratio ($p < 0.05$) when compared to the control group, with a statistically significant increase ($p < 0.01$) in brain to body weight ratio. For 125 mg/kg bw/day male group, there were statistically significant decreases ($p < 0.05$) in kidney to brain weight ratio.

There were no statistically significant differences in absolute organ weights or organ to brain weight ratios for treated female groups compared to the control. However, liver, kidney, and adrenal to body weight ratios for 250 mg/kg bw/day female group was statistically significantly increased ($p < 0.05$ or $p < 0.01$).

These findings did not correspond to any gross or microscopic pathology. Therefore, these findings are not considered to be toxicological importance.

Remarks – Results

Histopathology

No systemic effects related to test substance application were noted in male or female rats, with alterations limited to dermal effects in all test groups. Minimal hyperplasia observed in the control groups was likely due to the experimental procedure used in the study.

Several associated lesions occurred primarily in the treated skin of the test substance treated animals. Alterations included epidermal hyperplasia and hyperkeratosis, degeneration, suppurative inflammation and/or erosion/ulceration; suppurative hair follicle inflammation; and dermal fibrosis and chronic and chronic active inflammation. There was evidence of a dose related increase in incidence and/or mean severity of effects in these groups of animals. These findings are consistent with evidence of dose-related dermal irritation observed in these groups , and are judged to be a direct adverse effect of test substance exposure.

Ocular muscle and periscleral tissue inflammation of the eye and optic nerve gliosis and malacia occurred sporadically and with a low incidence and were considered the result of minor retro-orbital bleeding trauma that likely occurred during sampling for clinical pathology.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) could not be established due to adverse dermal effects after 90 days of dermal application of the test substance for male and female rats at all dose levels.

The No Observed Adverse Effect Level (NOAEL) for systemic effects was established as 250 mg/kg bw/day in female rats and 125 mg/kg bw/day in male rats in this study, based on adverse effects on body weight, daily body weight gain and daily food efficiency observed in 250 mg/kg bw/day group male rats.

TEST FACILITY Product Safety Laboratories (2005)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 471 Bacterial Reverse Mutation Test.
Screening study. Appears to use plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	Aroclor-induced rat liver (S9).
Concentration Range in Test 1	With metabolic activation, 10 to 5000 µg/plate for all strains Without metabolic activation, 1 to 5000 µg/plate for all strains.
Concentration Range in Test 2	With metabolic activation: 0.1 to 333 µg/plate for TA98 Without metabolic activation: 0.1 to 333 µg/plate for WP2uvrA With metabolic activation: 3.33 to 1000 µg/plate for WP2uvrA Without metabolic activation: 0.0333 to 100 µg/plate for TA 100 and TA 1537
Vehicle	Ethanol
Remarks - Method	Not a GLP study. All five bacterial strains were tested in Test 1, with and without metabolic activation. In Test 2 certain strains and test conditions were retested (WP2uvrA with and without metabolic activation, TA98 with metabolic activation, TA100 and TA1537 without metabolic activation) either because the positive controls did not perform in Test 1, or because fewer than three non-toxic concentrations were available for evaluation in Test 1.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Test 1	*Cytotoxicity in Test 2*	*Precipitation*	*Genotoxic Effect*
Absent				
Test	> 10.0	> 10.0	> 333	equivocal – WP2uvrA negative – other strains
Present				
Test	> 100	> 100	> 1000	equivocal –WP2uvrA negative – other strains

Remarks - Results The tester strain WP2uvrA showed a greater than two fold increase in the number of revertants at one dose level in Test 1 with and without metabolic activation, and in Test 2 with metabolic activation. No indications of positive responses were seen in the other strains.

CONCLUSION The notified chemical showed equivocal results for mutagenicity to bacteria under the conditions of the test.

TEST FACILITY Covance Laboratories Inc. (2002a)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD

Method similar to OECD TG 476 In vitro Mammalian Cell Gene Mutation Test. Screening assay.

Cell Type/Cell Line: L5178Y TK+/- 3.7.2c mouse lymphoma cell line

Metabolic Activation System: Aroclor-induced rat liver (S9).

