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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Substance in VANAX 882-A

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment and Energy.

This Public Report is available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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SUMMARY

The following details will be published in the NICNAS *Chemical Gazette:*

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1612	Valvoline (Australia) Pty. Ltd. and Stewart Lubricants & Service Co. Australia Pty. Ltd.	Substance in VANAX 882-A	Yes	≤ 100 tonne/s per annum	Component of lubricants

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

The environmental hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS) is presented below. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Hazard classification	*Hazard statement*
Acute Category 2	H401 – Toxic to aquatic life
Chronic Category 2	H411 – 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 is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical should be classified as follows:
  - Skin sensitisation (Category 1): H317 – May cause an allergic skin reaction

The above should be used for products/mixtures containing the notified chemical, if applicable, based on the concentration of the notified chemical present and the intended use/exposure scenario.

Health Surveillance

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

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure during the handling of products containing the notified chemical:
  - Enclosed and automated systems, where possible

- A person conducting a business or undertaking at a workplace should implement the following safe work practices to minimise occupational exposure during handling of products containing the notified chemical:
  - Avoid contact with skin and eyes

- A person conducting a business or undertaking at a workplace should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical:
  - Protective clothing
  - Goggles
  - Impervious gloves

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS)* as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- Where reuse or recycling are not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state, territory and local government legislation.

Emergency procedures

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

Regulatory Obligations

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

Therefore, the Director of NICNAS must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from component of lubricant, or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

No additional secondary notification conditions are stipulated.

Safety Data Sheet
The SDS of the products containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Valvoline (Australia) Pty Ltd (ABN: 000 446 855)
Suite 603, Level 6, 2 Burbank Place
BAULKHAM HILLS NSW 2153

Stewart Lubricants & Service Co. Australia Pty Ltd (ABN: 85 613 943 703)
1/6 Marina Beach Parade
MACKAY HARBOUR QLD 4740

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: chemical name, CAS number, molecular and structural formulae, molecular weight, spectral data, degree of purity, impurities, and additives/adjuvants.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: flash point, acute inhalation toxicity, genotoxicity (in vivo), and bioaccumulation.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Canada, 2013

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Chemical in VANAX 882-A

MOLECULAR WEIGHT
< 500 Da

3. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: yellow solid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	150.4–173.9 ± 0.5 °C	Measured
Boiling Point	Decomposes at 289 °C	Measured
Density	1910 kg/m^3 at 18.5 ± 0.5 °C	Measured
Vapour Pressure	< 1.6×10^{-7} kPa at 25 °C	Measured
Water Solubility	8.71×10^{-2} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{1/2}$ > 1 year at pH = 4, 7 and 9 at 25 °C	Measured
Partition Coefficient (n-octanol/water)	log Pow = 1.3 at 20 °C	Measured
Adsorption/Desorption	log K_{oc} < 1.25 at 40 °C	Measured
Dissociation Constant	Not determined	Expected to be ionised under environmental conditions (pH 4–9)
Particle Size	Inhalable fraction (< 100 µm): 17.6% Respirable fraction (< 10 µm): 10.4%	Measured
Flash Point	Not determinable	Estimated
Flammability	Non-flammable	Measured
Autoignition Temperature	Not shown to auto-ignite	Measured
Explosive Properties	Non-explosive	Measured

Oxidising Properties	Not determined	Contains no functional groups that would imply oxidising properties.

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia.

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The chemical will be imported in additive products (at < 20% concentration) for reformulation into lubricant and as a component of finished lubricant products (at < 1% concentration). The majority of the notified chemical is expected to be imported in end-use products (about 80%).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	100	100	100	100	100

PORT OF ENTRY
Sydney, Melbourne, Brisbane and Perth.

IDENTITY OF MANUFACTURER/RECIPIENTS
Valvoline (Australia) Pty. Ltd.
Stewart Lubricants & Service Co. Australia Pty. Ltd.

TRANSPORTATION AND PACKAGING
The notified chemical will be imported by sea and transported by road or rail, and stored in 1,361 kg totes, 227 kg metal drums or 18 kg plastic pails.

USE
The notified chemical is a component of lubricants for industrial machinery.

OPERATION DESCRIPTION
The notified chemical will not be manufactured in Australia. It will be imported in bulk for reformulation and in end-use products.

