File No: LTD/1954

June 2017

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Chemical in Desothane HS Topcoat Gloss Light Grey

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

TABLE OF CONTENTS

SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
LTD/1954	PPG Industries Australia Pty Ltd	Chemical in Desothane HS Topcoat Gloss Light Grey	Yes	< 1 tonne per annum	Component of coatings

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*
Flammable liquids (Category 4)	H227 – Combustible liquid
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage

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 3)	H402 - Harmful to aquatic life

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

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

Environmental risk assessment
On the basis of the low expected aquatic release 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:
  - Flammable liquids (Category 4): H227 – Combustible liquid
  - Serious eye damage/eye irritation (Category 1): H318 – Causes serious eye damage

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 (as classified by the notifier), 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 isolation and engineering controls to minimise occupational exposure to the notified chemical:
  - Enclosed and automated system during repackaging, where possible
  - Sufficient ventilation
  - Spray booth used for spray application 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 the notified chemical:
  - Avoid contact with skin and eyes
  - Avoid inhalation of aerosols

- 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
  - Impervious gloves
  - Eye protection
  - Respiratory protection during spray application

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

- Spray applications should be carried out in accordance with the Safe Work Australia Code of Practice for *Spray Painting and Powder Coating* (SWA, 2015) or relevant State or Territory Code of Practice.

- 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. Prevent spillage from entering drains or water courses.

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
- the importation volume exceeds one tonne per annum notified chemical;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a component of coatings, 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.

Safety Data Sheet
The SDS of a product containing the notified chemical provided by the notifier was 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)
PPG Industries Australia Pty Ltd (ABN: 82 055 500 939)
14-20 McNaughton Road
CLAYTON VIC 3168

NOTIFICATION CATEGORY
Limited-small volume: Chemical other than polymer (1 tonne or less per year).

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

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed for vapour pressure, adsorption/desorption, dissociation constant, flammability and oxidising properties.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Canada, European Union, New Zealand, South Korea and United States

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Desothane HS Topcoat Gloss Light Grey (contains < 10% notified chemical)

MOLECULAR WEIGHT
< 500 Da

ANALYTICAL DATA
Reference NMR, IR, UV/Vis spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
60–90%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Yellow liquid

Property	Value	Data Source/Justification
Freezing Point	< -50 °C	Measured
Boiling Point	189.3 °C at 99.9 kPa	Measured
Density	1,064 kg/m^3 at 20 °C	Measured
Vapour Pressure	Not determined	Will be imported and used in aqueous solution
Water Solubility	Not determined	Soluble, however, the notified chemical is not hydrolytically stable in water.
Hydrolysis as a Function of pH	Not determined	The notified chemical hydrolyses rapidly.
Partition Coefficient (n-octanol/water)	log Pow = 1.8	Measured
Adsorption/Desorption	Not determined	The notified chemical is not

		hydrolytically stable in water.
Dissociation Constant	Not determined	The notified chemical is not expected to ionise significantly in the environmental pH range (4–9).
Flash Point	76.1 °C at 101.3 kPa	Measured
Flammability	Not determined	Classified as combustible liquid based on the measured flash point
Autoignition Temperature	341 °C	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 decomposes rapidly (within 1 hour) in water or under acidic or basic conditions. However, it is expected to be stable under normal conditions of proposed use.

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, 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***
Flammable Liquids (Category 4)	H227 – Combustible liquid

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified polymer will not be manufactured or reformulated in Australia. It will be imported at < 10% concentration as a component of finished coatings.

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

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

PORT OF ENTRY
Melbourne (air and road)

TRANSPORTATION AND PACKAGING
The finished coatings containing the notified chemical at < 10% concentration will be imported in 1 L or 5 L UN approved cans. Local repackaging into smaller containers may occur. The coatings will be distributed by air and road to industrial customers.

USE
The notified chemical will be used as a component of industrial coatings at < 10% concentration and finished coatings containing the notified chemical will be applied by spray.

OPERATION DESCRIPTION

Repackaging
The finished coatings imported in 1 L or 5 L cans may be transferred into smaller containers through gravity feed or low pressure pumps.

End-use
Finished coatings may be manually decanted and the subsequent application is expected to occur in spray booths and to be automatic or semi-automatic through use of robotics and applicator-operated spray guns.