Vehicle: Acetone

Remarks - Method: Not a GLP study. In the main test, the initial assay was terminated due to a sharp toxicity curve. A repeat assay was initiated with the following concentrations: 0, 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, and 5.00 µg/mL with and without activation.
The minimal criterion for a positive response in the non-activation assay was 111.7×10^{-6}. This threshold value was equal to twice the average mutant frequency of the concurrent vehicle controls. The minimal criterion for a positive response in the assay with activation was 104.1×10^{-6}.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test	0, 0.500, 1.00, 1.50*, 2.00*, 2.50*, 3.00, 3.50, 4.00, 5.00	4 hours	48 hours	10 to 14 days
Present				
Test	0, 0.500, 1.00, 1.50, 2.00*, 2.50, 3.00*, 3.50*, 4.00, 5.00	4 hours	48 hours	10 to 14 days

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test	≥ 1.97	≥ 2.00	> 5.00	positive
Present				
Test	≥ 1.97	≥ 2.00	> 5.00	positive

Remarks - Results

Mutagenicity assay

In the mutation assay without activation, the test substance induced moderately high cytotoxicity at 2.50 µg/mL (27.3% relative total growth). A small increase in concentration from 2.50 to 3.00 µg/mL was excessively cytotoxic. Treatments at 2.00 and 2.50 µg/mL induced a mutant frequency that exceeded the minimum criterion with values 3.2 and 3.1 times (respectively) the average vehicle control value. The test substance was therefore considered mutagenic under non-activation conditions.

In the presence of S9 metabolic activation, treatment at 4.00 µg/mL was cloned, but was too toxic to score. The test substance induced weak cytotoxicity at 2.00 µg/mL (52.7% relative total growth) and high cytotoxicity (16.4 and 14.7% relative total growth) at 3.00 and 3.50 µg/mL respectively. Treatment at all three concentrations induced an increase in the mutant frequency that exceeded the minimal criterion with values 2.9 to 5.6 times the average vehicle control value. The test substance was therefore considered positive with activation.

Sizing analysis

Mutant colonies from the vehicle controls all showed expected bimodal distribution and mutant colonies from methyl methanesulfonate and methylcholanthrene treated cultures (positive controls) showed both small and large colonies. A preferential increase in small colonies was observed for cultures that included a positive response, suggesting a clastogenic mechanism of mutant induction.

CONCLUSION	The notified chemical was clastogenic to L5178Y TK+/- 3.7.2c mouse lymphoma cell line treated in vitro under the conditions of the test.
TEST FACILITY	Covance Laboratories Inc. (2002b)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	Method similar to OECD TG 473 In vitro Mammalian Chromosome Aberration Test. Screening assay to determine dose range.
Cell Type/Cell Line	Cultured human peripheral blood lymphocytes
Metabolic Activation System	Aroclor-induced rat liver (S9).
Vehicle	Acetone
Remarks - Method	Not a GLP study. A full chromosomal aberrations assay according to TG473 was not conducted since one dose level with suitable cytotoxicity was identified in the dose-range finding assay.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Dose-range Finding Test	0, 7.85, 15.7*, 31.3, 62.5, 125, 250, 500, 1000	22.2	22.2
Present			
Dose-range Finding Test	0, 7.85, 15.7*, 31.3, 62.5, 125, 250, 500, 1000	3.2	22.2

*Dose chosen for evaluation of structural chromosomal aberrations.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:* *Cytotoxicity in Dose-range Finding Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test	≥ 15.7	≥ 500	negative
Present			
Test	≥ 31.3	≥ 500	negative

Remarks - Results	No significant increase in the number of cells with structural chromosomal aberrations, polyploidy, or endoreduplication was observed in the assay in the presence and absence of metabolic activation, at one dose only.
CONCLUSION	The notified chemical was not clastogenic to cultured human peripheral blood lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Covance Laboratories Inc. (2002c)

B.10. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mice/Crl:CD-1 (ICR) BR
Route of Administration	Oral – gavage
Vehicle	Corn oil
Remarks - Method	Doses for the main study were determined by a rangefinding study using both male and female animals. As similar results were seen in both sexes, the main study was conducted with male animals only.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*

I (vehicle control)	12 M	0	24
			48
II (low dose)	6 M	250	24
III (mid dose)	6 M	500	24
IV (high dose)	12 M	1000	24
			48
V (positive control, CP)	6 M	80	24

CP=cyclophosphamide.

