Existing Chemical Secondary Notification Assessment Report STD/1300S

Australian Government

Department of Health

National Industrial Chemicals Notification and Assessment Scheme

Carbamic acid, N-(butylthio)thioxomethyl]-, butyl ester (Chemical in Reagent S-10104 Promoter)

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), to aid in the protection of the Australian people and the environment by assessing the risks of industrial chemicals, providing information and making recommendations to promote their safe use. NICNAS assessments are carried out by staff employed by the Australian Government Department of Health in conjunction with the Australian Government Department of the Environment.

For the purposes of subsection 78(1) of the Act, this Public Report may be inspected at our NICNAS office by appointment only at Level 7, 260 Elizabeth Street, Surry Hills NSW 2010.

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

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Background

Carbamic acid, N-[(butylthio)thioxomethyl]-, butyl ester (Chemical in Reagent S-10104 Promoter), Chemical Abstracts Service (CAS) Number 1001320-38-2, was assessed by NICNAS under a standard notification category in 2008 and is now listed on the Australian Inventory of Chemical Substances (AICS). In 2014, additional data on Chemical in Reagent S-10104 Promoter (the notified chemical) were provided that warranted secondary notification. This secondary notification assessment focuses on the new data provided.

Exempt Information (Section 75 of the Act)

Data items and details claimed exempt from publication: Analytical and spectral data, Identity of impurities which are not declared in the Safety Data Sheet and Details of manufacturing methods.

Importation and uses

The notified chemical is used as a froth-generating reagent in the mineral processing industry. No new uses of the notified chemical were identified during the secondary notification assessment, and the import volume remains unchanged (200 tonnes per annum) from the new chemical assessment.

Health effects

Toxicological studies on the notified chemical for eye irritation, skin irritation and skin sensitisation were submitted for the secondary notification assessment, whereas analogue data were used in the new chemical assessment to evaluate these endpoints. Based on these new studies, the notified chemical is not a skin irritant in rabbits or an eye irritant in bovine cornea. However, a murine local lymph node assay (LLNA) indicates that the notified chemical is a skin sensitiser.

Toxicological studies on the notified chemical for acute oral toxicity and genotoxicity were also submitted for the secondary notification assessment. These studies confirm that the notified chemical is of low acute oral toxicity in rats and is not genotoxic, and support the findings of the new chemical assessment.

Based on data submitted at the time of the new chemical assessment, the notified chemical is readily absorbed via the oral route, and dermal absorption cannot be ruled out. In addition, analogue data indicate that the notified chemical possesses low acute dermal toxicity, but has the potential to cause serious damage to the liver, the haemopoietic system and the kidney by prolonged exposure.

Occupational exposure and health, and physiochemical, risks

No changes in operational procedures for handling and formulating Reagent S-10104 Promoter were notified for this secondary notification assessment, and thus the occupational exposure scenario from the new chemical assessment is still applicable. Imported Reagent S-10104 Promoter (at a concentration of 50–70% notified chemical), may be blended locally into reformulated products (containing 1-30% notified chemical) prior to distribution to end-users in the mining industry. Occupational exposure during transport and warehousing is limited to accidental release. There is potential for dermal, and possibly ocular, exposure to the notified chemical (up to 70% concentration) during reformulation at the blending sites, and to a lesser extent during application in the mining industry at the end-user site.

Following the assessment of the new data provided for the secondary notification, the notified chemical is assessed to be a skin sensitiser. It may pose a risk for workers involved in reformulation and end-use. However, the control measures already in place to minimise the risk of causing serious damage to health by prolonged exposure (i.e. the use of automated processes and personal protective equipment (PPE)), are also applicable to manage the newly-identified sensitisation hazard.

Based on a new flash point study submitted for the secondary notification assessment, the notified chemical is considered a flammable liquid and decomposition may generate toxic and flammable gases. Therefore, there is a risk of fire during reformulation, transport, storage and end-use. Provided the notified chemical is stored and transported according to the *Australian Dangerous Goods Code* (NTC, 2014), and that the notified chemical is only used under controlled conditions by trained workers, this risk is not considered to be unacceptable.

Public exposure and health risks

No changes in public exposure were notified and thus no public exposure is still expected. When used in the proposed manner, the notified chemical is not considered to pose an unacceptable risk to public health.

Environmental effects

Ecotoxicity studies on the notified chemical for algal and daphnia toxicity were submitted for the secondary notification assessment, where previously analogue data were used to evaluate daphnia toxicity. The new data indicate that the notified chemical is very toxic to daphnia, and still very toxic to algae (median effective concentration (E_rC50) < 1 mg/L), but overall the new ecotoxicity data do not significantly differ from those used in the new chemical environmental effects assessment. Therefore, the predicted no-effect concentration (PNEC) for the aquatic compartment calculated by the new chemical assessment (1.5 mg/L) is still applicable.

Environmental exposure and risks

The environmental exposure scenario from the new chemical assessment is still applicable. At the blending site, an estimated maximum of 0.5% of the notified chemical will continue to be lost from spillage. Spills are contained such that no notified chemical enters the sewer system. During use in the mining industry, waste containing the notified chemical goes through a recycling process before being stored in a settling dam. Release from the settling dam walls is possible and, in such an event, significant quantities of notified chemical may be released to the environment. However, notified chemical that leaches into groundwater is still expected to eventually degrade via biotic and abiotic means to form simple organic compounds.

The worst case predicted environmental concentrations (PECs) calculated by the new chemical assessment (0.4 µg/L in river and 0.04 µL in ocean) are still applicable. These PECs are several orders of magnitude lower than the most sensitive observed effect to *Daphnia magna* and the calculated Risk Quotient (Q = PEC/PNEC) is still less than 1. Therefore, the risk to the aquatic environment through reformulation and end-use is still expected to be low.

Recommendations

This section provides the recommendations arising from the secondary notification assessment of the notified chemical, and incorporates the applicable recommendations from the new chemical assessment report (NICNAS, 2008). The hazard classifications presented below are according to the GHS (United Nations, 2009), whereas those presented in the new chemical assessment report (NICNAS, 2008) were presented according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). New recommendations arising from this assessment are denoted by **ND**.

Recommendations are directed principally at regulatory bodies and importers and reformulators of the notified chemical. Implicit in these recommendations is that best practice is implemented to minimise occupational exposure.

Recommendations to national bodies

The notified chemical is currently not listed in Safe Work Australia's HSIS. Based on the toxic effects of the notified chemical, it is recommended that the chemical be listed in the HSIS.

According to the GHS (United Nations, 2009), the notified chemical is classified as:

- Skin sensitiser (Category 1A): H317 - May cause an allergic skin reaction (**ND**)
- Specific Target Organ Toxicant - Repeated Exposure (Category 1): H372 - Causes damage to organs through prolonged or repeated exposure
- Flammable liquid (Category 3): H226 - Flammable liquid and vapour (**ND**)

The neat notified chemical is not introduced into Australia. The introduced substance, Reagent S-10104 Promoter, comprises roughly 50–70% of the notified chemical. The concentration cut-offs for products/mixtures containing Reagent S-10104 Promoter are shown in the table below. These cut-offs take into account that Thioimidodicarbonic acid ((HO)C(O)NHC(S)(OH)), C,C'-dibutyl ester (present at 10–30% in the imported product) is classified as a Category 2 Mutagen (H341: Suspected of causing genetic defects) and a Category 4 Acute Oral Toxicant (H302: Harmful if swallowed).

Concentration cut-offs for products/mixtures containing Reagent S-10104 Promoter

Risk Phrases	Concentration cut-off
H372/H317/H341/H302	Conc ≥ 25%
H372/H317/H341/H303	10% ≤ conc < 25%
H373/H317/H341	1% ≤ conc < 10%
H317	0.1% ≤ conc < 1%

The following precautionary statements are also recommended:

- P210: Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking (**ND**)
- P242: Use only non-sparking tools (**ND**)
- P261: Avoid breathing dust/fume/gas/mist/vapours/spray (**ND**)
- P273: Avoid release to the environment
- P280: Wear protective gloves/protective clothing/eye protection/face protection
- P303+P361+P353: IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower (**ND**)
- P308+P313: If exposed or concerned, get medical advice/attention (**ND**)
- P363: Wash contaminated clothing before reuse (**ND**)
- P391: Collect spillage

- AUH031: Contact with acids liberates toxic gas (**ND**)

This classification should be reflected in Safe Work Australia's HSIS and should be adopted by industry on publication of this report.

Recommendations to importers and state and territory governments

Hazard communication

Labels

It is recommended that importers of the notified chemical update their labels to reflect the new hazards identified by this assessment. In addition, it is recommended that importers review their labels for compliance with the *Labelling of workplace hazardous chemicals - Code of practice* (Safe Work Australia, 2011a).

Safety Data Sheets

Under the *Model Work Health and Safety Regulations* (Safe Work Australia, 2014) and the Commonwealth, state and territory regulations introduced in accordance with these model regulations, employees shall have ready access to SDSs for hazardous substances at their workplace. SDSs, previously called material safety data sheets, provide information to those who use the hazardous substance.

It is recommended that importers of the notified chemical update their SDSs to reflect the new hazards identified by this assessment. In addition, it is recommended that importers review their SDSs for compliance with the *Preparation of safety data sheets for hazardous chemicals - Code of practice* (Safe Work Australia, 2011b). A copy of the SDS should be easily accessible to employees.

Control measures

Occupational controls

Employers should ensure that the facility is equipped such that operations involving the notified chemical are performed in a highly controlled manner. The following isolation and engineering controls should be in place to minimise occupational exposure to the notified chemical:

- Automated processes
- Local exhaust ventilation
- Sealed equipment
- Explosive-proof electrical, ventilating, light and other equipment (**ND**)
- Non-sparking tools (**ND**)

Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:

- If swallowed, seek medical advice immediately
- Avoid skin contact
- Workers must have adequate education & training before handling notified chemical
- Take precautionary measures against static charge (**ND**)

Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical when worker handling is required for limited activities such as pipe disconnection and cleaning:

- Safety glasses
- Gloves

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

If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the GHS (United Nations, 2009) 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

The applicant's SDS recommends the notified chemical should be disposed of by thermal treatment or incineration at approved facilities (**ND**). If such facilities are not available, the notified chemical should be disposed of to landfill.