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)*
Stevedores	2–3	10–15
Transportation and storage workers	6	260
Coating applicators	6	260
Cleaning and maintenance workers	4	260

EXPOSURE DETAILS
Transport and storage workers are not expected to be exposed to the notified chemical except in the unlikely event of an accident. In the event of large spills, the use of spark-proof tools and explosion-proof equipment is recommended for the notified chemical (classified as a flammable liquid) as introduced.

Repackaging process
Dermal and ocular exposure to the notified chemical at < 10% concentration may occur during transferring and cleaning and maintenance of equipment. Exposure should be minimised through the use of enclosed and automated systems where possible and personal protective equipment (PPE: goggles, impervious gloves, protective clothing as anticipated in the occupational settings). Inhalation exposure is not expected to be significant as aerosols are not generated in this process.

Coating application
Dermal, ocular and inhalation exposure to the notified chemical (at < 10% concentration) may occur during spray applications of the finished coatings, and when cleaning equipment. Exposure should be minimised through the use of automatic or semi-automatic processes (including robotics and applicator-operated spray guns), local exhaust ventilation, spray booths and PPE (including goggles, impervious gloves, protective clothing and respirators as anticipated by the notifier).

Once the coating is dried and cured, the notified chemical will be bound into an inert solid matrix and will be unavailable for exposure.

6.1.2. Public Exposure
The finished products containing the notified chemical (< 10% concentration) will be used in industrial settings only and will not be made available to the public. Once the coating is dried and cured, the notified chemical will be bound into an inert solid matrix and will be unavailable for exposure.

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 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	severely irritating
Guinea pig, skin sensitisation – adjuvant test	inadequate evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 150 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosome aberrations	genotoxic
Genotoxicity – in vivo bone marrow micronucleus test	non genotoxic

Toxicokinetics
Based on the low molecular weight (< 500 Da) and high water solubility (soluble) of the notified chemical, there is potential for the chemical to cross biological membranes. In addition, the notified chemical decomposes rapidly (within 1 hour) in water or under acidic or basic conditions. The breakdown products of the notified chemical are expected to have low molecular weight (< 500 Da) and high water solubility; therefore, there is potential for the breakdown products to cross biological membranes.

Acute toxicity
The notified chemical was found to be of low toxicity via the oral and dermal routes in studies conducted in rats.

Irritation
In studies conducted in rabbits, the notified chemical was found to be slightly irritating to the skin and severely irritating to eyes. Skin irritation was limited to very slight to moderate erythema, very slight oedema, petechial haemorrhage, atonia and desquamation which were fully resolved at the end of the observation period (14 days).

Sensitisation
The notified chemical showed equivocal evidence of skin sensitisation in a study conducted in guinea pigs. Irritant effects were observed in test animals during the first challenge; however, the response in the test group was not significantly more severe or persistent than the maximum control response. The notifier has classified the notified chemical as skin sensitisation (Category 1) in the provided SDS, consistent with the classification on the ECHA C&L inventory.

Repeated dose toxicity
A repeated dose oral (gavage) toxicity study on the notified chemical was conducted in rats, in which the test substance was administered at 150, 500 and 1,000 mg/kg bw/day for 28 consecutive days.

The No Observed Adverse Effect Level (NOAEL) was determined as 150 mg/kg/day in the study, based on decreased body weight gain, spinal cord vacuolation and forestomach gastritis (which were noted at 500 mg/kg/day and 1,000 mg/kg/day). However, there is uncertainty with this conclusion as it couldn't be determined whether the animals received the target amount of the test substance due to the known reactivity of the notified chemical in a number of liquid vehicles.

Mutagenicity/Genotoxicity
The notified chemical was negative in a bacterial reverse mutation assay but gave a positive response in an *in vitro* chromosome aberration test in human peripheral lymphocytes. However, the notified chemical tested negative in an *in vivo* mouse bone marrow micronucleus test via the oral route. Based on weight of evidence, the notified chemical is not predicted to be genotoxic.

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*
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the available toxicological data, the notified chemical is of low acute systemic toxicity, slightly irritating to the skin and severely irritating to eyes. The notified chemical was classified as a skin sensitiser by the notifier. The potential for adverse effects after repeated exposure cannot be ruled out.

Irritation effects are not expected at the proposed concentration (< 10%). Furthermore, exposure to the notified chemical during repackaging and applications is expected to be limited by the use of engineering controls and PPE. Once the coating is dried and cured, the notified chemical will be bound within an inert solid matrix and will not be bioavailable.