RESULTS

Doses Producing Toxicity	The test substance induced signs of clinical toxicity in the treatment animals up to 1000 mg/kg, which include mortality in one animal at 1000 mg/kg, rough haircoat, brown haircoat (anal area), loose stools, squinted eyes, ataxia, and/or hypoactivity.
Genotoxic Effects	The test substance did not induce statistically significant increases in micronucleated PCEs at any dose levels. The test substance was not cytotoxic to the bone marrow at any dose levels (no statistically significant decreases in the PCE:NCE ratios).
Remarks - Results	The vehicle control group had less than approximately 0.4% micronucleated PCEs and the group mean was within the historical control range. The positive control, cyclophosphamide, induced a statistically significant increase in micronucleated PCEs as compared to that of the vehicle controls. These results validated the test system. It is not clear whether the test substance reached the bone marrow, as bone marrow cytotoxicity was not evident. The adverse clinical signs after dosing would usually suggest that systemic exposure had been achieved, however the clinical signs could also have been a result of irritation.

CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo micronucleus test in the mouse.
TEST FACILITY	Covance Laboratories Inc. (2003)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Biochemical/chemical oxygen demand (BOD/COD)

TEST SUBSTANCE	CHED 10%
METHOD	Reported as "Standard Methods. APHA 5210B/4500-O G 2005. 21th [sic] Ed." (BOD) and "Standard Methods. APHA 5220 D, 2005 21th [sic] Ed." (COD)
Inoculum	"Seed" from grit chamber inlet of a domestic sewerage treatment works
Exposure Period	5 days
Auxiliary Solvent	None reported
Analytical Monitoring	Dissolved Oxygen (DO) Probe (BOD), Spectrophotometer (COD)
Remarks – Method	An airtight container was filled to overflowing with test substance solution and incubated for 5 days at 20 ± 0.1°C. Dissolved oxygen is measured initially and after incubation. The BOD is computed from the difference between the initial and final DO. A positive control (solution of glucose and glutamic acid, each at 3 mg/L) was run in parallel. To determine the COD, the test substance was oxidised with potassium dichromate and sulphuric acid at 150°C.

RESULTS

BOD (5 days) mg/L	*COD mg/L*	*BOD/COD*
868,000	1,500,000	0.58

Remarks – Results	The control substance had a BOD_5 of 222.5 mg/L slightly higher than the validity criteria of 198 mg/L. The microbial activity of the inoculum was considered sufficient for the purpose of the test. Since the ratio of $BOD_5/COD \geq 0.5$ the test substance is considered to be rapidly biodegradable in the environment.
CONCLUSION	The test substance is likely to be rapidly biodegradable.
TEST FACILITY	Buckman Laboratories International, Inc. (2011c)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish (Study 1)

TEST SUBSTANCE	Notified chemical (purity 73.3%)
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static
Species	*Oncorhynchus mykiss* (rainbow trout)
Exposure Period	96 hours
Auxiliary Solvent	None reported
Water Hardness	18 - 19 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	Following a range finding test, a definitive test was conducted at nominal concentrations 0.04 – 0.73 mg/L under static conditions with daily renewal according to the guidelines above. Test conditions were: 14.4 – 16.2°C, pH 7.0 – 7.3, 9.2 – 10.4 mg/L dissolved O_2, photoperiod 16 hours light and 8 hours dark. In a separate test, test organisms were exposed to a reference toxicant (phenol). The 96 h LC50 was calculated using the binomial method.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality*			
Nominal (corrected for purity)	*Measured (time weighted mean)*		*24 h*	*48 h*	*72 h*	*96 h*
Negative control	N/A	10	0	0	0	0
pH-adjusted control	< LOD*	10	0	0	0	0
0.04	0.004	10	0	0	0	0
0.09	0.008	10	0	0	0	1
0.18	0.013	10	0	7	10	10
0.37	0.032	10	10	10	10	10
0.73	0.037	10	10	10	10	10

*Limit of Detection = 0.002 mg/L

LC50	0.010 mg/L at 96 hours. (Based on time weighted mean measured concentrations) (95% CI 0.008 – 0.013 mg/L)
NOEC	Not determined. However the highest concentration with no mortality was 0.004 mg/L at 96 hours. (Based on time weighted mean measured concentrations)
Remarks – Results	The measured concentrations of the test substance decreased between water renewals and hence the time weighted mean measured concentrations were calculated to take into account the variation in concentration of the test substance over time. As the measured test substance concentrations were not within 80 – 120% of nominal concentrations, the LC50 was calculated based on the time weighted measured concentrations. All validity criteria for the test were satisfied and no significant deviations to protocol were reported. The 96 hr LC50 for the reference toxicant was 11.4 mg/L which was considered to be within the acceptable range for previous tests conducted in the laboratory.
CONCLUSION	The test substance is very toxic to fish.
TEST FACILITY	Vizon SciTec Inc. (2005a)