Storage

Containers should be securely closed and stored according to container label instructions.

Emergency procedures

Spills or accidental release of the notified chemical should be handled by adsorbing with inert adsorbent material. Sweep up and place in suitable container for disposal. Flush spill area with water and collect flush water with adsorbent material; do not allow entry into drains or waterways.

Health surveillance

The notified chemical is a health hazard; it causes damage to the liver, kidneys and haematopoietic system through prolonged or repeated exposure. This damage was observed at the lowest dose (15 mg/kg bw/day) in a repeat dose rat study, and the exposure assessment calculates a systemic dermal exposure to workers of 0.42 mg/kg bw/day from incidental contact to the chemical without the use of PPE.

The absence of a measured no-effect level, and the relatively small (30-fold) difference in the predicted levels of exposure to humans compared to the lowest dose studied in rats, indicates the potential for significance health effects. Employers should consider carrying out health surveillance for any worker involved in the handling of the notified chemical if there is a concern that PPE practices may not provide adequate protection. Employers should review the publication *Health Monitoring For Exposure to Hazardous Chemicals - Guide for Medical Practitioners* (Safe Work Australia, 2013).

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 Act) 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.

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

- adverse incidents involving the notified chemical occur;
- regulatory action on the notified chemical is undertaken by other jurisdictions;
- details of the operation description are altered such that exposure to workers or the environment may be increased;

or

(2) Under Section 64(2) of the Act; if

- the function or use of the chemical has changed from a froth-generating reagent in the mineral processing industry, or is likely to change significantly;
- the amount of chemical being introduced has increased from 200 tonnes, or is likely to increase, significantly;
- if 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.

Abbreviations and acronyms

AICS	Australian Inventory of Chemical Substances
bw	body weight
CAS	Chemical Abstracts Service
conc	concentration
DPM	disintegrations per minute
EASE	Estimation and Assessment of Substance Exposure
EC	European Commission
EC50	median effective concentration
EU	European Union
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
HPLC	high pressure liquid chromatography
HSIS	Hazardous Substances Information System
HPV	high production volume
IUCLID	The International Uniform Chemical Information Database
IVIS	in vitro irritancy score
kPa	kilopascal
LD50	median lethal dose
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
mN/m	millinewton per meter
MOE	margin of exposure
MTD	maximum tolerated dose
NCE	Normochromatic erythrocytes
ND	new data
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NOAEL	no-observed adverse effect level
NOEC	no-observed effect concentration
NOEL	no-observed effect level
NOHSC	National Occupational Health and Safety Commission
NTC	National Transport Commission
OD	optical densities
OECD	Organisation for Economic Cooperation and Development
PCE	Polychromatic erythrocytes

PEC	predicted environmental concentration
PNEC	predicted no-effect concentration
PPE	personal protective equipment
ppm	parts per million
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SIDS	screening information data set
SD	standard deviation
SDS	safety data sheet
TG	test guideline
TWA	time weighted average
US EPA	United States Environmental Protection Agency

1. Introduction

1.1 Background

Carbamic acid, N-[(butylthio)thioxomethyl]-, butyl ester (Chemical in Reagent S-10104 Promoter), CAS Number 1001320-38-2, was notified by Cytec Australia Holdings Pty Limited and assessed by NICNAS as a new chemical under Section 32 of the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) under the standard notification category. The new chemical assessment report STD/1300 (NICNAS, 2008) was published in July 2008, and the notified chemical was listed on the AICS in July 2013.

In 2014, NICNAS was notified by Cytec Australia Holdings Pty Limited that new studies are now available using Chemical in Reagent S-10104 Promoter (the notified chemical) for some (eco)toxicity endpoints that were evaluated using analogue data at the time of the new chemical assessment. The new hazard data indicated that a secondary notification assessment was warranted to review the hazard profile of the notified chemical and the related effect on the risks to human health.

This secondary notification assessment focuses on the new health hazard and physico-chemical hazard data, as these were considered likely to significantly impact on the original human health risk assessment. Where additional data have been provided, they have been incorporated into this report and the implications for the related health risks have been considered, as appropriate. Details of the physico-chemical data provided for the new chemical assessment are reproduced in the Appendix. Although new ecotoxicity data were provided for this assessment, the data did not significantly affect the outcomes of the original environmental risk assessment. Therefore, details of the environmental hazards and risks have been reproduced from the new chemical assessment report without significant modification. Details of the studies provided for assessment as a new chemical are reproduced in the Appendix of this report. New data submitted for this assessment are identified by the abbreviation **ND**.

Data were also provided by the applicant in relation to a change in manufacturing process, but this was regarded as not significantly impacting on the substance as introduced into Australia. The applicant also changed the composition of the material used for toxicity and physico-chemical testing to reflect the changed manufacturing process.

1.2 Declaration

A notice was published in the Chemical Gazette of November 2014, requiring a secondary notification of Chemical in Reagent S-10104 Promoter, in accordance with Section 65(2) of the Act. The declaration required the provision of any information relevant to assessment of the notified chemical that was not covered in the new chemical assessment and included the following:

1) Name(s) under which the chemical is marketed by the introducer
2) All of the introducer's uses of the chemical, specifying uses not covered in the original assessment of the chemical
3) Proposed annual import quantity of the chemical for the next 5 years
4) The concentration and purity (including details of any hazardous impurities) of the chemical in imported products
5) If reformulation will occur in Australia, the concentration of the chemical in finished products
6) Information on occupational exposure during the proposed new uses, including handling procedures and any monitoring data
7) Information on whether handling procedures for the existing uses have changed and if so the impact on occupational exposure
8) If any new uses, provide information on any likely public exposure
9) Details of any adverse health effects observed since the assessment certificate was issued
10) Australian SDS(s) and Labels for the chemical and any product containing the chemical
11) Full studies on the chemical for acute oral toxicity, skin and eye irritation, skin sensitisation and genotoxicity. Studies previously provided to NICNAS need not be included

12) Any additional data available on toxicological and/or ecotoxicological effects of the chemical

1.3 Objectives

The objectives of this assessment are to review the new data made available since the publication of the new chemical assessment report and, where appropriate, to revise the original assessment to:

- re-assess the human health hazards associated with the notified chemical;
- re-assess the risks of adverse effects resulting from exposure to workers and the general public from the use of the notified chemical; and
- based on the above, make appropriate recommendations to control exposures and/or reduce potential health risks for workers and the general public, as required.

1.4 Peer review

During all stages of preparation, this report has been subject to internal peer review by NICNAS.

1.5 Applicant

Following the secondary notification declaration of Chemical in Reagent S-10104 Promoter, one company applied for assessment of this chemical.

In accordance with the Act, NICNAS provided the applicant with a draft copy of the report for comment during the corrections/variations phase of the assessment. The applicant details are as follows:

Cytec Australia Holdings Pty Limited
Suite 1, Level 1 Norwest Quay
21 Solent Circuit
Norwest Business Park
Baulkham Hills NSW 2153

1.6 Exempt information

The applicant has claimed the following data items as exempt from publication under Section 75 of the Act: Analytical and spectral data, Identity of impurities which are not declared in the Safety Data Sheet and Details of manufacturing methods.

2. Chemical identity, physical and chemical properties

2.1 Chemical identity

Chemical name: Carbamic acid, N-[(butylthio)thioxomethyl]-, butyl ester

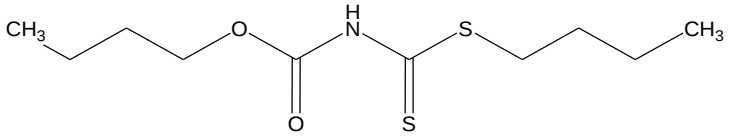
CAS number: 1001320-38-2

Marketing name: Chemical in Reagent S-10104 Promoter

Other names: S-10903 (90-100% notified chemical)
Reagent S-10104 Promoter (50-70%)
Aero® MaxGold® 900 Promoter (50-70%) (**ND**)
Aero® MaxGold® 900-QN Promoter (50-70%) (**ND**)

Molecular formula: $C_{10}H_{19}NO_2S_2$

Structural formulae:



Molecular weight: 249.39 g/mol (**ND**)

Analytical data: Analytical spectra were provided that confirm the identity and purity of the notified chemical

2.2 Composition

The notified chemical is manufactured overseas, and introduced into Australia as an inseparable component of Reagent S-10104 Promoter. At the time of the new chemical assessment, according to the SDS provided for Reagent S-10104 Promoter, the substance introduced into Australia was comprised roughly 50–70% of the notified chemical, 10–30% Thioimidodicarbonic acid ((HO)C(O)NHC(S)(OH)), C,C'-dibutyl ester (CAS Number 39142-36-4) and various impurities, including 1–3% residual catalyst.

The applicant reported a change in the overseas manufacturing process of the notified chemical, resulting from a change in the manufacturing process of Reagent S-10104 Promoter that occurred in 2008, whereby a hazardous catalyst was no longer used (**ND**). As a result, the final substance currently being introduced into Australia, Reagent S-10104 Promoter, no longer contains a hazardous residual catalyst, but does otherwise contain the same mixture of notified chemical (50–70%) and Thioimidodicarbonic acid ((HO)C(O)NHC(S)(OH)), C,C'-dibutyl ester (10–30%).

The following information relates to the purity and composition of the substance used for toxicological and physico-chemical testing (known as S-10903). This primarily comprises the notified chemical, and is prepared by the applicant to reflect the hazardous impurities used in/generated by the manufacturing process. Hence the composition of the test substance S-10117 (purity of notified chemical >95%) that formed the basis of the new chemical assessment is slightly different to the test sample S-10903 (purity of notified chemical 93.2%) used as the basis of this secondary notification assessment. A comparison of the impurity profile of the sample of notified chemical used for toxicity and physico-chemical in the new chemical assessment report (S-10117) compared to this assessment (S-10903) is presented in the table below. In both cases, however, these two test substances are not representative of the purity of the notified chemical as found in the final substance Reagent S-10104 Promoter that is introduced into

Australia (**ND**; Cytec 2014a).