Therefore, given the expected low exposure under the conditions of the occupational settings, the risk to workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health

The notified chemical will be used in industrial settings only and will not be made available to the public. Members of the public may come into contact with surfaces coated with products containing the notified chemical. However, once the coatings have dried and cured, the notified chemical will be bound within the inert solid matrix and will not be bioavailable.

Based on the assessed use patterns, the risk to the public from use of the notified chemical 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 as component of formulations and may be repacked into smaller containers. No significant release of the notified chemical is expected from transportation, storage and potential repackaging processes, except in the unlikely event of accidental spills or leaks. In the event of spills, the notified chemical is expected to be collected with inert adsorbents, and disposed of to landfill in accordance with local government regulation.

RELEASE OF CHEMICAL FROM USE

Industrial paints and coatings containing the notified chemical will be used by professional users in industrial settings only. During use, paints and coatings containing the notified chemical are expected to be applied by spray techniques. Spray applications are expected to occur within spray booths with engineering controls to collect particulate overspray. Overspray and solid wastes from application of the industrial paints and coatings containing the notified chemical will be collected and disposed of to landfill. Residues containing the notified chemical in application equipment are expected to be rinsed into containers, recycled, or allowed to cure before disposal as solid wastes to landfill.

RELEASE OF CHEMICAL FROM DISPOSAL

The notified chemical in industrial paints and coatings is expected to share the fate of the substrate to which it has been applied. These are predominantly expected to be disposed to landfill, or thermally decomposed during metal reclamation.

7.1.2. Environmental Fate

The majority of the notified chemical is expected to be cured within an inert matrix, and is expected to share the fate of the articles to which it has been applied. These will involve eventual disposal to landfill, or thermal decomposition during metal reclamation. The notified chemical is also expected to enter landfill as collected wastes and residues. Once cured, the notified chemical is not expected to be either bioavailable or biodegradable.

In the unlikely event of the notified chemical's release to surface water, the notified chemical will not readily biodegrade but will rapidly hydrolyse as indicated by submitted studies. For the details of the environmental fate studies refer to Appendix C. As the notified chemical is not stable in the aquatic environment and has low n-octanol-water partition coefficient (log P_{OW} = 1.8), it is not expected to bioaccumulate. In surface waters and landfill, the notified chemical is expected to degrade via biotic and abiotic processes to form water and oxides of carbon and nitrogen.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has not been calculated, as significant release of the notified chemical to the aquatic environment is not expected, based on its reported use pattern in industrial paints and coatings.

7.2. Environmental Effects Assessment

The results from ecotoxicological investigations conducted on the notified chemical (~75% concentration) are summarised in the table below.

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h LC50 = 85.7 mg/L	Harmful to fish
Daphnia Toxicity	48 h EC50 >100 mg/L	Not harmful to aquatic invertebrates
Algal Toxicity	72 h EC50 = 93.1 mg/L	Harmful to algae
Inhibition of Bacterial Respiration	3 h IC50 > 1,000 mg/L	Not inhibitory to microbial respiration

Based on the above ecotoxicological endpoints, the notified chemical is harmful to aquatic life. Therefore, the notified chemical is classified as 'Acute Category 3: Harmful to aquatic life' according to the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009). Based on its acute toxicity endpoints, rapid hydrolytic degradability and low partition coefficient, the notified chemical is not formally classified under the GHS for chronic toxicity.

7.2.1. Predicted No-Effect Concentration

The predicted no-effects concentration (PNEC) has been calculated from the most sensitive endpoint for fish. A safety factor of 100 was used given three acute endpoints are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
LC50 (Fish).	85.70	mg/L
Assessment Factor	100	
Mitigation Factor	1	
PNEC:	857	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient (Q = PEC/PNEC) of the notified chemical has not been calculated as a PEC is not available due to the low potential for release to the aquatic compartment based on its assessed use pattern in industrial coatings. The majority of the notified chemical is expected to be disposed of to landfill bound within the inert coating matrix and is not expected to be mobile and bioavailable in this form. Therefore, on the basis of maximum annual importation volume, low expected aquatic exposure and assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Freezing Point < -50 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	Freezing point tube method
Test Facility	Covance (1998a)

Boiling Point 189.3 °C at 99.9 kPa

Method	OECD TG 103 Boiling Point.
Remarks	Siwoloboff procedure
Test Facility	Covance (1998a)

Density 1,064 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	Determined by a pyknometer
Test Facility	Covance (1998b)