C.2.2. Acute toxicity to fish (Study 2)

TEST SUBSTANCE	Notified chemical (purity 73.3%)
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static
Species	*Lepomis macrochirus* (bluegill sunfish)
Exposure Period	96 hours
Auxiliary Solvent	None reported
Water Hardness	112 – 122 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	Following a range finding test, a definitive test was conducted at nominal concentrations 0.02 – 0.73 mg/L under static conditions with daily renewal according to the guidelines above. Test conditions were: 21.9 – 24.0°C, pH 6.9 – 7.9, 91 – 107% dissolved O_2, photoperiod 16 hours light and 8 hours dark. The 96 h LC50 was calculated using the binomial method.

RESULTS

Concentration mg/L		*Number of Fish*	*Cumulative Mortality*			
Nominal (corrected for purity)	*Measured (time weighted mean)*		*24 h*	*48 h*	*72 h*	*96 h*
Negative control	< LOD*	10	0	0	0	0
0.02	0.0027	10	0	0	0	1
0.04	0.0028	10	0	0	0	2

0.09	0.006	10	10	10	10	10
0.18	0.013	10	10	10	10	10
0.37	0.023	10	10	10	10	10
0.73	0.054	10	10	10	10	10

*Limit of Detection = 0.001 mg/L

LC50	0.0036 mg/L at 96 hours. (Based on time weighted mean measured concentrations) (95% CI 0.0027– 0.0060 mg/L)
LOEC	0.0027 mg/L at 96 hours. (Based on time weighted mean measured concentrations)
Remarks – Results	The measured concentrations of the test substance decreased between water renewals and hence the time weighted mean measured concentrations were calculated to take into account the variation in concentration of the test substance over time. As the measured test substance concentrations were not within 80 – 120% of nominal concentrations, the LC50 was calculated based on the time weighted measured concentrations. All validity criteria for the test were satisfied and no significant deviations to protocol were reported.
CONCLUSION	The test substance is very toxic to fish.
TEST FACILITY	Vizon SciTec Inc. (2005b)

C.2.3. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical (purity 73.3%)
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Semi-static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None reported
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks - Method	Following a range finding test, a definitive test was conducted at nominal concentrations 0.004 – 0.073 mg/L under static conditions with daily renewal according to the guidelines above. Test conditions were: 20.0 – 21.5°C, pH 6.9 – 7.6, 8.5 – 8.9 mg/L dissolved O_2, photoperiod 16 hours light and 8 hours dark. In a separate test, test organisms were exposed to a reference toxicant ($ZnSO_4 \bullet 7H_2O$). The 48 h EC50 was calculated using the maximum likelihood probit method and ToxCalc™.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised after 48 h*
Nominal (corrected for purity)	*Modelled (see Remarks)*		
Negative control	0	4 × 5	0
pH adjusted control	0	4 × 5	0
0.004	0.0006	4 × 5	0
0.009	0.0039	4 × 5	8
0.018	0.0098	4 × 5	19
0.037	0.0222	4 × 5	20
0.073	0.0458	4 × 5	20

EC50	0.0044 mg/L at 48 hours (95% CI 0.00031 – 0.0056) (based on modelled concentrations)
NOEC	0.0006 mg/L at 48 hours (based on modelled concentrations)