Reformulation
The notified chemical is a component of a lubricant additive (< 20% concentration), to be added through a closed process into the lubricant, and mixed with other ingredients to form the final product (< 1% concentration).

End use
This final lubricant product is intended for use within vehicle equipment, and expected to be contained within the vehicle for its entire usage lifetime. Any spent or waste product containing the notified chemical is expected to be recycled or disposed of by an approved waste management company.

The finished lubricant product will be primarily used by professional workers, but may eventually be available for public use. Commercial distribution to the public is estimated to be < 15% of the total imported quantity.

5. 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	2–3	25
Process operator (formulation)	2–3	25
Quality control	1–2	4–5
Packaging	2–3	25
Waste management	1	40

EXPOSURE DETAILS

Transport and Storage

Transport and storage workers will handle the notified chemical at < 20% concentration in containers of various sizes. Exposure of these workers will be limited to events where there is a discharge, spill or leakage from damaged containers. If such an event occurs, a worker may be exposed to the notified chemical through dermal or ocular contact.

The notifier states that dockside and warehouse workers wear personal protective equipment (PPE) such as impervious gloves, coveralls and boots to minimise exposure to the notified chemical.

Reformulation

Reformulation and quality control workers may be exposed to the notified chemical at up to 20% concentration via the dermal and ocular route during the transfer of the chemical for reformulation, sampling for quality control and packaging of reformulated products. Cleaning and maintenance workers may also be exposed to the notified chemical during the cleaning and maintenance of blending equipment.

The notifier states that exposure to the notified chemical during reformulation is expected to be minimised by the use of automated equipment and closed systems for reformulation, as well as the requirement for PPE such as safety goggles, safety shoes, impervious gloves and coveralls or aprons. Cross-ventilation and exhaust ventilation is recommended and assumed to be used at exposure points.

End-use

The final products containing the notified chemical at < 1% concentrations will be used in lubricants used in industrial machinery.

At industrial service sites, workers may experience dermal or ocular exposure to the engine lubricant products containing the notified chemical at < 1% concentration when filling engine lubricants to vehicles. The potential for dermal and ocular exposure may be mitigated through the use of appropriate PPE. Inhalation exposure is not expected given that aerosols are not likely to be generated and the notified chemical has a low vapour pressure.

6.1.2. Public Exposure

Public exposure to the notified chemical as the lubricant additive (at < 20% concentration) is unlikely unless there is an accidental spill during transportation.

In the future, the final formulated products (containing < 1% of the notified chemical) may be available to the public. Consumers will perform DIY oil changes for their vehicles, and dermal and potential ocular exposure to the notified chemical at < 1% concentration may occur. Inhalation exposure to the notified polymer for consumer users is not expected under normal use conditions. Dermal and potential ocular exposure is expected to be minimised by following the safe handling precautions on product labels.

6.2. Human Health Effects Assessment

The results from toxicological investigations conducted on the notified chemical are summarised in the following table. For full details of the studies, refer to Appendix B.

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,500 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,500 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL 150 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic

Toxicokinetics, metabolism and distribution
No information on toxicokinetics of the notified chemical was provided. The notified chemical has a low molecular weight (< 500 Da); therefore absorption across biological membranes may occur. This is supported by systemic effects observed in the 28-day repeated dose oral toxicity study. Based on the molecular weight, water solubility (8.71×10^{-2} g/L at 20 °C) and partition coefficient (log Pow = 1.3) of the notified chemical, absorption across the skin may occur, although the extent of absorption may be limited.

Acute toxicity
The notified chemical was found to have low acute oral and dermal toxicity in rats. No information is available on inhalation toxicity.

Irritation and sensitisation
Based on studies conducted in rabbits, the notified chemical was considered to be non-irritating to the skin and slightly irritating to eyes. Information on irritation to the respiratory tract is not available.

The notified chemical was a skin sensitiser in a local lymph node assay (LLNA) in mice, with reported stimulation indices of 3.06, 3.66 and 3.09 at 10, 25 and 50% concentration, respectively. An EC3 value of < 10% was determined by the study authors.

Repeated dose toxicity
A 28-day repeat dose study was conducted in rats, with the notified chemical administered through the diet at dose levels of 0, 15, 150 and 650 mg/kg bw/day. The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day for both males and females in this study, based on the test substance-related adverse signs of systemic toxicity noted at the highest dose, also considering clinical pathology and pathology parameters.