Partition Coefficient (n-octanol/water) log Pow = 1.8

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method. The notified chemical is known to hydrolyse readily.
Test Facility	Covance (1998a)

Flash Point 76.1 °C at 101.3 kPa

Method	EC Directive 92/69 Annex V Method A.9 Flash Point.
Remarks	Closed cup method
Test Facility	Covance (1998a)

Autoignition Temperature 341 °C

Method	EC Directive 92/69 Annex V Method A.15 Auto-Ignition Temperature (Liquids and Gases).
Test Facility	Covance (1998b)

Explosive Properties Non-explosive

Reference	Bretherick's Handbook of Reactive Chemical Hazards – Butterworth –Heinemann 1990.
Remarks	Determined by a theoretical assessment and a differential scanning calorimetry screening test
Test Facility	Covance (1998b)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity – Fixed Dose Procedure.
Species/Strain	Rat/Hsd.Brl:WH
Vehicle	Desiccated corn oil
Remarks - Method	No significant protocol deviations. A preliminary study was conducted in groups of 2 female animals at doses of 500 or 2,000 mg/kg bw. The dose of 2,000 mg/kg bw was selected for the main study based on the results of the preliminary study (no mortality or significant toxicity).

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2000	0/10

LD50	> 2,000 mg/kg bw
Signs of Toxicity	There were no overt signs of systemic toxicity.
Effects in Organs	No abnormalities were noted at macroscopic examination in 9/10 animals. One eye of an animal was found to be distended. This finding was not considered by the study authors to be test substance-related due to the absence of corroborative in-life observations.
Remarks - Results	The animals showed body weight gain over the observation period.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Covance (1998c)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain	Rat/ Hsd.Brl:WH
Vehicle	None
Type of dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations. A preliminary study was conducted in 2 female animals at dose of 2,000 mg/kg bw. The dose of 2,000 mg/kg bw was selected for the main study based on the results of the preliminary study (no mortality or significant toxicity).

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 per sex	2,000	0/10

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	
Signs of Toxicity - Systemic	Staining of the snout was seen in 1 male and 3 female animals on Day 1 and/or Day 2. All animals were overtly normal by Day 3.
Effects in Organs	No effects were noted at the test site of the majority of animals. Multiple, small foci of eschar were seen at the test site of one female animal on Days 11–15 but not noted at necropsy. Gaseous distension of the colon was noted in 1 female and a slight sore was noted in another female animal during macroscopic examination.

Remarks - Results	The animals showed expected body weight gain over the observation period.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	Covance (1998d)

B.3. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	None
Observation Period	14 days
Type of Dressing	Semi-occlusive
Remarks - Method	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	1.7	1.3	2.3	3	< 15 days	0
Oedema	0	0	0.3	1	< 8 days	0

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

Remarks - Results	No mortality or signs of systemic toxicity were noted. Very slight to moderate erythema was noted in all animals up to 72-hour observation. Resolution of the effects was advanced by Day 8 and complete by Day 15. Very slight oedema was noted in all animals at 72-hour observation and resolved by Day 8. Petechial haemorrhage, atonia and desquamation were noted at 24-hour, 48-hour and Day 8 observations, respectively. All signs of irritation resolved at the end of the observation period (14 days).
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	Covance (1998e)

B.4. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (1F, 2M)
Observation Period	4 days
Remarks - Method	No significant protocol deviations. Initial sting reaction noted in the female animal necessitated the administration of a corneal anaesthetic for the 2 other test animals.

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	0	1	2	2	N/A	N/A
Conjunctiva: chemosis	0	1	2	2	N/A	N/A
Conjunctiva: discharge	0.7	3	3	3	N/A	N/A
Corneal opacity	0	2	2	2	N/A	N/A
Iridial inflammation	0	2	2	2	N/A	N/A

* Calculated on the basis of the scores at 24, 48, and 72 hours
^ The scores at 24 hours only for EACH animal due to termination
N/A: Not applicable as two animals were euthanised on Day 2

Remarks - Results

No signs of systemic toxicity were noted.

Injection of the conjunctive blood vasculature and inflammation of the iris were noted immediately after treatment in one animal without eye anaesthesia. Iridial inflammation resolved within 1.5 hours of treatment while conjunctival irritation relations persisted for up to 24 hours. The cornea reminded overtly unaffected. All irritation reactions resolved within 48 hours of treatment.