Summary of the hazardous impurities in test samples of the notified chemical

Hazardous impurity	% weight	
	S-10117*	S-10903
Carbamic acid, butyl ester (CAS Number 592-35-8)	0-2%	< 1%
1-Butanethiol (CAS Number 109-79-5)	0-2%	< 1%
n-Butanol (CAS Number 71-36-3)	-	< 1%
n-Butyoxycarbonyl-O-butyl thionocarbamate (CAS Number 39142-36-4)	-	2.1%

*Other unidentified impurities to 100%.

Degree of purity: 93.2% (Cytec 2013a; **ND**)

Hazardous impurities/residual monomers:

*Chemical name***:** Thioimidodicarbonic acid ((HO)C(O)NHC(S)(OH)), C,C'-dibutyl ester (**ND**)

CAS number 39142-36-4

Weight percentage: 2.1% (Cytec 2013a)

Hazardous properties: Based on HSIS and a previous new chemicals assessment this chemical has the following classification:

Xn: R68 Possible risk of irreversible effects
T: R48/25 Toxic: Danger of serious damage to health by prolonged exposure if swallowed
Xn: R22 Harmful if swallowed

Concentration (conc) cut-off:

Conc ≥ 25%: R68, R48/25, R22
10% ≤ conc < 25%: R68, R48/25
1% ≤ conc < 10%: R68; R48/22

Under the GHS (United Nations, 2009) this chemical has the following classification (**ND**):

H341: Suspected of causing genetic defects
H372: Causes damage to organs through prolonged or repeated exposure
H302: Harmful if swallowed

Chemical name: Carbamic acid, butyl ester

CAS number 592-35-8

Weight percentage: 0.4% (Cytec, 2014b; **ND**)

Hazardous properties: Based on the The International Uniform Chemical Information Database (IUCLID) data set for this chemical and the SDS of the imported product this chemical has the following classification:

Xn: R22 Harmful if swallowed
Xi: R41 Risk of serious eye damage

Xi: R43 May cause sensitisation by skin contact

Concentration cut-off:

Conc ≥ 25%: R22, R41, R43
10% ≤ conc < 25%: R41, R43
5% ≤ conc < 10%: R36, R43
1% ≤ conc < 5%: R43

Under the GHS (United Nations, 2009) this chemical has the following classification (**ND**):

H302: Harmful if swallowed
H318: Causes serious eye damage
H317: May cause an allergic skin reaction

Chemical name: 1-Butanethiol (n-butyl mercaptan)

CAS number: 109-79-5

Weight percentage: 0.2% (Cytec, 2014b; **ND**)

Hazardous properties: Based on a screening information data set (SIDS) Dossier (Organisation for Economic Cooperation and Development (OECD) high production volume (HPV) Chemical Program) and the SDS of the imported product this chemical has the following classification:

F: R11 Highly flammable
Xn: R20/22 Harmful by inhalation and if swallowed
Xi: R36/37/38 Irritating to eyes, respiratory system and skin

Concentration cut-off:

Conc ≥ 25%: R20/22, R36/37/38
20% ≤ conc < 20%: R36/37/38

Under the GHS (United Nations, 2009) this chemical has the following classification (**ND**):

H225: Highly flammable liquid and vapour
H302/H332: Harmful if inhaled or swallowed
H315/H319: Causes serious eye and skin irritation
H335: May cause respiratory irritation

Also a possible sensitiser.

This chemical has an exposure standard in Australia: time weighted average (TWA) = 0.5 ppm / 1.8 mg/m^3

Chemical name: 1-Butanol (**ND**)

CAS number: 71-36-3

Weight percentage: 0.1% (Cytec, 2014b)

Hazardous properties: Based on HSIS this chemical has the following classification:

F: R10 Flammable
Xn: R22 Harmful if swallowed
Xi: R37/38-41 Irritating to respiratory system and skin. Risk of serious eye damage.
R67: Vapours may cause drowsiness and dizziness

Concentration cut-off:

Conc ≥ 25%: R22, R37/38, R41
20% ≤ conc < 25%: R37/38, R41
10% ≤ conc < 20%: R41
5% ≤ conc < 10%: R36

Under the GHS (United Nations, 2009) this chemical has the following classification (**ND**):

H226: Flammable liquid and vapour
H302: Harmful if swallowed
H335: May cause respiratory irritation
H315: Causes skin irritation
H318: Causes serious eye damage
H336: May cause drowsiness and dizziness

This chemical has an exposure standard in Australia: TWA = 50 ppm / 152 mg/m^3

2.3 Physical and chemical properties

The physical and chemical data on the sample S-10903 of notified chemical used for toxicity and physico-chemical testing are shown in the table below. For full details of tests submitted for the new chemical assessment report, refer to the Appendix.

Summary of the notified chemical's physical and chemical properties

Property	Value	Data Source/Justification
Appearance at 20ºC and 101.3 kPa	Yellow grease-like solid (**ND**)	
Melting point	23.2–28.6ºC (**ND**)	Measured
Boiling point	164 ± 0.5ºC at 101.3 kPa (**ND**)	Measured
Density	1098 kg/m^3 at 21.8ºC (**ND**)	Measured
Vapour pressure	4.8 x 10^{-4} kPa at 30ºC (**ND**)	Measured
Water solubility	(1.85 ± 0.8) x 10^{-3} g/L at 20.0°C (**ND**)	Measured
Hydrolysis as a function of pH	Half-lives at 25°C to be 46.3, 37.2 and 14.1 days at pH 4, 7 and 9, respectively.	Measured
Partition coefficient (n-octanol/water)	log P_{OW} = 4.69 (**ND**)	Measured
Surface tension	72.0 mN/m at 20°C (**ND**)	Measured
Adsorption/ desorption	log K_{OC} = 3.72	Measured
Dissociation constant	Not applicable	The notified chemical does not contain any dissociable

		functionality
Particle size	Not determined	The notified chemical is not granular and is thus not suitable for analysis
Flash point	28.9°C at 101.3 kPa (**ND**)	Measured
Flammability	Not highly flammable (**ND**)	Measured
Autoignition temperature	278 ± 5°C	Measured
Explosive properties	Not explosive	Estimated based on chemical structure and information on the analogue
Oxidising properties	Not oxidising (**ND**)	Measured

kPa = kilopascal; mN/m = millinewton per meter; ppm = parts per million.

Comments on physical and chemical properties

The change in composition of the sample of notified chemical used for toxicity and physico-chemical testing has resulted in a change in the appearance of the chemical - it is now a yellow grease-like solid as opposed to a yellow solid (Cytec, 2013b; **ND**). As the notified chemical is no longer granular, the particle size cannot be determined.

The melting point of the notified chemical was re-evaluated using the capillary/metal block method, as outlined in OECD test guideline (TG) 102 (Melting Point/Melting Point Range), and was slightly lower (23.2–28.6°C; Cytec, 2013b; **ND**) than data submitted at the time of the new chemical assessment (30.85 ± 0.5°C; NICNAS, 2008). The boiling point of the notified chemical was re-evaluated using the same methods as outlined in the new chemical assessment report, and was found to be slightly lower (164°C; Cytec, 2013b; **ND**) than previously reported (211.9°C; NICNAS, 2008).

New data are available for the surface tension and density of the notified chemical; however, the values are not significantly different (72.0 mN/m and 1098 kg/m^3 respectively; Cytec, 2013b; **ND**) from those submitted at the time of the new chemical assessment (61.7 mN/m and 1180 kg/m^3 respectively; NICNAS, 2008) and are therefore not discussed further.

The vapour pressure of the notified chemical was re-evaluated using an effusion method incorporating isothermal thermogravimetric analysis (Cytec, 2013b; **ND**). Evaporation rates were measured at several temperatures and linear regression analysis used to determine the vapour pressure at 30°C, as the notified chemical transitions from a solid to a liquid at 25°C. The vapour pressure was determined to be higher (4.8 x 10^{-4} kPa) than previously reported (9.8 x 10^{-6} kPa) at 25°C, but confirms that the notified chemical still possesses low volatility.

New data are available for the water solubility and partition coefficient of the notified chemical; however, the values are not significantly different (1.80 x 10^{-3} g/L and 4.69 respectively; Cytec, 2013b; **ND**) from those submitted at the time of the new chemical assessment (2.58 ×10^{-3} g/L and 4.09 respectively; NICNAS, 2008). As these studies indicate that the notified chemical is still not readily water soluble or hydrophilic, these studies are not discussed further.

A flammability (solids) study (Cytec, 2013c; **ND**) was submitted for the secondary notification assessment, conducted according to test method A.10 Flammability (solids) as outlined in Annex V of the European Commission (EC) Directive 67/548/EEC. The notified chemical was not highly flammable by ignition.

A new flash point study submitted for the secondary notification assessment, which used the Pensky-

Martens closed cup method, indicates a flash point significantly lower (28.9°C; Cytec, 2013d; **ND**) than previously reported (134 ± 2°C; NICNAS, 2008). Given the decomposition products of the notified chemical (e.g. hydrogen sulfide, carbon disulfide) are also flammable gases (Cytec, 2014a; Cytec, 2014c; **ND**), the notified chemical should be considered flammable.

Data to assess the oxidising properties of the notified chemical were not available at the time of the new chemical assessment. In a corrosion-to-metals study (WIL Research Europe, 2013a; **ND**) submitted for the secondary notification assessment, aluminium and steel samples were immersed in solutions of the notified chemical (at concentrations of 1.92 mg/L) for 7 days at 55°C. Localised corrosion was not observed and weight loss was not sufficient (less than 14%) for classification as corrosive to aluminium and steel.

3. Importation and use

No new uses of the notified chemical were notified for the secondary notification assessment. The following information regarding importation and use has been reproduced from the new chemical assessment report (NICNAS, 2008) without significant modification.

Importation

The notified chemical is not manufactured in Australia. It is imported by ship as a component of Reagent S-10104 Promoter (50–70% concentration) at 200 tonnes per year.

Reagent S-10104 Promoter (50–70% notified chemical) is imported in 20,000 L isotainers, one tonne totes or 20 L pails. The applicant has indicated the port of entry is Sydney. If reformulation is to occur, Reagent S-10104 Promoter is transported from the dock to the formulator's warehouse for storage. Imported products, or the reformulated products (containing 1–30% notified chemical), are transported to the end-use sites by road in 20,000 L isotainers.