It was not possible to establish a No Observable Effect Level (NOEL) due to microscopic renal changes observed at all dose levels.

Mutagenicity/Genotoxicity
The notified chemical was not mutagenic in a bacterial reverse mutation study and was not considered to be genotoxic in an in vivo micronucleus test.

Health hazard classification
Based on the available information, the notified chemical is recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	***Hazard statement***
Skin sensitisation (Category 1)	H317 – May cause an allergic skin reaction

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

Based on the information available the notified chemical has potential to be a slight eye irritant. The critical health effect of the notified chemical is as a skin sensitiser.

As the EC3 is < 10%, there is a potential risk of sensitising effects at the concentrations workers are exposed to during repackaging. During repackaging, workers may be exposed to the notified chemical at < 20% concentration. For end-use of the finished product, professional workers may be exposed to the notified chemical at < 1% concentration when manually decanting product containing the notified chemical into industrial vehicles. Appropriate PPE (coveralls, impervious gloves, eye protection) will be used to limit workers' exposure.

Therefore, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health

It is estimated by the notifier that < 15% of lubricant products containing the notified chemical will be used by do-it-yourself (DIY) consumers. Therefore, the public may have dermal or ocular exposure to products containing the notified chemical at < 1% concentration, but less frequently than professional workers. Given the toxicological profile of the notified chemical, the risk of adverse effects from the notified chemical at these concentrations is considered to be low, provided that the safe handling precautions on product labels are correctly followed.

Overall, the risk to public health associated with the proposed use of the notified chemical in lubricants is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be imported into Australia as a component of additive packages for reformulation into lubricants and as a component of finished lubricant products. No significant release of the notified chemical is expected from transportation and storage, except in the unlikely event of accidental spills or leaks.

Local blending and repackaging of the additive containing the notified chemical into lubricants is expected to occur within enclosed automated systems. Empty containers containing residues of the notified chemical and spilt material will be collected and disposed of in accordance with local government regulations, most likely to landfill.

RELEASE OF CHEMICAL FROM USE

The finished lubricant products containing the notified chemical will be mainly used by professionals. Release during use may arise from spills when pouring lubricants into automotive vehicles or from vehicle leaks, and is expected to be very low. It is estimated by the notifier that < 15% of lubricant products containing the notified chemical will be used by do-it-yourself (DIY) consumers.

A survey by the Australian Institute of Petroleum (AIP, 1995) indicates that of the annual sales of engine oils in Australia, 60% of oils are potentially recoverable (i.e. not burnt in the engines during use). This report also indicates that around 86% of oil changes take place in specialised automotive service centres, where old oil drained from crankcases is disposed of responsibly (e.g. oil recycling). Assuming this is the case, negligible amounts of the notified chemical should be released from these professional activities. The remaining 14% of oil is expected to be used by DIY consumers.

According to a survey tracing the fate of used lubricating oil in Australia (Snow, 1997), approximately 20% of oil used by DIY consumers is collected for recycling, 25% is buried or disposed of to landfill, 5% is disposed of into stormwater drains, and the remaining 50% is used in treating fence posts, killing grass and weeds or disposed of in other ways. In a worst case scenario involving the 15% of oil used by DIY consumers, up to

0.75% (15% × 5% stormwater disposal) of the total import volume of the notified chemical (or 750 kg) may enter the aquatic environment via disposal to stormwater drains. Since the use of the engine oils will occur throughout Australia, all releases resulting from use or disposal of used oil will be very diffuse.

RELEASE OF CHEMICAL FROM DISPOSAL

Any spent or waste product containing the notified chemical is expected to be recycled, re-refined or used as low grade burner fuel, or disposed of by approved waste management. It is likely that the notified chemical will be degraded into simpler compounds during refining, with any residue partitioning to the heavy fractions such as lubricating oils or asphalt.

7.1.2. Environmental Fate

Based on the results of a biodegradability study, the notified chemical is not expected to be readily biodegradable (41% in 28 days). For details of the environmental fate study, please refer to Appendix C. The notified chemical has hydrolysable functionalities and expected to hydrolyse slowly under the environmental conditions. The submitted studies have also indicated that the notified chemical may photodegrade. Volatilisation of the notified chemical is not significant, based on its vapour pressure and water solubility.