The male animals had practically no initial sting response and diffuse opacity of the greater part of the cornea and inflammation of the iris and conjunctivae were noted 1.5 hours after treatment. Four hours after treatment, the treated cornea appeared translucent and conjunctive reactions included a crimson red appearance; chemosis was sufficient to cause partial eversion of the eyelids and a moderate ocular discharge. On the following day, the iridial reflex of both animals was found to be absent and the animals were euthanised on humane grounds.

The study authors noted that although it was accepted that use of anaesthetic appeared to have exacerbated the irritation effects of the test substance, the test substance was concluded to be severely irritating to the eye.

CONCLUSION

The notified chemical is severely irritating to the eye.

TEST FACILITY

Covance (1998f)

B.5. Skin sensitisation

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 406 Skin Sensitisation - Magnusson and Kligman.

Species/Strain

Guinea pig/albino

PRELIMINARY STUDY

Maximum Non-irritating Concentration:
intradermal: < 0.1% in Alembicol D (slight erythema persisted until 72 hour observation at 2.5% in Alembicol D)
topical: 80% in Alembicol D

MAIN STUDY

Number of Animals

Test Group: 20 Control Group: 10

Vehicle

Positive control

Not conducted in parallel with the test substance, but had been conducted previously in the test laboratory using 2-mercaptobenzothiazole.

INDUCTION PHASE

Induction Concentration:
intradermal: 2.5% in Alembicol D
topical: 80% in Alembicol D

Signs of Irritation	intradermal: well defined erythema (anterior site exposed to FCA)/slight erythema (middle site exposed to 2.5% test substance in Alembicol D)/ slight erythema (posterior site exposed to 2.5% test substance in FCA) topical: well defined erythema to moderate erythema
CHALLENGE PHASE	
1st challenge	topical: 25% (anterior site)/12.5% (posterior site)
2nd challenge	topical: 10% (anterior site)/5% (posterior site)
Remarks - Method	

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	25% (A)/12.5% (P) 10% (A)/5% (P)	16A/16P/12C	16A/18P/5C	16A/13P/2C	19A/19P/3C
Control Group	25% (A)/12.5% (P) 10% (A)/5% (P)	5A/6P/8C	3A/4P/0C	7A/6P/1C	6A/5P/0C

A = anterior site; P = posterior site, C = control site exposed to in Alembicol D

Remarks - Results	No clinical observations of ill health or toxicity were noted and all animals gained weight. Following the 1st challenge, the skin reactions in the treated animals were generally not more severe/persistent than those of the control group. Fifteen lower challenge application sites developed well defined erythema in the treated group but the difference in incidence between test and control groups was considered by the study authors to be insufficient to classify the test substance as a sensitiser. Three treated animals developed additional dermal changes, scabbing or induration. The response was considered by the study authors to be an equivocal indication of an enhanced reaction to the test substance. Following the 1st challenge, the reaction to the vehicle in the control group was negligible. The treated sites in the control group developed reactions not exceeding well defined erythema, desquamation and induration with the response persisting at the 48-hour observation. The response in the test group was not significantly more severe or persistent than the maximum control response and consequently none of the animals was considered by the study authors to have a positive result. The presence of eschar at two sites was considered by the study authors to be equivocal responses. Overall, the responses of 5 animals were considered by the study authors to be inconclusive and the result for the remaining treated animals was negative.
CONCLUSION	The notified chemical may have skin sensitising ability but the test conditions employed are inadequate or not sufficiently documented. Therefore, on the basis of inadequate evidence, no conclusion is made.
TEST FACILITY	Covance (1998g)

B.6. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Hsb:Brl:WH
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days

	Dose regimen: 7 days per week Post-exposure observation period:
Vehicle	Corn oil
Remarks - Method	No significant protocol deviations. The test substance is known to degrade in a number of liquid vehicles and the study was not designed to specifically determine any degradation products from the test substance. The dose levels were selected based on the results of the acute oral toxicity study (Covance, 1998c).

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0/10
low dose	5 per sex	150	0/10
mid dose	5 per sex	500	0/10
high dose	5 per sex	1,000	0/10

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

Decreased body weight gain was noted in animals of the high dose group. There were no effects on body weight gain in the low- and mid-dose groups. No effects on food consumption and no changes in functional observational battery were noted.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Decreases in haemoglobin concentration and packed cell volume were noted in the mid- and high-dose groups. A decrease in red blood cell count was noted in female animals of the mid dose group and in both sexes of the high dose group. No changes in the myelograms were noted.