Use

The notified chemical is used as a froth flotation agent in the recovery of sulphide minerals. It is used at mine sites around Australia for the separation of gold in the mineral processing industry.

4. Exposure

No new uses of the notified chemical, and no changes in operational procedures for handling and formulating Reagent S-10104 Promoter, were notified for the secondary notification assessment. Therefore, the public and occupational exposure sections have been reproduced from the new chemical assessment report (NICNAS, 2008) without significant modification.

A new environmental fate study based on the test substance S-10903 (WIL Research Europe, 2014b; **ND**) was submitted for the secondary notification assessment, and the new data confirm that the notified chemical is still not readily biodegradable. Therefore, no significant impact on environmental exposure is expected, and the environmental exposure assessment has therefore been reproduced from the new chemical assessment report (NICNAS, 2008) without significant modification.

4.1 Public exposure

As the notified chemical is only used for the process of flotation extraction in the mining industry, public exposure is unlikely.

4.2 Occupational exposure

4.2.1 Operational description

Reformulation of Reagent S-10104 Promoter

Reagent S-10104 Promoter, containing 50–70% of the notified chemical, may be blended locally with other non-reactive mineral collectors, prior to distribution to end-users. If reformulation occurs, imported Reagent S-10104 Promoter is received at the local blending site in 20,000 L isotainers, 1 tonne totes or 20 L pails. All material is stored in a bunded, dedicated Dangerous Goods Area. When required, Reagent S-10104 Promoter is transferred on a pallet by forklift from the warehouse area to the blending area. Reagent S-10104 Promoter is pumped using an automated pumping system into a 20,000 L isotainer. The blending vessels are sealed at all times during the blending of a batch, except during the charging of the vessels. During the blending process, quality control samples may be taken from the 20,000 L isotainer via a valve. Once the blending process is completed, the 20,000 L isotainer containing the reformulated product are closed off and transported by road to the customer site for use. Blending takes approximately two hours, and does not require the use of heat. Reformulated products will contain 1–30% notified chemical.

End-user

At the end-user site, metered quantities of the reformulated or imported products (containing the notified chemical at up to 70% concentration) are pumped or gravity fed from the 20,000 L isotainer through fixed lines to a flotation cell. The floatation reagent is in a closed-loop water recirculation circuit, and thoroughly mixed with the slurry to chelate the ore. The typical usage of the notified chemical in the closed-loop water recirculation circuit is in the range of 5–75 ppm. The residence time in this tank is sufficient to allow the reagent(s) to react with (adsorb to) the surface of the desirable sulphide minerals.

Approximately 70% of the notified chemical adheres to the beneficiated mineral surface with the remainder adhering to the gangue (waste) material or remaining in the solution. After conditioning, the slurry is usually diluted to around 30% solids with more water, and pumped to the flotation machines where the sulphide minerals attach themselves to air bubbles (generated by an impellor or gas sparging at the bottom of the flotation chamber), and float to the surface of the pulp. Here they are skimmed off, collected and filtered. The concentrated floated sulphides are finally drawn off and transported to a smelter for metal recovery, where the notified chemical is destroyed within the smelting process.

The gangue material that has not been made sufficiently hydrophobic to attach to the bubbles remains in the slurry, and is pumped out of the flotation cells to the tailings thickener. Here this waste is

allowed to settle (usually with the aid of flocculants) into a high solid pulp, and pumped to the tailings storage dam for final disposal. The excess water overflows from the thickener, and is returned to the flotation process. The tailings slurry is then pumped to tailings storage dams where the solids settle to the bottom and the excess water forms a shallow layer overlying these solids. This water usually becomes highly polluted with acid and dissolved heavy metals and is allowed to evaporate in shallow, large surface area ponds called evaporation dams. The deposit in the evaporation dams may be eventually smelted for recovery of metal and the high temperature of the furnaces would decompose the notified chemical into water, oxides of carbon, sulphur and nitrogen. Some of the remaining reagent becomes attached to the surface of the gangue minerals, which are deposited into the tailings dams. However, the compound has a low affinity for the surface of these particles, and only a fraction of the reagent is released in this manner.

Routine cleaning and minor maintenance of the plant is carried out regularly, and shut-downs occur for major maintenance.

The reagent storage/mixing and flotation processes are automated, continuous and recycling, thus minimising worker exposure. The reagent storage and flotation areas are open and well ventilated. Typically, within the reagent storage area, where other hazardous chemicals are also handled, the plant operators wear respirators, impervious gloves, coveralls and eye protection.

4.2.2 Estimates of occupational exposure

The table below summarises the number and category of workers.

Summary of worker exposure estimates

Category of worker	Number	Exposure duration	Exposure frequency
Storage and transport:			
Waterside and Transport	3-6	2-3 hours/day	10-15 days/year
Warehouse	2-3	2-3 hours/day	10-15 days/year
At blending site:			
Blending	2	8 hours/day	25 days/year
Quality control	1	0.75 hours/day	25 days/year
End-users:			
Plant operators	6-12	1-8 hours/day	300 days/year

Storage and transportation

It is anticipated that waterside workers, transport drivers and warehouse workers would only be exposed to the material in the event of an accident.

Reformulation of Reagent S-10104 Promoter

Dermal exposure to the notified chemical (up to 70% concentration) may occur as a result of drips and spills during the sampling process or during the connection/disconnection of pumps. Inhalation exposure is not considered to be significant due to the low vapour pressure of the notified chemical. Blending areas are equipped with general and local exhaust ventilation. Blending workers wear chemical resistant overalls, chemically resistant gloves, safety glasses/face shield, and safety shoes. The laboratory worker undertaking the quality control activities wears a lab coat, chemically resistant gloves and safety glasses.

End-use: Mining industry

The transfer, mixing and flotation processes are automated, continuous and recycling, with little need for worker intervention. However there is potential for dermal and possibly ocular exposure to the notified chemical (up to 70% concentration) while connecting and disconnecting lines and cleaning pumping and ancillary apparatus. Inhalation exposure is not considered to be significant due to the low vapour pressure of the notified chemical. The reagent storage and flotation areas are open and well ventilated. The plant operators in the reagent storage area wear respirators, impervious gloves, coveralls and eye protection due to the presence of other hazardous chemicals. The personnel in other areas wear impervious gloves, coveralls and chemical splash goggles.

The quantitative exposure estimate is similar for both reformulation and mining industry personnel (if it is assumed that in the worst case a 70% solution of the notified chemical will be handled at both sites) since the worker processes are similar. Estimation and Assessment of Substance Exposure (EASE) modelling of these processes (connecting/disconnecting hoses and cleaning operations) was performed during the new chemical assessment to estimate the dermal exposure of the workers to the notified chemical. The following assumptions were made: direct handling, non-dispersive use (only used by workers with knowledge of the processes and use of controls), incidental contact level (assumed to be one event per day), and 70% concentration. The predicted dermal exposure was 0–0.085 mg/cm^2/day. Assuming exposure to a surface area equivalent to one hand (420 cm^2), a body weight of 70 kg, and 100% dermal absorption, this is equivalent to a systemic exposure of 0–0.42 mg/kg body weight (bw)/day. This estimate does not take into account the use of PPE.

4.3 Environmental exposure

4.3.1 Releases

Release of chemical at site

The notified chemical is imported as a component (up to 70%) of the manufactured substance Reagent S-10104 Promoter in 20,000 L isotainers, one tonne totes or 20 L pails. The imported product containing the notified chemical may be further blended.

The blending vessels are sealed at all times during the blending of a batch, except during the charging of the vessels. The transfer of the concentrated product containing the notified chemical between vessels occurs via pumps or by gravity. During the blending process, water used to flush the pumps is reused as part of the finished batch. The 20,000 L isotainers containing the finished product are returned to the blender for reuse. It is estimated that a maximum of 0.5% of the notified chemical is lost during spillage as a result of connecting and disconnecting pumps. Spill kits are in place in the storage and production areas. Spills are contained in bunded areas or collected with inert absorbent material and disposed of through a licensed waste disposal contractor. No notified chemical enters the sewer system.

Release of chemical from use

Release to the environment of the notified chemical is minimal. The areas where the chemical will be handled, pumped and stored are bunded and any spilt material is collected and disposed of appropriately in accordance with local, state and federal regulations.

Approximately 30% of the reagent that is discarded to tailing ponds, following use, typically comprises of one-third adsorbed to the tailings (gangue), and the remaining two-thirds dissolved in the water which is reused in the flotation process. At steady state approximately 20% of the dosed amount remains in the tailings dam - this equates to 1–15 ppm (20% × 5–75 ppm).

Settling dam walls are constructed using tailings and are designed to permit water to leach. Therefore, some water will inevitably enter the groundwater. Based on the apparent relatively low water solubility of the notified chemical, only a small proportion of the total annual import volume will be mobile and could enter groundwater. However, given the very large quantities used, this release could be

significant. Settling dam walls occasionally breach during periods of intense precipitation, releasing the contents of the dam. It is possible that in such an event, significant quantities of notified chemical may be released and enter terrestrial waterways. Notified chemical that leaches into groundwater will eventually degrade via biotic and abiotic means to form simple organic compounds.

Release of chemical from disposal

Imported isotainers containing the notified chemical are returned to supply for reuse.

The residual notified chemical in blending pumps stays in the flush and cleaning water that is reused as part of the diluted product. The release is estimated to be 0.5% and is collected and disposed of properly.

The majority of the notified chemical is destroyed by oxidation in the smelting process. Residual product left in the drums (~0.5%) is rinsed out with water and the rinsate is fed into the recirculating water loop and is reused.

During the floatation process, approximately 20% of the notified chemical remains in the tailings dam - significant seepage is predicted, and this is expected to move eventually into the aquatic environment via groundwater.

4.3.2 Fate

In a ready biodegradability study (WIL Research Europe, 2014b; **ND**) submitted for the secondary notification assessment, the notified chemical (i.e. the test sample S-10903) at a concentration of 12 mg Carbon/L was exposed to activated sewage sludge micro-organisms for 28 days. Degradation was assessed by the determination of carbon dioxide produced, and the notified chemical demonstrated lower levels of degradation (23–25%) compared to the study submitted at the time of the new chemical assessment (46% degradation). Therefore, the notified chemical continues to not be classifiable as readily biodegradable. Result deviations may have arisen from a number of insignificant factors (i.e. different test samples of the notified chemical, different sources of activated sludge, different testing laboratories).