The majority of the notified chemical will be thermally decomposed during use, or collected for recycling and re-refined. Up to 0.75% of annual import volume of the notified chemical (or 750 kg) may be released by DIY consumers into stormwater drains from incorrect disposal of wastes and used engine oils. In sewage treatment plants, a significant proportion of the notified chemical is expected to partition to the aqueous phase due to its low partition coefficient (log Pow = 1.3). The notified chemical is expected to have low bioaccumulation potential due to low P_{OW} value. The notified chemical is expected to degrade into water and oxides of carbon, nitrogen and sulphur by thermal decomposition during its use and via biotic and abiotic pathways in landfill and surface water.

7.1.3. Predicted Environmental Concentration (PEC)

For the worst case scenario, the percentage of the imported quantity of notified chemical inappropriately disposed to stormwater drains is estimated to be 0.75%. That is, 15% (fraction collected by DIY users) × 5% (fraction disposed to stormwater). The release of the notified chemical may be up to 750 kg/year (= 100 tonnes/year × 0.75%). In this worst case scenario, it is assumed that the release goes into stormwater drains in a single metropolitan area with a geographical footprint of 500 km^2 and an average annual rainfall of 500 mm, all of which drains to stormwater. With a maximum annual release into this localised stormwater system of 750 kg and the annual volume of water drained from this region estimated to be 250 × 10^6 m^3, the calculated PEC will be up to 3.00 µg/L. This result reflects a worst-case scenario upper limit, as in reality releases of the notified chemical will be distributed over multiple regions and it will be further diluted if it reaches the ocean.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 > 100 mg/L (WAF*)	Not harmful to fish
Daphnia Toxicity	48 h EC50 = 18 mg/L (WAF*)	Harmful to aquatic invertebrates
Algal Toxicity	72 h EC50 =3.9 mg/L (WAF*)	Toxic to algae
Inhibition of Bacterial Respiration	3 h IC50 =230 mg/L (WAF*)	Not inhibitory to microbial respiration

*Water accommodated fraction

Based on the above ecotoxicological endpoints, the notified chemical is toxic to algae. Therefore, the notified chemical is classified as 'Acute Category 2: Toxic to aquatic life' according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009). On the basis of acute toxicity data and low biodegradation rates, the notified chemical is formally classified as 'Chronic Category 2: Toxic to aquatic life with long lasting effects'.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentrations (PNEC) for the notified chemical has been calculated from the acute algal toxicity, and an assessment factor of 100 has been applied as three measured toxic endpoints are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
EC50 (Alga).	3.90	mg/L
Assessment Factor	100	
Mitigation Factor	1.00	
PNEC:	39.00	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q – River	3.00	39.00	0.077
Q - Ocean	0.30	39.00	0.008

The Risk Quotients (Q = PEC/PNEC) for the worst case scenario have been calculated to be < 1 for the river and ocean compartments. The notified chemical will not reach ecotoxicologically significant concentrations in surface waters, based on its maximum annual importation quantity and use pattern. On the basis of the maximum annual importation volume, low expected aquatic exposure and assessed use pattern in engine oils, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point 150.4–173.9 ± 0.5 °C

Method Commission Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Differential scanning calorimetry (DSC)
Test Facility SafePharm Laboratories Ltd. (2003)

Boiling Point Decomposes at 289 °C at 101.3 kPa

Method Commission Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Differential scanning calorimetry (DSC)
Test Facility SafePharm Laboratories Ltd. (2003)

Density 1.91×10^3 kg/m^3 at 18.5 ± 0.5 °C

Method Commission Directive 92/69/EEC A.3 Relative Density.
Remarks Gas comparison pycnometer
Test Facility SafePharm Laboratories Ltd. (2006)

Vapour Pressure 1.6×10^{-7} kPa at 25 °C

Method Commission Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Vapour pressure balance
Test Facility SafePharm Laboratories Ltd. (2006)

Water Solubility 8.71×10^{-2} g/L at 20 °C

Method Commission Directive 92/69/EEC A.6 Water Solubility.
Remarks Flask Method
Test Facility SafePharm Laboratories Ltd. (2003)

Hydrolysis as a Function of pH > 1 year at 25 °C

Method Commission Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.

pH	*T (°C)*	*$t_{½}$ (year)*
4	50	> 1
7	50	> 1
9	50	> 1

Remarks HPLC. A 1% and 2% co-solvent of methanol was used to solubilise the notified chemical. Less than 10% hydrolysis was observed after 5 days at pH of 4, 7 and 9 at 50 °C.
Test Facility SafePharm Laboratories Ltd. (2006)