A decrease in absolute neutrophil counts was noted in male animals of the mid- and high-dose groups. A decrease in monocytes was noted in the mid- and high-dose groups. A slight decrease in total white blood cell count was also noted in female animals of the high dose group.

An increase in alkaline phosphatase and dose-related increase in aspartate aminotransferase were noted in male animals of the mid- and high-dose groups. An increase in aspartate aminotransferase was also noted in female animals of the high dose group. A decrease in cholesterol levels was noted in male animals of the mid dose group and in female animals of the high dose group. These changes were considered by the study authors to correlate with adaptive changes in the liver, i.e. enzyme induction and lipid metabolism.

Effects in Organs

An increase in the weights of liver and kidneys were noted in the mid- and high-dose groups.

At necropsy, yellow appearance, thickening and raised or irregular surface were noted in the stomach of 2 animals of the low dose group, 5 animals of the mid dose group and 6 animals of the high dose group. Pallor of liver was noted in 2 animals of the mid dose group and 3 animals of the high dose group. Large liver was noted in 1 animal of the mid dose group and 1 animal of the high dose group.

Microscopically, dose-related changes were noted in stomach, liver, kidney, thyroid and spinal nerve roots.

Periportal vacuolation was noted in all male animals of the high dose group and to a lesser extent in male animals of the low-and mid-dose groups. Hepatic centrilobular hypertrophy was noted in the mid- and high-dose groups (notably female animals). These finding were considered by the study authors to correlate with the increase in liver weight in the mid- and high-dose groups and with the pallor noted macroscopically. The study authors stated that hepatic centrilobular hypertrophy was commonly associated with metabolising enzyme induction in response to increased metabolism of a xenobiotic and these liver changes could be considered as adaptive changes rather than a toxicological effect.

Cortical tubular vacuolation of the proximal convoluted tubules of the pars recta was noted in some male

animals of the low dose group and in all male animals of the mid- and high-dose groups. Hyaline droplets were noted in all control male animals and in some male animals of the low dose group but not in male animals of the mid- and high-dose groups. Vacuolation was noted in most treated female animals, with cortical tubular basophilia of this region occurring in all female animals of the mid- and high-dose groups. Single cell necrosis was occasionally noted in the basophilic tubules of kidneys.

Thyroid follicular hypertrophy was noted to a minor extent in all animals of the high dose group and in 2 male animals of the mid dose group. The study authors stated that follicular cell hypertrophy was commonly associated with liver cell hypertrophy and was generally considered to be an adaptive change due to increased thyroid hormone metabolism.

Spinal nerve root vacuolation was noted in all animals of the high dose group and in 2 male animals of the mid dose group and characterised by vacuoles in the spinal nerve roots. No changes were noted in the sciatic nerve. This finding was considered by the study authors to arise from separation of splitting of the myelin sheath and its significance was uncertain. The number of incidence of occasional behavioural observations such as tiptoe gait did not correlate with the number of animals with spinal cord vacuolation.

Remarks – Results

It was stated by the study authors that most of the findings were of an adaptive nature rather than toxicological nature. The decrease in body weight gain, spinal cord vacuolation and forestomach gastritis in the mid dose and high dose groups were findings of toxicological significance. However, due to the test substance being known to degrade in a number of liquid vehicles, the actual dose couldn't be determined. The study authors considered 150 mg/kg/day as the No Observed Adverse Effect Level (NOAEL).

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was considered as 150 mg/kg/day, based on decrease in body weight gain, spinal cord vacuolation and forestomach gastritis were noted at 500 mg/kg/day and 1000 mg/kg/day. However, there is uncertainty with this conclusion due to the known reactivity of the notified chemical in a number of liquid vehicles.