4.3.3 Predicted environmental concentration (PEC)

Minimal release of the notified chemical to the environment, from reformulation or spills, occurs at mine sites during use. Most of the notified chemical becomes associated with the surface of mineral particles in metal concentrates, and is destroyed during smelting. The chemical decomposes to water vapour and oxides of carbon, nitrogen and sulphur. The most likely release is from seepage of the notified chemical in the tailing dams.

A well-designed and maintained clay liner has a permeability of 10^{-6} cm/sec or less, and is between 2–4 feet (61–132 cm) thick. Similarly, synthetic liners have a permeability of 10^{-9} to 10^{-14} cm/sec, and have a thickness of 40 to 60 mils (0.10–0.15 cm, a mil is defined as 1/1000th of an inch) (US EPA 1994).

The PEC, calculated for the new chemical assessment, assumed the maximum concentration of the notified chemical (15 ppm) was in the dam and the notified chemical degraded as it permeated through the tailings liner. Sulphidic tailings dams are acidic with minimal microbiological life; and the main route of degradation was therefore expected to be hydrolysis. The minimum time taken to permeate through the liners is the thickness (61 cm) ÷ the highest permeability rate (1×10^{-6} cm), which results in 61×10^6 seconds or 706 days. For synthetic liners, the minimum permeation time is 100×10^6 seconds or ~1157 days. At acidic pH values (pH 4), the notified chemical has a half-life of 46.3 days. Accordingly, it was concluded that the notified chemical would take approximately 15.2 half-lives (706–46.3) to permeate through the liner. A worst case PEC at release from the tailings dam was subsequently calculated to be 0.4 µg/L (15 ppm × $0.5^{15.2}$).

5. Hazard assessment

5.1 Physicochemical and human health hazard assessment

This section contains a summary of all the data relevant to the physicochemical and human health hazard assessment of the notified chemical, with a focus on new data. The robust summaries of the toxicological data available for the assessment of the notified chemical as a new chemical are reproduced from the new chemical assessment report (NICNAS, 2008), without modification, in the Appendix of this report. The robust summaries of the new human health studies on the notified chemical submitted for the secondary notification assessment are summarised in this section and designated as **ND**.

5.1.1 Physicochemical effects assessment

The flash point (134 °C; NICNAS, 2008) of the notified chemical, reported for the new chemical assessment, did not indicate a flammability hazard. A new flash point study was identified during this secondary notification assessment and, as the notified chemical is a liquid (melting point 23.2–28.6ºC) at its flash point (28.9°C; Cytec, 2013d; **ND**), the notified chemical is now considered a flammable liquid. It may decompose to carbon disulfide (CAS Number 75-15-0; F; R11 Repr. Cat. 3; R62-63 T; R48/23 Xi; R36/38) under fire conditions, and contact with acid may generate toxic and flammable hydrogen sulfide gas (CAS Number 7783-06-4; F+; R12 T+; R26 N; R50; Cytec, 2014a; Cytec, 2014c).

5.1.2 Human health effects assessment

Some endpoints (eye irritation, skin irritation and skin sensitisation) were evaluated using an appropriate analogue at the time of the new chemical assessment, and data are now available for these endpoints using the notified chemical. The notified chemical tested at the time of the new chemical assessment had a purity of 97%, and the current toxicity data on the notified chemical were acquired on a sample with a purity of 93%. The table below summarises all available toxicological information.

Summary of toxicity data for the notified chemical or analogue

Endpoint	Previous data	New data (ND)
Rat, acute oral	LD50 > 2000 mg/kg bw (Notified chemical)	LD50 > 2000 mg/kg bw (Notified chemical)
Rat, acute dermal	LD50 > 2000 mg/kg bw (Analogue)	–
Rabbit, skin irritation	Slightly irritating (Analogue)	Slightly irritating (Notified chemical)
EpiSkin reconstructed human skin tissue- in vitro skin irritation	–	Inconclusive (Notified chemical)
Rabbit, eye irritation	Slightly irritating (Analogue)	–
Bovine corneal- in vitro eye irritation/corrosion	–	Not severely irritating or corrosive (Notified chemical)

Guinea pig, skin sensitisation - Maximization test	Limited evidence of sensitisation (Analogue)	
Mouse, skin sensitisation - LLNA	–	Sensitising (Notified chemical)
Rat, oral (gavage) repeat dose toxicity - 28 days.	No NOEL/NOAEL was determined, as toxicologically significant effects were observed at all dose levels (100, 40 and 15 mg/kg/day) (Analogue)	–
Genotoxicity -bacterial reverse mutation	Non-mutagenic (Notified chemical)	Non-mutagenic (Notified chemical)
Genotoxicity - in vivo Mammalian bone marrow chromosome aberration test in the rat	Non-clastogenic (Analogue)	–
Genotoxicity - in vivo Micronucleus test in the mouse	Non-genotoxic (Notified chemical)	–

LD50 = median lethal dose; NOAEL = no-observed adverse effect level; NOEL = no-observed effect level

Toxicokinetics

The new chemical assessment report (NICNAS, 2008) concluded that the notified chemical would be absorbed across biological membranes, based on the relatively low molecular weight and favourable physical-chemical properties. Absorption of the notified chemical across the gastrointestinal tract was confirmed by the observation of toxic effects after acute oral exposure. While no evidence for acute toxic effects was reported in an acute dermal toxicity study, the possibility of dermal absorption of the notified chemical could not be ruled out.

Acute toxicity

In an acute oral toxicity study (WIL Research Europe, 2014a; **ND**) submitted for the secondary notification assessment, the notified chemical was of low oral toxicity (LD50 > 2000mg/kg bw) to Wistar rats. No mortality was observed at any of the tested concentrations, no abnormalities were noted at necropsy, and animals appeared normal two to four days after dosing. The data provided for the new chemical assessment report (NICNAS, 2008) also indicated that the notified chemical was of low toxicity via the oral route, and an acute dermal toxicity study in rats on an analogue chemical concluded that the notified chemical is of low toxicity after dermal exposure.

No data are available to assess the acute inhalation hazard of the notified chemical. However, given the low volatility of the notified chemical (vapour pressure of 4.8×10^{-4} kPa at 30°C) and the fact that it is not introduced in its solid form, it is not expected to pose a significant inhalation hazard.

Skin irritation

Data for skin irritation on the notified chemical were not available at the time of the new chemical assessment, and an appropriate analogue was used to evaluate this endpoint. Based on these data, the notified chemical was considered slightly irritating to skin.

In a skin irritation study (WIL Research Europe, 2014b; **ND**) submitted for the secondary notification assessment, undiluted notified chemical was administered to the skin of three female New Zealand

White rabbits under semi-occlusive conditions. After four hours, the dressings were removed and skin reactions assessed 1, 24, 48, 72 hours, and 7 and 14 days later. The mean scores calculated on the basis of the scores at 24, 48, and 72 hours for each animal are shown in the below table. Yellow staining of the skin was noted at the application site, but did not hamper scoring. Scaliness was observed at all treated skin sites 48 hours after exposure, and had resolved within 72 hours, 7 or 14 days. At the 24-hour observation, very slight erythema was observed in two animals, and very slight oedema in one animal. At the 48-hour observation, very slight oedema was observed in one animal, very slight erythema in two animals, and well-defined erythema in one animal. Skin irritation resolved within 72 hours or 7 days after exposure. This study indicates that undiluted notified chemical is slightly irritating to the skin in rabbits.

Lesion	*Mean score Animal No.*			*Maximum value*	*Maximum duration of any effect*	*Maximum value at end of observation period*
	1	2	3			
Erythema/Eschar	0.6	0.6	1.3	2	< 72 hours	0
Oedema	0	0	0.6	1	< 48 hours	0

An in vitro skin irritation study (WIL Research Europe, 2013c; **ND**), using a reconstituted human epidermis model (EPISKIN-SM™), was also submitted for the secondary notification assessment. Undiluted notified chemical was applied to the tissues in triplicate and, following 15-minute exposure periods, tissues were rinsed and then incubated at 37 °C for 42 hours. Cell viability was calculated from optical densities (OD) at 570 nm following MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] treatment (wherein MTT changes colour in the presence of living cells), and the results are summarised in the table below. The positive controls did not give satisfactory results, and in a repeat experiment both the negative and positive controls also did not give satisfactory results. Therefore, no consistent outcome can be drawn from this assay.

Test material	*Mean OD_{570} of triplicate tissues*	*± SD of OD_{570}*	*Relative mean viability (%)*	*± SD of relative mean viability (%)*
Negative control	1.270	0.092	100*	0
Positive control	0.228	0.288	18	24
Test substance	0.717	0.012	56	3.5

SD = standard deviation; *The mean viability of the negative control tissues is set as 100%.

Based on the available data, the notified chemical is only slightly irritating to the skin of rabbits.

Eye irritation

Data for eye irritation were not available at the time of the new chemical assessment, and an appropriate analogue was used to evaluate this endpoint. Based on these data, the notified chemical was considered slightly irritating to the eye.

In an in vitro Bovine Corneal Opacity and Permeability study (WIL Research Europe, 2014d; **ND**) submitted for the secondary notification assessment, conducted in accordance with OECD TG 437, undiluted notified chemical was topically applied to the epithelium of isolated bovine cornea for 10 minutes. The mean opacities and permeability measurements are presented in the table below. The notified chemical did not induce ocular irritation, and a mean in vitro irritancy score (IVIS) of 0.97 was calculated. This study indicates that undiluted notified chemical is not corrosive or a severe eye irritant under the conditions of the test.

Test material	*Mean opacities of triplicate tissues (SD)**	*Mean permeabilities of triplicate tissues (SD)**	*IVIS (SD)*
Negative control	-0.33 (0.94)	0.00 (0.001)	-0.33 (0.94)
Test substance	1.00 (1.41)	-0.001 (0.003)	0.97 (1.44)
Positive control	92.7 (11.6)	2.42 (0.204)	128.9 (12.6)

*Corrected for background values

Sensitisation

Data for skin sensitisation were not available at the time of the new chemical assessment, and an appropriate analogue was used to evaluate this endpoint. Based on a Guinea pig maximization test, the analogue, and by extension the notified chemical, was considered not to be a skin sensitiser.