Partition Coefficient (n-octanol/water) log Pow = 1.3 at 20 °C

Method Commission Directive 92/69/EEC A.8 Partition Coefficient.
Remarks HPLC Method. The mobile phase was adjusted to pH 3 to make sure that the notified chemical is in its non-ionised form. Lower Pow is expected at pH of 7.
Test Facility SafePharm Laboratories Ltd. (2003)

Adsorption coefficient log K_{oc} < 1.25 at 40 °C

Method Commission Directive 2001/59/EC C.19 Estimation of Adsorption Coefficient
Remarks HPLC Method. More than 10% of the test material was ionised within the pH range of 5.5 to 7.5. This test produced inconsistent chromatography likely due to the ionisation state of the notified chemical. However, the pH did not influence the Koc value at pH 5–7.

Test Facility SafePharm Laboratories Ltd. (2006)

Particle Size

Method OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions.

Range (μm)	*Mass (%)*
< 100 μm	17.6
< 10.2 μm	10.4
< 5.4 μm	1.50

Remarks Sieve method and cascade impactor method used
Test Facility SafePharm Laboratories Ltd. (2006)

Flash Point Could not be determined

Method Estimated
Remarks Refer to vapour pressure results for more information
Test Facility SafePharm Laboratories Ltd. (2006)

Flammability Non-flammable

Method Commission Directive 92/69/EEC A.10 Flammability (Solids).
Remarks
Test Facility SafePharm Laboratories Ltd. (2003)

Autoignition Temperature Not shown to auto-ignite

Method Commission Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks
Test Facility SafePharm Laboratories Ltd. (2006)

Explosive Properties Non-explosive

Method Commission Directive 92/69/EEC A.14 Explosive Properties.
Remarks BAM fall hammer, BAM friction and Koenen steel tube test
Test Facility SafePharm Laboratories Ltd. (2006)

Oxidizing Properties Non-oxidising

Method Commission Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks Estimated based on chemical groups
Test Facility SafePharm Laboratories Ltd. (2006)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Sprague-Dawley CD strain
Vehicle	Arachis oil BP
Remarks - Method	GLP Certificate. No significant protocol deviations.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	No signs of toxicity were noted.
Effects in Organs	No abnormalities were noted at necropsy.
Remarks - Results	Hunched posture was noted in five out of six animals during the day of dosing. Animals appeared normal for remaining days of study. All animals showed expected gains in bodyweight over the study period.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	SafePharm Laboratories Ltd. (2003)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test. Commission Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.
Species/Strain	Rat/Sprague-Dawley CD strain
Vehicle	None. Notified chemical was directly applied with moistening with water.
Type of dressing	Semi-occlusive
Remarks - Method	GLP Certificate. No significant protocol deviations.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	None
Signs of Toxicity - Systemic	None
Effects in Organs	None
Remarks - Results	There were no deaths or signs of systemic toxicity. There were no signs of dermal irritation. All animals showed expected bodyweight gain over the study period.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.

TEST FACILITY SafePharm Laboratories Ltd. (2007)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
Commission Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	None. Notified chemical was directly applied with moistening with water.
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	GLP Certificate. No significant 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	0	0	0	0	0	0
Oedema	0	0	0	0	0	0

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

Remarks - Results A faint yellow-coloured staining was noted at all treated skin sites during the test period. No skin irritation reactions were observed in any of the animals.

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

TEST FACILITY SafePharm Laboratories Ltd. (2003)

B.4. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
Commission Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	7 days
Remarks - Method	GLP Certificate. No significant 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			
Conjunctiva: redness	2	2	1	2	72 h	0
Conjunctiva: chemosis	2	1.7	1	2	72 h	0
Conjunctiva: discharge	2	1.3	0	2	48 h	0
Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results Yellow coloured residual test material in all treated eyes, and a yellow-coloured staining of the fur around all treated eyes was noted at the 1 hour

observation period. No corneal of iridial effects were noted during the study. Moderate conjunctival irritation was noted in all treated eyes one hour after treatment. Petechial haemorrhage, scattered over the nictitating membrane, was noted in all treated eyes at the 24- and 40-hour observations. All treated eyes appeared normal after 7 days.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY SafePharm Laboratories Ltd. (2003)

B.5. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay
Species/Strain Mouse/CBA/Ca strain
Vehicle DMF
Preliminary study Yes – notified chemical in DMF at 50% w/v
Positive control Conducted in parallel with the test substance α-hexylcinnamaldehyde in acetone/olive oil 4:1 at 5%, 10% and 25% v/v.
Remarks - Method GLP Certificate.
No significant protocol deviations.