TEST FACILITY Covance (1999a)

B.7. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure (Test 1 in the absence or presence of metabolic activation and Test 2 in presence of metabolic activation for TA102)/Pre incubation procedure (Test 2 in presence of metabolic activation)
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100, TA102
Metabolic Activation System	S9 mix from Aroclor 1254 induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 312.5–5,000 µg/plate b) Without metabolic activation: 312.5–5,000 µg/plate
Vehicle	Dimethyl sulphoxide
Remarks - Method	A dose range-finding study was carried out at 8–5,000 µg/mL in TA100. The dose selection for the main tests (the dose-range study was reported as Test 1 for TA100) was based on toxicity observed in the range-finding study. Positive controls: With metabolic activation: 2-aminoanthracene Without metabolic activation: 2-nitrofluorene (TA98); sodium azide (TA1535, TA100); 9-aminoacridine (TA1937); glutaraldehyde (TA102)

RESULTS

Metabolic	*Test Substance Concentration (µg/plate) Resulting in:*

Activation	*Cytotoxicity in Preliminary Test*	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 5,000	> 5,000	> 5,000	negative
Test 2		> 5,000	> 5,000	negative
Present				
Test 1	> 5,000	> 5,000	> 5,000	negative
Test 2		> 1,250*	> 5,000	negative

* Slight thinning of background lawn was noted when pre-incubation procedure was used.

Remarks - Results

No dose-dependent significant increases in the frequency of revertant colonies were observed for any of the bacterial strains, with any dose of the test substance, either with or without metabolic activation.

The positive and negative controls gave a satisfactory response confirming the validity of the test system.

CONCLUSION

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

TEST FACILITY

Covance (1998h)

B.8. Genotoxicity – in vitro

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 In vitro Mammalian Chromosome Aberration Test.

Species/Strain: Human

Cell Type/Cell Line: Peripheral lymphocytes

Metabolic Activation System: S9 mix from Aroclor 1254 induced rat liver

Vehicle: Dimethyl sulphoxide

Remarks - Method: A single test was carried out at 24.22 – 2500 µg/mL.

Vehicle and positive controls (4-nitroquinoline-1-oxide and cyclophosphamide) were run concurrently with the notified chemical.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	24.22, 34.6, 49.43, 70.62, 100.9, 144.1, 205.9, 294.1, 420.2, 600.3*, 1225*, 2500*	3	20
Present			
Test 1	24.22, 34.6, 49.43, 70.62, 100.9, 144.1, 205.9, 294.1, 420.2, 600.3*, 1225*, 2500*	3	20

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:* *Cytotoxicity in Test*	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 2,500	> 420.2	positive
Present			
Test 1	> 2,500	> 420.2	positive

Remarks - Results

In the absence or presence of metabolic activation, a significant increase of aberrant metaphase cells was noted at the concentration of 2,500 µg/mL.

The results of the positive controls confirmed the validity of the test

system.

CONCLUSION The notified chemical was clastogenic to human peripheral lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY Covance (1998i)

B.9. Genotoxicity – in vivo

TEST SUBSTANCE Notified chemical

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain Mouse/out-bred CD-1
Route of Administration Oral – gavage
Vehicle Corn oil
Remarks - Method A dose range-finding study was carried out at 500–2,000 mg/kg. The dose selection for the main test was based on toxicity/body weight observed in the range-finding study.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	8M	0	24*
II (low dose)	8M	500	24*
III (mid dose)	8M	1,000	24*
IV (high dose)	8M	2,000	24*
V (positive control, CPA)	8M	40	24

CPA = cyclophosphamide
* Animals were sampled 24 hours after the final two administrations (24 hours apart).

RESULTS
Doses Producing Toxicity All animals survived until the scheduled sacrifice. No clinical signs of toxicity or significant weight loss were noted in treated animals.

The ratios between the polychromatic and normochromatic erythrocytes in all treated animals (all dosage levels) were comparable to that of the control data.
Genotoxic Effects The number of micronucleated polychromatic erythrocytes was similar to the negative control group and were not significantly different by χ^2 analysis, except in the mid dose group where a small but significant increase was noted ($p \leq 0.05$). In addition, the statistical test for linear trend indicated a small but significant dose-response relationship ($p \leq 0.05$). These effects were not considered by the study authors to be of biological relevance given the frequency of micronucleated polychromatic erythrocytes in all dose groups fell within the historical negative control range.
Remarks - Results The concurrent negative/positive controls gave satisfactory responses confirming the validity of the test system.

Although there was no analysis showing the test substance reached the bone marrow, the study authors stated that the exposure to the test substance over the 24 to 48 hours through the two administrations procedure (24 hours apart and animals sampled 24 hours after the final administration) had been shown to be of sufficient duration for the expression of any genotoxic potential.

CONCLUSION The notified chemical was not clastogenic under the conditions of this in vivo micronucleus test.