In a murine LLNA submitted for the secondary notification assessment, the notified chemical (WIL Research Europe, 2014e; **ND**) in acetone/olive oil (4:1(v/v)) was topically applied to the dorsal surface of the ears of female CBA/J mice. The measured proliferation responses and stimulation indices are presented in the table below. No mortality occurred and no clinical signs of systemic toxicity were observed. The data showed a dose response and an EC3 (the estimated test substance concentration that will give a Stimulation Index = 3) of 1.1% was calculated. This study indicates that the notified chemical is a skin sensitiser.

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test substance		
0 (vehicle control)	304	1.0
0.5	438	1.4
1.0	788	2.6
2.5	4086	13.5
Positive control		
0	570	1.0
5	658	1.2
10	924	1.6
25	4371	7.7

DPM = disintegrations per minute

Repeated dose toxicity

The new chemical assessment report (NICNAS, 2008) considered a 28-day oral repeat dose study in rats using an analogue chemical and concluded that the notified chemical had the potential to cause serious damage to health by prolonged exposure. In this study adverse effects were observed at all dose levels (15, 40, and 100 mg/kg/day) and were dose dependent. The main effects observed involved the liver with centrilobular hepatocyte degeneration and necrosis at all dose levels, the haemopoietic system and the kidney. The effects observed at the lowest dose (15 mg/kg/day) were relatively minimal, but were still considered to be treatment-related. Therefore, the lowest observed adverse effect level (LOAEL) was the lowest dose (15 mg/kg/day) and a NOAEL could not be established. No new data are currently available to re-assess this endpoint.

Genotoxicity

The new chemical assessment report (NICNAS, 2008) considered an in vivo rat bone marrow chromosome aberration test on an analogue chemical, and concluded that the notified chemical was unlikely to be clastogenic. In addition, the notified chemical was found to be non-clastogenic in an in vivo erythrocyte micronucleus test in the mouse.

In a bacterial reverse mutation test submitted for the secondary notification assessment (WIL Research Europe, 2013f; **ND**), the notified chemical was not mutagenic (with and without metabolic activation) in *Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100, and the *Escherichia coli* strain WP2uvrA. The results of this study are summarised in the table below.

Metabolic activation	*Test substance concentration (µg/plate) resulting in:*			
	Cytotoxicity in preliminary Test	*Cytotoxicity in main test*	*Precipitation*	*Genotoxic effect*
Absent				
Test 1	1000 µg/plate	1000 µg/plate	3330 µg/plate	negative
Test 2		1000 µg/plate	1000 µg/plate	negative
Present				
Test 1	Not cytotoxic	3330 µg/plate	3330 µg/plate	negative
Test 2		Not cytotoxic	1000 µg/plate	negative

Overall, the data indicate that the notified chemical is not genotoxic.

5.1.3 Hazard classification

The new chemical assessment report (NICNAS, 2008) concluded that the notified chemical had the potential to cause serious damage to health by prolonged exposure and recommended a hazard classification of R48 according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). This classification is still applicable and according to the GHS (United Nations, 2009), as adopted for industrial chemicals in Australia, the notified chemical should be classified as a Category 1 specific target organ toxicant (repeated exposure).

New data identified during this secondary notification assessment have identified that the notified chemical is flammable, so it is recommended that the notified chemical also be classified as a Category 3 Flammable liquid according to the GHS (United Nations, 2009).

New data submitted for the secondary notification assessment have identified an additional health hazard of skin sensitisation, so it is recommended that the notified chemical also be classified as a Category 1A skin sensitiser according to the GHS (United Nations, 2009).

The recommended hazard classification for the notified chemical, based on data provided for a test sample of the notified chemical (S-10903; purity 93.2%), which is not representative of the purity of the notified chemical as found in the final substance Reagent S-10104 Promoter, are presented in the following table.

Human health hazard classification

Hazard classification	Hazard statement
Skin sensitiser (Category 1A)	H317 - May cause an allergic skin reaction
Specific target organ toxicity - Repeated exposure (Category 1)	H372 - Causes damage to organs through prolonged or repeated exposure
Flammable (Category 3)	H226 - Flammable liquid and vapour

Based on the available information, the notified chemical is recommended for hazard classification according to the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004), with the following risk phrases:

- R43 - May cause sensitisation by skin contact
- T: R48/25 - Danger of serious damage to health by prolonged exposure if swallowed
- F: R10 - Flammable
- R31 - Contact with acid liberates toxic gas

5.2 Environmental hazard assessment

This section contains a short summary of the data relevant to the environmental hazard assessment of the notified chemical, with a focus on new data. The robust summaries of the data available for the assessment of the notified chemical as a new chemical are reproduced from the new chemical assessment report (NICNAS, 2008) without modification in the Appendix of this report.

5.2.1 Environmental effects assessment

New ecotoxicity data were submitted for the secondary notification assessment of the notified chemical. The notified chemical tested at the time of the previous assessment had a purity of 97%, and the current ecotoxicity data on the notified chemical were acquired on a sample with a purity of 93.2%. The table below summaries the data, wherein **ND** indicates for which endpoints new data are available.

Summary of ecotoxicity data for the notified chemical or analogue

Endpoint	Previous data	New data (ND)
Fish toxicity	LC50 > 0.78 mg/L (Analogue)	–
Algal toxicity	E_rC50 = 0.15 mg/L (Notified chemical)	E_rC50 = 0.82 mg/L (Notified chemical)
Daphnia toxicity	EC50 > 1.0 mg/L (Analogue)	EC50 = 0.42 mg/L (Notified chemical)
Inhibition of bacterial respiration	EC50 = 240 mg/L (Analogue)	–

An algal growth inhibition study (WIL Research Europe, 2013g; **ND**) submitted for the secondary notification assessment confirms that the notified chemical is very toxic to algae, in agreement with data submitted for the new chemical assessment. Data for daphnia toxicity were not available at the time of the new chemical assessment, and an appropriate analogue was used to evaluate this endpoint. The daphnia toxicity study (WIL Research Europe, 2013h; **ND)** submitted for the secondary notification assessment indicates higher toxicity (EC50 = 0.42 mg/L) as compared to the analogue (EC50 > 1.0 mg/L).

As the new data indicate that the notified chemical is very toxic to *Daphnia magna*, and very toxic to

algae (E_rC50 < 1 mg/L), overall the new ecotoxicity data do not significantly impact on the initial environmental effects assessment. Therefore, the environmental hazard classification from the new chemical assessment report is still applicable.

5.2.2 Predicted No-Effect Concentration

The lowest measured EC50 from the new ecotoxicity data provided for this assessment (EC50 (daphnia) = 0.42 mg/L) is higher than the lowest measured EC50 of 0.15 mg/L (E_rC50 algae) used by the new chemical assessment to calculate the PNEC for the Aquatic Compartment. Therefore, the new data do not significantly change the original environmental risk assessment and the previously calculated, more conservative, PNEC value is still applicable.

PNEC for the Aquatic Compartment		
E_rC50 algae	0.15	mg/L
Assessment Factor	100	
PNEC:	1.5	µg/L

5.2.3 Hazard classification

The environmental hazard classification according to the GHS (United Nations, 2009) is presented below, which is unchanged compared to the original assessment of the notified chemical as a new chemical. Environmental classification under the GHS is not mandated in Australia and carries no legal status but is presented for information purposes.

Environmental hazard classification

Hazard classification	**Hazard statement**
Acute (Category 1)	H400 - Very toxic to aquatic life
Chronic (Category 1)	H410 - Very toxic to aquatic life with long lasting effects

6. Risk characterisation

The occupational health risk estimation has been updated to allow for the new sensitisation and flammability hazards posed by the notified chemical. The public health and environmental risk estimations have been reproduced from the new chemical assessment report (NICNAS, 2008) without modification.

6.1 Public health risk estimation

As the public is not exposed to the notified chemical, the risk to public health is considered to be negligible.

6.2 Occupational health risk estimation

The main route of exposure to the notified chemical (up to 70% concentration) for both reformulation and mining industry workers is dermal, during processes such as connecting/disconnecting hoses, cleaning and sampling.

Following the assessment of the new data provided for the secondary notification assessment, the notified chemical is assessed to be a skin sensitiser. This may pose a risk for workers involved in blending, quality control, connecting and disconnecting lines, and cleaning pumping and ancillary apparatus. However, provided that control measures are in place to minimise worker exposure, including the use of automated processes and PPE, the risk of the notified chemical causing skin sensitisation in workers is not considered to be unacceptable.

The new chemical assessment determined that, while the notified chemical was found to be of low acute toxicity via the oral route, health effects after repeated dermal exposure could not be ruled out, particularly given the systemic toxicity observed following repeated oral exposure of the analogue chemical and the favourable physical-chemical properties for dermal absorption. EASE modelling of the reformulation/mining processes estimated the exposure as 0–0.42 mg/kg/day. No dermal NOAEL was determined. In the oral sub-acute toxicity study only a LOAEL (15 mg/kg/day) could be established as adverse effects were observed at all dose levels. Use of this LOAEL resulted in a margin of exposure (MOE) of 36. MOEs greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. This MOE therefore indicates that the risk is not acceptable if workers are exposed to the notified chemical repeatedly on the skin. The MOE is based on conservative assumptions (e.g. 100% dermal absorption, no PPE) and may overestimate the risk.

Given the risk of causing serious damage to health by prolonged or repeated exposure, the risk to workers is only acceptable when the notified chemical is used under highly controlled conditions, and with the appropriate PPE. As the operations are highly controlled, and good worker practices (including PPE) are in place during limited activities where worker handling is required, the risk of adverse effects is significantly reduced and is considered acceptable under the occupational settings described. However, if PPE practices are inadequate, then there is a risk of on-going exposure to the notified chemical from incidental contact with the chemical during blending and reformulation activities.

The notified chemical is a flammable liquid, and decomposition may generate toxic and flammable gases – in particular, contact with heat or acid should be avoided. Therefore, a potential fire risk exists for the notified chemical during reformulation, transport, storage and end-use. Provided the notified chemical is stored and transported according to the regulations of Class 3 Flammable goods within the *Australian Dangerous Goods Code* (NTC, 2014), the risks are not unreasonable. The risks during reformulation and end-use are also considered acceptable if the notified chemical is used under highly controlled conditions, with the appropriate PPE, and by suitably trained workers.