RESULTS

Concentration (% w/w)	*Number and sex of animals*	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance			
0 (vehicle control)	5F	1,695.58	n/a
10%	5F	5,184.80*	3.06
25%	5F	6,208.19**	3.66
50%	5F	5,231.72*	3.09
Positive Control			
5%	5^	-	2.0
10%	5^	-	1.9
25%	5^	-	6.8

^ Animal sex not stated
* = Significantly different from vehicle control group $p < 0.05$
** = Significantly different from vehicle control group $p < 0.01$

EC3 < 10% (all concentrations tested resulted in a stimulation index > 3)
Remarks - Results No deaths or signs of systemic toxicity observed. Yellow-coloured staining of the fur was noted.

CONCLUSION There was evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY SafePharm Laboratories Ltd. (2003)

B.6. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Commission Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).
Species/Strain Rat/Sprague-Dawley Crl:CD (SD) IGS BR strain
Route of Administration Oral – gavage
Exposure Information Total exposure days: 28 days
Dose regimen: 7 days per week

Vehicle	Arachis oil
Remarks - Method	GLP Certificate. No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5M, 5F	0	0
low dose	5M, 5F	15	0
mid dose	5M, 5F	150	0
high dose	5M, 5F	600	1

Mortality and Time to Death

One male in the high-dose group had body weight loss, hunched posture, dehydration and tiptoe gait on Day 8. On Day 9, additional symptoms included lethargy, pilo-erection, pallor of extremities, staining of ano-genital region, waddling gait and red urination. This animal was euthanised on Day 9 due to its declining condition. Necropsy revealed enlarged and pale kidneys, stomach contents were dark, had a raised limiting ridge and sloughing of the non-glandular region. Marked renal changes affecting both kidneys were found, which accounted for the declining condition of the animal.

Renal damage to a lesser extent was observed inn other males in the high-dose group.

Clinical Observations

Increased transient post-dosing salivation was observed in several animals. For animals in the mid-dose group, this observation was found in 2 males and 2 females, on one or two occasions during the study. For animals in the high-dose group, 3 males and 4 females showed this observation. These instances were attributed by the study authors to the palatability/irritancy of the test material rather than the systemic effect of treatment.

One male and one female in the high-dose group showed hunched postures on Day 27 and 16 respectively; these signs were no longer present in subsequent days and were unlikely to have any toxicological significance.

No clinical signs were observed for any animal in the low-dose group.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

For males in the high-dose group, mean cell haemoglobin concentration was lower than the controls ($p < 0.05$). However, no significant changes were observed for the mean corpuscular haemoglobin and mean corpuscular volume, so this observation was not considered to be of toxicological significance by the study authors.

For females in the mid- and high-dose groups, there was a decrease in the mean number of neutrophils compared to the controls. In the absence of any histopathological correlates, this finding was not considered to be of toxicological significance.

Effects in Organs

Nephropathy characterised by tubular basophilia, tubular dilation, papillary degeneration/necrosis, hyperplasia of the papillary/pelvic epithelium, and hypertrophy of the collecting duct epithelium was observed for all male rats in the high-dose group. Vacuolar degeneration of the proximal tubular epithelium was seen for 2 female rats in the high-dose group.

Yellow pigments were deposited in the tubular epithelium of all animals in the high-dose group. Animals in the low- and mid-dose group also had pigment deposition, but no tubular degenerative changes were observed at these dose levels. The pigment was likely to be accumulations of the notified chemical or its metabolite.

Hypertrophy of the follicular epithelium in the thyroid was observed for all animals in the high-dose group and for all males in the mid-dose group. This change is frequently observed as an adaption in rats when they are given xenobiotic chemicals.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 150 mg/kg bw/day in this study, based on the absence of any renal tubular degenerative changes. However, it was not possible to establish a No Observable Effect Level (NOEL) due to microscopic renal changes observed at 15, 150 and 600 mg/kg/day.