TEST FACILITY Covance (1999b)

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: CO2 Evolution Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical CO_2 yield (titration measurements)
Remarks - Method	The product containing the notified chemical was weighted onto PTFE discs and added directly to the test vessels to give 25 mg/L of the test substance.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	29*	6	53*
15	42	15	69
23	44	23	79
28	47	28	85

*Mean value

Remarks - Results	The reference compound, sodium benzoate, reached the pass levels of biodegradation indicating the suitability of the inoculum. The toxicity control showed 136% as final CO_2 yield indicating that the notified chemical did not inhibit the microbial degradation of the reference substance. The degree of degradation of the test substance after 28 days was 47% and did not reach the pass level of 60%.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Covance (1998j)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test.
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Theoretical oxygen demand, dissolved oxygen meter.
Remarks - Method	The test substance was prepared at a concentration of 2.0 mg/L.

RESULTS

Test substance		*Sodium Benzoate*	
Day	*% Degradation (mean)*	*Day*	*% Degradation (mean)*
7	7	7	34
14	16	14	61
21	15	21	63
28	26	28	64

Remarks - Results	All validation criteria were satisfied. The reference compound, sodium benzoate, reached the pass levels of biodegradation indicating the

suitability of the inoculum. The toxicity control exceeded 25% biodegradation (required by guideline) 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 26%.

CONCLUSION The notified chemical is not readily biodegradable.

TEST FACILITY SafePharm (2007)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD OECD TG 203 Fish, Acute Toxicity Test –Semi-static.

Species	*Oncorhynchus mykiss*
Exposure Period	96 h
Auxiliary Solvent	None
Water Hardness	46.85 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography
Remarks – Method	A 100 mg/L stock solution was prepared by adding the test substance to test media and stirring it for approximately 2 hours.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
6.3	ND*	7	0	0	0	0	0
12.5	ND	7	0	0	0	0	0
25	ND	7	0	0	0	0	0
50	ND	7	0	0	0	0	0
100	ND	7	0	0	0	5	6

*ND=not detected

LC50	85.7 mg/L at 96 hours.
Remarks – Results	The notified chemical was not hydrolytically stable and was not detected in test media at different time. However, major degradation products were observed in test media. The 96 h LC50 was calculated based on nominal concentrations.

CONCLUSION The notified chemical is harmful to fish.

TEST FACILITY Covance (1999c)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – Static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	166 mg $CaCO_3$/L
Analytical Monitoring	Gas Chromatography
Remarks - Method	A 100 mg/L stock solution was prepared by adding the test substance to test media and stirring it for approximately 2 hours.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	ND*	20	0	0
100	ND	20	0	0

*ND=not detected

EC50	> 100 mg/L at 48 hours
NOEC	100 mg/L
Remarks - Results	The notified chemical was not hydrolytically stable and was not detected in test media at different time. However, major degradation products were observed in test media. The 48 h EC50 was calculated based on nominal concentrations.

CONCLUSION The notified chemical is not harmful to aquatic invertebrates.

TEST FACILITY Covance (1999d)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Selenastrum capricornutum*
Exposure Period	72 hours
Concentration Range	Nominal: 3.2, 6.3, 12.5, 25, 50, 100 mg/L Actual: not detected
Auxiliary Solvent	None
Water Hardness	Not reported
Analytical Monitoring	Gas Chromatography
Remarks - Method	A 100 mg/L stock solution was prepared by adding the test substance to test media and stirring it for approximately 2 hours.

RESULTS

Biomass		*Growth*	
EC50	*NOEC*	*EC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L at 72 h*	*mg/L*
21.6*	3.2*	93.1* >100§	6.3*

*Definitive test
§Confirmatory test

Remarks - Results	The notified chemical was not hydrolytically stable and was not detected in test media at different time. However, major degradation products were observed in test media. During the definitive test anomalous high background counts were obtained and three experimental points were excluded. The confirmatory test was conducted using manual counting and the result was based on the average specific growth rate.

CONCLUSION The notified chemical is harmful to algae.

TEST FACILITY Covance (1999e)

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: 1, 10, 100, 1000 mg/L Actual: not determined

Remarks – Method	Electrochemical dissolved oxygen measurements were made with a DO meter. The notified chemical was added to the vessels and untrasonicated prior to inoculation. 3,5-Dichlorophenol was used as the reference control.
RESULTS	
IC50	> 1,000 mg/L
Remarks – Results	All validity criteria were met.
CONCLUSION	The notified chemical is not inhibitory to microbial respiration.
TEST FACILITY	Covance (1998k)

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