6.3 Environmental risk estimation

The new ecotoxicity data for the notified chemical do not significantly affect the conclusions of the

environmental effects assessment, and the previously calculated, more conservative, PNEC value is still applicable. Therefore, the related risk estimations from the new chemical assessment of the notified chemical are still applicable and are reproduced below.

Risk Assessment	*PEC µg/L*	*PNEC µg/L*	**PEC/PNEC**
River:	0.4	1.5	0.27
Ocean:	0.04	1.5	0.03

The calculated Risk Quotient (Q = PEC/PNEC) is less than 1 even when estimated based on the worst case scenarios for both river and ocean. Therefore, the notified chemical is not predicted to pose an unacceptable risk to the aquatic environment.

Appendix

A1 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties data submitted for the new chemical assessment of the notified chemical are reproduced here without modification.

Melting point/Freezing point 30.85 ± 0.5°C

METHOD	EC Directive 92/69/EEC A.1 Melting/Freezing Temperature
Remarks	The melting point was determined using differential scanning calorimetry.
	No significant protocol deviations
TEST FACILITY	Safepharm Laboratories (2008a)

Boiling point 211.85°C at 103.15 to 103.87 kPa

METHOD	EC Directive 92/69/EEC A.2 Boiling Temperature
Remarks	The boiling point was determined using differential scanning calorimetry.
	The notified chemical underwent a colour change to a brown solid at 210°C which is indicative of decomposition.
	No significant protocol deviations
TEST FACILITY	Safepharm Laboratories (2008a)

Density 1180 kg/m^3 at 20.3 ± 0.5°C

METHOD	EC Directive 92/69/EEC A.3 Relative Density
Remarks	The relative density was determined using the pycnometer method.
	No significant protocol deviations
TEST FACILITY	Safepharm Laboratories (2008a)

Vapour pressure 9.8 x 10^{-6} kPa at 25°C

METHOD	EC Directive 92/69/EEC A.4 Vapour Pressure
Remarks	The vapour pressure was determined using a vapour pressure balance at several temperatures, with linear regression analysis used to determine the vapour pressure at 25°C.
	No significant protocol deviations
TEST FACILITY	Safepharm Laboratories (2008b)

Water solubility 2.58 ×10^{-3} g/L at 20.0 ± 0.5°C

METHOD	EC Directive 92/69/EEC A.6 Water Solubility
Remarks	Flask Method, with analysis using high pressure liquid chromatography (HPLC). The pH of the solution was between 5.4 and 6.3.

TEST FACILITY Safepharm Laboratories (2008a)

Hydrolysis as a function of pH Half-life estimated to be 46.3, 37.2 and 14.1 days at pH 4, 7 and 9, respectively, at 25 ˚C

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

pH	*T (°C)*	*$t_{½}$ (days)*
4	25	46.3
7	25	37.2
9	25	14.1

Remarks HPLC was used for the analysis of solution concentrations.

A preliminary test at 50°C was conducted at pH 4, 7 and 9. The preliminary test at pH 4 was found to be inconsistent with the 40, 60 and 70°C tests and was not included in the test report. The preliminary test results at pH 7 and 9 were 12.7 and 10.3 hours, respectively. The kinetics of the study were determined to be consistent with that of a pseudo-first order reaction as graphs of $\log_{10}$ concentration versus time are straight lines.

TEST FACILITY Safepharm Laboratories (2008a)

Partition coefficient (n-octanol/water) $\log P_{OW} = 4.09$

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient

Remarks HPLC Method. The notified chemical eluted between the reference substances naphthalene ($\log P_{OW}= 3.6$) and phenanthrene ($\log P_{OW}=4.5$). The estimated $\log P_{OW}$ is considered reasonable based on the formula structure.

TEST FACILITY Safepharm Laboratories (2008a)

Surface tension 61.7 mN/m at 20.2 ± 0.5°C (2.16×10^{-3} g/L solution)

METHOD EC Directive 92/69/EEC A.5 Surface Tension

Remarks The surface tension determination was conducted using a White Electrical Institute interfacial torsion balance and a procedure based on the ISO 304 ring method, which complies with Method A5 of the Commission Directive, except for the lack of correction (which is not applicable to the apparatus used). This deviation is not considered to have affected the integrity of the study.

The surface tension was determined using a 2.16×10^{-3} g/L solution at pH 5.4. The notified chemical is not considered to be significantly surface active based on the test result.

TEST FACILITY Safepharm Laboratories (2008a)

Adsorption/Desorption log K_{OC} = 3.72

METHOD EC Directive 2001/59/EC C.19 Estimation of the Adsorption Coefficient (K_{OC}) on Soil and on Sewage Sludge using High Performance Liquid Chromatography

Remarks The notified chemical eluted between the reference substances Fenthion (log K_{OC}=3.31) and α-Endosulfan (log K_{OC}=4.09). The estimated log K_{OC} is considered in compliance with the formula structure.

TEST FACILITY Safepharm Laboratories (2008a)

Particle size

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

Range (μm)	*Mass (%)*
< 100 μm	11.3%
< 10 μm	0.65%
< 5.5 μm	0.17%

Remarks Measured using a cascade impactor after a preliminary sieve test.

TEST FACILITY Safepharm Laboratories (2008a)

Flash point 134 ± 2°C at 101.3 kPa

METHOD EC Directive 92/69/EEC A.9 Flash Point

Remarks The flash point was determined using a closed cup equilibrium method

No significant protocol deviations

TEST FACILITY Safepharm Laboratories (2008b)

Autoignition temperature 278 ± 5°C

METHOD EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases)

Remarks No significant protocol deviations

TEST FACILITY Safepharm Laboratories (2008b)

A2 TOXICOLOGICAL INVESTIGATIONS

The robust summaries of the toxicological studies analysed for the assessment of the notified chemical as a new chemical are reproduced here without modification.

A2.1 Acute toxicity - oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 420 Acute Oral Toxicity - Fixed Dose Method.
	EC Directive 2004/73/EC B.1bis Acute Oral Toxicity - Fixed Dose Method
Species/Strain	Rat/ Sprague-Dawley CD (Crl: CD® (SD) IGS BR)
Vehicle	Arachis oil BP
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and sex of animals*	*Dose mg/kg bw*	*Mortality*
1	1 female	300	0
2	1 female	2000	0
3	4 females	2000	1

LD50	> 2000 mg/kg bw
Signs of toxicity	No signs of systemic toxicity were noted for the female treated at a dose level of 300 mg/kg bw. Signs of systemic toxicity in animals dosed at 2000 mg/kg bw were hunched posture, lethargy, piloerection, decreased respiratory rate, and laboured respiration. Surviving animals dosed at 2000 mg/kg bw appeared normal two or three days after dosing.
	The surviving animals showed expected gains in bodyweight over the study period.
Effects in organs	Abnormally red lungs, dark liver, and dark kidneys were noted at necropsy of the animal that died. No abnormalities were noted at necropsy of animals that were killed at the end of the study.
Remarks - Results	One female animal dosed at 2000 mg/kg bw died.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Safepharm Laboratories Limited (2008c)

A2.2. Acute toxicity - dermal

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 402 Acute Dermal Toxicity
	EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal)
Species/Strain	Rat/Sprague-Dawley CD (Crl:CD® (SD) IGS BR)
Vehicle	Administered as supplied

Type of dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and sex of animals*	*Dose mg/kg bw*	*Mortality*
1	5 males	2000	0
2	5 females	2000	0

LD50	> 2000 mg/kg bw
Signs of toxicity - Local	There were no signs of dermal irritation.
Signs of toxicity - Systemic	There were no signs of systemic toxicity.
Effects in organs	No abnormalities were noted at necropsy.
Remarks - Results	All animals showed expected gains in body weight over the study period.
CONCLUSION	The analogue chemical is of low toxicity via the dermal route.
TEST FACILITY	Safepharm Laboratories Limited (2005a)

A2.3. Irritation - skin

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion.
	EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation)
Species/Strain	Rabbit/New Zealand White
Number of animals	3 males
Vehicle	Administered as supplied
Observation period	7 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	1	1	2	< 7 days	0
Oedema	0.3	0.3	0.3	1	< 48 hours	0

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

Remarks - Results	A single 4-hour, semi-occluded application of the test substance to the intact skin of the three rabbits produced very slight to well-defined erythema and very slight oedema at the 24-hour observation. Slight erythema was noted at all treated skin sites at 48 hours. Two treated skin sites appeared normal at the 72-hour observation and the

remaining treated skin site appeared normal at the 7-day observation.

In 3-minute and 1-hour semi-occluded applications of the test substance to the intact skin of one rabbit, no evidence of skin irritation was observed.

No corrosive effects were noted.

CONCLUSION The analogue chemical is slightly irritating to the skin.

TEST FACILITY Safepharm Laboratories Limited (2005b)

A2.4. Irritation - eye

TEST SUBSTANCE Analogue chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.

EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation)

Species/Strain Rabbit/New Zealand White

Number of animals 3 males

Observation period 72 hours

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			
Conjunctiva: redness	0.33	0.33	0.33	1	< 48 hours	
Conjunctiva: chemosis	0	0	0	1	< 24 hours	
Conjunctiva: discharge	0	0.33	0.33	1	< 48 Hours	
Corneal opacity	0	0	0	0	0	
Iridial inflammation	0	0	0	0	0	

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

Remarks - Results A single application of the test substance to the non-irrigated eye of three rabbits produced minimal conjunctival irritation. All animals showed mild conjunctival irritation at the 1-hour observation, with all reactions clearing by 48 hours.

CONCLUSION The analogue chemical is slightly irritating to the eye.