TEST FACILITY SafePharm Laboratories Ltd. (2007)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Commission Directive 2000/32/EC B.13/14 Reverse Mutation Test Bacteria

Species/Strain	*S. typhimurium*: TA100, TA1535, TA102, TA1537, TA98
Metabolic Activation System	S9 from Phenobarbitone (PB)/β-napthoflavone (NF) induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 15–5,000 µg/plate b) Without metabolic activation: 1.5–5,000 µg/plate
Vehicle	DMSO
Remarks - Method	GLP Certificate. No significant protocol deviations.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	≥ 150	≥ 150	None	Negative
Test 2		≥ 1,500	None	Negative
Present				
Test 1	≥ 1,500	≥ 1,500	None	Negative
Test 2		≥ 5,000	None	Negative

Remarks – Results No test material precipitate was observed at any doses tested. No significant increases in the frequency of revertant colonies were recorded for any of the *Salmonella* strains. The concurrent positive controls gave satisfactory responses confirming the validity of the test system.

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

TEST FACILITY SafePharm Laboratories Ltd. (2003)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Commission Directive 2000/32/EC B.10 in vitro Mammalian Cytogenetic Test

Species/Strain	*Homo sapiens*
Cell Type/Cell Line	Lymphocytes from whole blood samples
Metabolic Activation System	S9 from Phenobarbitone (PB)/β-napthoflavone (NF) induced rat liver
Vehicle	DMSO
Remarks – Method	GLP Certificate. No significant protocol deviations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			

Test 1	0*, 62.5*, 125*, 250*, 500*, 625, 750, 1000, MMC 0.4*	4	20
Test 2	0*, 62.5*, 125*, 250*, 500, 625, 750, MMC 0.2	24	0
Present			
Test 1	0*, 62.5, 125*, 250*, 500*, 625, 750, 1000, CP 5*	4	20
Test 2	0*, 62.5, 125*, 250*, 500*, 625, 750, CP 4*	4	20

*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	≥ 500	750	≥ 1,500	Negative
Test 2	≥ 250	500	≥ 2,000	Negative
Present				
Test 1	≥ 500	1,000	≥ 1,500	Negative
Test 2		1,000		Negative

Remarks – Results

In the presence of metabolic activation, the test substance induced a small but statistically significant increase in the number of aberrant cells at the highest dose tested, which was marginally greater than the historical control for this exposure group. The study authors considered it to not have toxicological significance.

The test material did not induce a statistically significant increase in the numbers of polyploidy cells at any dose level.

The concurrent negative and positive controls gave satisfactory responses confirming the validity of the test system.

CONCLUSION

The notified chemical was not clastogenic to lyphocytes treated in vitro under the conditions of the test.

TEST FACILITY

SafePharm Laboratories Ltd. (2006)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test. Commission Directive 92/69/EEC C.4C Carbon Dioxide (CO_2) Evolution
Inoculum	Activated sewerage sludge
Exposure Period	29 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical Amount of Carbon Dioxide ($ThCO_2$)
Remarks - Method	The test was conducted in accordance with the test guideline above, with no significant deviation in protocol reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	14	6	60
14	29	14	77
22	39	22	82
29	41	29	90

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound surpassed the threshold level of 60% by 6 days, and attained 90% degradation in 29 days. Therefore, the test indicates the suitability of the inoculums. The percentage degradation of the toxicity control surpassed the threshold level of 25% by 2 days, showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the test substance after 28 days was 41%.
CONCLUSION	The notified chemical is not considered to be readily biodegradable.
TEST FACILITY	SafePharm Laboratories Ltd. (2003)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Limit Test. Commission Directive 92/69/EEC C.1 Acute Toxicity for Fish
Species	*Oncorhynchus mykiss* (rainbow trout)
Exposure Period	96 hours
Auxiliary Solvent	None
Water Hardness	140 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	The notified chemical was prepared as water accommodated fraction (WAF) due to its low water solubility. The test substance was prepared by dispersing an excess of the notified chemical (500 mg/L) with the aid of ultrasonication for about 15 min and then removing any undissolved test material by filtration to give a saturation solution from which dilutions were prepared. The test solutions were renewed every 24 hours during the 96 h test period.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
100		7	0	0	0	1*	1
100		7	0	0	0	0	0

*Mortality was due to natural causes/handling stress as no other mortality was observed throughout test.