Remarks - Results	The test substance concentration was not measured at all test concentrations. Hence, the available measured geometric mean concentrations were plotted against nominal concentrations to generate a linear regression equation (R^2 = 0.9937). This equation was used to model the geometric mean concentrations of the test substance and calculate the EC50. As the measured test substance concentrations were not within 80 – 120% of nominal concentrations, the EC50 was calculated based on the modelled test substance concentrations. All validity criteria for the test were satisfied and no significant deviations to protocol were reported. The 48 hr EC50 for the reference toxicant was 0.52 mg Zn^{2+}/L which was considered to be within the acceptable range for previous conducted in the laboratory.
CONCLUSION	The test substance is very toxic to invertebrates
TEST FACILITY	Vizon SciTec Inc. (2005c)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical (purity 73.3%)
METHOD	OECD TG 201 Alga, Growth Inhibition Test
Species	*Selenastrum capricornutum*
Exposure Period	72 hours
Concentration Range	Nominal: 0.42, 0.84, 1.75, 3.50 and 6.93 mg/L Measured: Not reported
Auxiliary Solvent	None reported
Water Hardness	0.138 mmol/L (Ca^{2+} and Mg^{2+})
Analytical Monitoring	None reported
Remarks - Method	Following a range finding test, a definitive test was conducted at nominal concentrations 0.42 – 6.93 mg/L according to the guidelines above. Test conditions were: 25°C, pH 7.1 – 7.6, photoperiod 24 hours. In a separate test, test organisms were exposed to a reference toxicant ($ZnSO_4 \bullet 7H_2O$). The EC50 was determined by fitting an exponential regression model to the AUGC (area under the growth curves) versus concentration of test substance. The NOEC was determined by one-way analysis of variance (ANOVA) and Dunnett's multiple comparison test.

RESULTS

Biomass		*Growth*	
E_yC50	*NOEC*	*E_rC50*	*NOEC*
Not reported	*Not reported*	*0.30 mg/L at 72 h (95% CI 0.26 – 0.34 mg/L)*	*< 0.31 mg/L*

Remarks - Results	All validity criteria for the test were satisfied and no significant deviations to protocol were reported. The reported endpoints are based on purity corrected nominal concentrations. The 48 hr EC50 for the reference toxicant was 0.018 mg Zn^{2+}/L which was considered to be within the acceptable range for previous conducted in the laboratory. In the other submitted ecotoxicity studies for the test substance the measured concentrations of the test substance were lower than the purity corrected nominal concentrations. The concentration of the test substance was not determined analytically in this study and therefore these results should be treated with caution. However, based on the differences between nominal and measured concentrations observed in the other

studies, algae is not likely to be the most sensitive trophic level.

CONCLUSION The test substance is very toxic to algae.

TEST FACILITY Vizon SciTec Inc. (2005d)

C.2.5. Toxicity to Bacteria

TEST SUBSTANCE Notified chemical (purity 60% w/w)

METHOD In-house method. Reported to be "not conducted in accordance with a protocol".

Species *Vibrio fischeri*

Exposure Period 5 minutes

Remarks – Method An untreated sample of test substance was prepared as follows: the test substance (0.1119 g) was dissolved in THF (100 mL) and made up to volume in 50% DI water/50% THF solution. A working solution was prepared by diluting to 1% (v/v) in DI water with pH 5.5 to 7 using NaOH.

A treated sample of test substance was prepared as follows: the test substance (0.1115 g) was dissolved in THF (50 mL) and made up to volume in HPLC grade water. Two drops of NaOH was added and the mixture was stirred for 30 min at room temperature before being neutralised with 2 drops of H_3PO_4. A working solution was prepared by diluting 1% (v/v) in DI water with pH 3.5 to 6.8 using NaOH.

The bioluminosity of *V. fischeri* (ocean dwelling gram negative rod-shaped bacterium) was measured by spectrophotometry prior to, and 5 minutes after the application of the untreated and treated test substance working solutions to the test organism. Toxicity (EC50) was expressed in terms of the concentration of test substance required to reduce light output of the test organism by 50%. A negative control was not reported (i.e organisms that were not exposed to the test substance).

RESULTS

EC50 0.222 mg/L at 5 minutes (as active ingredient, untreated sample)
(95% CI 0.162 – 0.0248 mg/L)

EC50 1.2915 mg/L at 5 minutes (as active ingredient, treated sample)
(95% CI 0.0917 – 0.1375 mg/L)

Remarks – Results The NaOH treated test substance was less toxic to the test organism than the untreated test substance. This result was interpreted by the authors to demonstrate that the hydrolysis products of the test substance had a lower toxicity than the test substance. There was no attempt to identify any hydrolysis products in the study.

CONCLUSION The NaOH treated test substance was less toxic to *Vibrio fischeri* than the untreated test substance.

TEST FACILITY Buckman Laboratories International, Inc. (2008)

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