LC50	> 100 mg/L at 96 hours.
NOEC (or LOEC)	100 mg/L
Remarks – Results	All validity criteria for the test were satisfied. The actual concentrations of the test substance ranged from 104% to 117% of nominal concentrations in fresh media. Analysis of old media at 24, 48, 72 and 96 hours showed measured test concentrations to be in the range of 105 to 120% of nominal concentrations. The 96 h LC50 and NOEC for fish were determined to be > 100 mg/L and 100 mg/L, respectively, based on nominal loading concentrations.

CONCLUSION The notified chemical is not considered to be harmful to fish.

TEST FACILITY SafePharm Laboratories Ltd. (2007)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test – Static.
Commission Directive 92/69/EEC C.2 Acute Toxicity for Daphnia

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC, Total Organic Carbon Analyser
Remarks - Method	The test substance was prepared by dispersing an excess of test material in water by using the ultrasonication for approximatey 15 min and then removing any undissolved test material by filtration to give a saturated solution of the test material at a concentration of 192 mg/L. The test was conducted in dark as the test substance was unstable under light conditions. The test solutions were not renewed during the 48 h test period.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h [acute]*	*48 h [acute]*
Control	Control	20	0	0
1.4	1.59	20	0	0
2.4	2.87	20	0	0
4.4	5.03	20	0	0
7.6	9.16	20	0	0
14	14.8	20	0	3
24	25.9	20	8	17
44	48.2	20	13	20
76	82.9	20	10	20
136	138	20	20	20

EC50	18 mg/L at 48 hours
NOEC	7.6 mg/L
Remarks - Results	Concentration dependent differences in pH were observed. The analytical

procedure had low recoveries of test material in test medium which were corrected. The actual concentrations of the test substance were 101–120% of nominal concentrations at 0 hours and were 94–114% of nominal concentrations at 48 hours. The 48 hr EC50 for the notified chemical to *Daphnia magna* was 18 mg/L with 95% confidence limits of 16–21 mg/L based on nominal test concentrations.

CONCLUSION The notified chemical is considered to be harmful to aquatic invertebrates.

TEST FACILITY SafePharm Laboratories Ltd. (2007)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.
Commission Directive 92/69/EEC C.3 Algal Inhibition Test

Species	*Desmodesmus subspicatus* (green alga)
Exposure Period	72 hours
Concentration Range	Nominal: 4.8, 10, 21, 45, 96 mg/L Geometric mean measured test concentrations: 1.1, 2.1, 5.1, 8.0, and 73 mg/L
Auxiliary Solvent	None
Water Hardness	Not given
Analytical Monitoring	HPLC, Total Organic Carbon Analyser
Remarks - Method	The test material was prepared by dispersing an excess of test material in culture medium by using ultrasonication for ~15 min prior to removal of any undissolved test material by filtration through 0.2 µm Sartorius Sartopore filter in order to produce a saturated solution of the test material with a measured concentration of 96 mg/L.

RESULTS

Biomass		*Growth*	
EC_{50}	*NOEC (biomass integral)*	*EC_{50}*	*NOEC (growth rate)*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
16 (2.8*)	10 (2.1*)	14 (3.9*)	10 (2.1*)

* Values are based on the geometric mean measured test concentrations

Remarks - Results All validity criteria were satisfied. Preliminary tests showed that the notified chemical was unstable in light conditions. Test solutions showed a decline in measured concentrations in the range of 4% to 8% of the initial measured concentrations at 72 hours. Therefore, the results were based on the geometric mean measured test concentrations.

CONCLUSION The notified chemical is considered to be harmful to algae.

TEST FACILITY SafePharm Laboratories Ltd. (2007)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum	Activated sewage sludge
Exposure Period	3 hours
Concentration Range	Nominal: 28, 50, 90, 157, 252 mg/L
Remarks – Method	An excess of material was dispersed in culture medium by applying ultrasonication for ~20 min prior to removal of any undissolved test material by filtration through 0.2 µm Sartorius Sartopore filter in order to

	produce a saturated solution of the test material with a measured concentration of 280 mg/L.
RESULTS	
IC50	230 mg/L
NOEC	28 mg/L
Remarks – Results	The validation criteria for the control respiration rates and reference material IC50 values were satisfied. The pH values at the beginning and at the end of the exposure period showed a concentration dependent decrease when compared to control vessels which may contribute to the toxic nature of the test material but was considered not to affect the integrity of the study.
CONCLUSION	The notified chemical is not inhibitory to microbial activity.
TEST FACILITY	SafePharm Laboratories Ltd. (2007)

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