TEST FACILITY Safepharm Laboratories Limited (2005c)

A2.5. Skin sensitisation

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 406 Skin Sensitisation - Guinea pig maximization test (Magnusson-Kligman)
Species/Strain	Guinea pig/Hartley Albino
PRELIMINARY STUDY	Maximum Non-irritating Concentration:
	intradermal: 25%
	topical: 50%
	Maximum concentration causing mild-moderate irritation:
	topical: 100%
MAIN STUDY	
Number of animals	Test Group: 20 Control Group: 10 (100% corn oil)
INDUCTION PHASE	Induction Concentration:
	intradermal injection: 25%
	topical application: 100% (with SLS (10%) pre-treatment)
Signs of irritation	For test substance - erythema was discrete to intense
	For vehicle control - erythema was absent to intense
CHALLENGE PHASE	
1st challenge	topical application: 50%
2nd challenge	topical application: not conducted
Remarks - Method	The scoring time was not recorded for the topical screen animals at 24 hours post patch removal. Upon review of the data, it appeared that the topical screen animals were scored following observations of the intradermal screen animals. The oversight did not impact on the study results, since all screen animals were observed and the scores were recorded on the data.

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	50%	3/20	2/20	-	-
Control group	50%	0/10	0/10	-	-

Remarks - Results	There were no deaths, or substance-related signs of toxicity, during the study. On first challenge 3/20 (15%) animals showed a score of 1 at 24 hours. This was below the 30% cut-off for evidence of positive responses to meet the classification criteria. The positive control confirmed the sensitivity of the test system.
CONCLUSION	There was limited evidence of reactions indicative of skin sensitisation

	to the analogue chemical under the conditions of the test.
TEST FACILITY	MB Research Laboratories (2005)

A2.6. Repeat dose toxicity

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
	EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral)
Species/Strain	Sprague-Dawley Crl:CD® (SD) IGS BR strain
Route of administration	Oral - gavage
Exposure information	Total exposure days: 28 days
Vehicle	Arachis oil BP
Remarks - Method	No recovery period. Overnight fasting before collection of blood samples was not conducted.

RESULTS

Dose mg/kg bw/day	*Number and sex of animals*	*Mortality*
0	5 male, 5 female	0
15	5 male, 5 female	0
40	5 male, 5 female	0
100	5 male, 5 female	0

Mortality and time to death

No unscheduled deaths occurred during the study.

Clinical observations

Incidences of increased salivation immediately after dosing, and on occasions prior to dosing, and up to one and five hours after dosing were detected for all treated animals throughout the study period. On Day 1 of the study, incidents of hunched posture were detected in animals of both sexes treated with 100 or 40 mg/kg/day, while lachrymation was detected in animals of both sexes treated with 100 mg/kg/day, or noisy respiration detected for females only of this treatment group.

Behavioural assessment

There were no treatment-related changes in the behavioural parameters measured.

Functional performance tests

There were no toxicologically significant changes in the functional performance parameters measured.

Sensory reactivity assessments –

There were no treatment-related changes in sensory reactivity.

Bodyweight

A reduction in bodyweight development was detected in males treated with 100 and 40 mg kg/day during Week 1 of the study. This reduction persisted throughout the remainder of the study in 100 mg/kg/day males, while subsequent recovery was observed after the first week of treatment in males

treated with 40mg/kg/day.

Food consumption

A reduction in food consumption was detected in animals of both sexes treated with 100 mg/kg/day during the first week of treatment. This reduction subsequently recovered in 100 mg/kg/day females, while the reduction continued in 100 mg/kg/day males for the remainder of the study period.

Water consumption

An increase in water consumption was detected in animals treated with 100 mg/kg/day during the first week of treatment, and in all treated males during the remainder of the study when compared to controls. Females treated with 100 or 40 mg/kg/day had increased water consumption throughout the study period. No such observations were detected in animals of both sexes treated with 15 mg/kg/day.

Laboratory findings - Clinical chemistry, haematology, urinalysis

Haematology - Animals of both sexes treated with 100 mg/kg/day showed a reduction in haemoglobin, haematocrit and haematocrit and erythrocyte count, and elevations in reticulocyte count. In addition, males of this treatment group showed reductions in neutrophil count, while females showed an increase in main cell volume.

At 40 mg/kg/day, reductions in haemoglobin and haematocrit were detected in animals of both sexes, whilst females of this treatment group also showed a reduction in erythrocyte count and an elevation in reticulocyte count. No such observations were detected in animals of both sexes treated with 15 mg/kg/day.

Blood chemistry - At 100 mg/kg/day, animals of both sexes showed a decrease in total protein and an increase in alkaline phosphatase levels. In addition, males had elevated cholinesterase and plasma urea levels; whilst females of this treatment group showed reductions in both glucose and cholesterol levels. The reduction in plasma cholesterol levels extended to females treated with 40 and 15 mg/kg/day.

Males treated with 40 mg/kg/day had reduced total protein levels and showed elevations in plasma glucose levels.

No treatment related changes were detected in the blood parameters measured in males treated with 15 mg/kg/day.

Effects in organs

All treated males showed increases in both relative liver and kidney weights, while females treated with 100 and 40 mg/kg/day also showed elevations in liver weight. In addition, all treated animals had reduced thymus weight, and animals of both sexes treated with 100 mg/kg/day had elevated spleen weights. Three males treated with 100 mg/kg/day had pallor of the liver and kidneys. 3 females treated with 100 mg/kg/day, and one treated with 40 mg/kg/day, also had pallor of the kidneys.

Liver - Histopathological changes characterised by centrilobular hepatocyte enlargement, vacuolation of centrilobular hepatocytes, centrilobular hepatocyte inflammatory cell infiltrates, pigment deposits, and a higher incidence and generally higher grades of severity of generalized hepatocyte vacuolation (glycogen type in appearance), were seen in relation to treatment in animals of both sexes treated with 100 mg/kg/day, and to a lesser extent in animals treated with 40 and 15 mg/kg/day. Vacuolation of centrilobular hepatocytes was demonstrated to be a consequence of lipid accumulation as frozen sections, stained with Oil Red O. Pigment deposits, positively stained with Perl's stain and were thus likely to be haemosiderin.

Centrilobular hepatocyte degeneration and necrosis were observed in animals of both sexes treated with 100 mg/kg/day; in one female and two males treated with 40 mg/kg/day, and in three males treated with 15 mg/kg/day. This is considered to be an adverse morphological change.

Spleen - Higher grades of severity of extramedullary haemopoiesis and haemosiderin pigment deposition, positively stained with Perl's stain, were seen in relation to treatment in animals of bothr sexes treated with 100 mg/kg/day. Higher grades of severity of extramedullary haemopoiesis were also seen in males treated with 40 and 15 mg/kg/day, and higher grades of severity of extramedullary haemopoiesis and pigment deposition were seen in females treated with 40 mg/kg/day.

Kidneys - Tubular basophilia and karyomegaly of tubular cells, affecting tubules of the inner cortex, were seen in animals of both sexes treated with 100 mg/kg/day, but not convincingly at any other treatment level.

Thyroid - Follicular cell hypertrophy was observed in relation to treatment in animals of both sexes treated with 100 and 40 mg/kg/day.

Thymus - Atrophy of the thymus was seen as a variable response among treated animals of both sexes, but no evidence of a dose relationship was observed. Although the condition may be associated with treatment, it is regarded as a secondary effect.

Remarks - Results

Haemopoietic system - The haematological findings (i.e. reductions in haemoglobin, haematocrit and erythrocyte count) are associated with haemolytic anaemia, and are supported by the histopathological evidence of disruptions to the haemopoietic system (effects on spleen).

Liver - Adverse morphological changes were detected in the liver in animals from all treatment groups. These findings were supported by haematological and organ weight evidence.

Kidney - Macroscopic and microscopic evidence of kidney damage correlated with the elevation in plasma urea and elevate kidney weights.

At the lowest dose of 15 mg/kg/day, the primary dose related effects in the liver, kidney and spleen were relatively minimal compared to animals treated with 100 or 40 mg/kg/day. However the occurrence of these effects still precludes the determination of a NO(A)EL.

CONCLUSION

Oral administration of the test substance to rats for a period of 28 consecutive days, at dose levels of 100, 40 and 15 mg/kg/day, resulted in toxicologically significant effects in animals of both sexes from all dose levels.

The NOEL was therefore, not achieved. The LOAEL was determined to be 15 mg/kg/day in this study.

TEST FACILITY Safepharm Laboratories Limited (2007a)

A2.7. Genotoxicity - bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test
	EC Directive 2000/32/EC B.13/14 Mutagenicity - Reverse Mutation Test using Bacteria
	Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100.
	E. coli: WP2uvrA$^-$
Metabolic activation system	Rat S9 fraction from phenobarbitone/β-napthoflavone induced rat liver

Concentration range in main test	a) With metabolic activation: 5 - 5000 µg/plate (*S. typhimurium*) 50-5000 µg/plate (*E. coli*) b) Without metabolic activation: 5 - 5000 µg/plate (*S. typhimurium*) 50-5000 µg/plate (*E. coli*)
Vehicle	Dimethyl sulphoxide, test substance added as solution
Remarks - Method	No significant protocol deviations. In the preliminary toxicity test, conducted on TA100 and WP2uvrA$^-$, the test substance was initially toxic at 500 µg/plate to T100 in the absence of metabolic activation and was non-toxic to WP2uvrA.

RESULTS

Metabolic activation	*Test substance concentration (µg/plate) resulting in:*			
	Cytotoxicity in preliminary test	*Cytotoxicity in main test*	*Precipitation*	*Genotoxic effect*
Absent				
Test 1	500 µg/plate	1500 µg/plate	1500 µg/plate	negative
Test 2		1500 µg/plate	1500 µg/plate	negative
Present				
Test 1	1500 µg/plate	5000 µg/plate	1500 µg/plate	negative
Test 2		1500 µg/plate	1500 µg/plate	negative

Remarks - Results	The test substance was tested up to the maximum recommended dose level of 5000 µg/plate. No toxicologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at all doses, either with or without metabolic activation. All positive controls induced marked increases in the frequency of revertant colonies to confirm the activity of the S9-mix and the sensitivity of the bacterial strains.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (2006a)

A2.8. Genotoxicity - in vivo

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 475 Mammalian Bone Marrow Chromosome Aberration Test. EC Directive 2000/32/EC B.11 Mutagenicity - In vivo Mammalian Bone Marrow Chromosome Aberration Test.
Species/Strain	Rat/Sprague-Dawley Crl:CD®(SD) IGS BR
Route of administration	Oral - gavage

Vehicle: Arachis oil

Remarks - Method: No significant protocol deviations

As it was suspected that the response, if any, would be quite modest the animal numbers for the vehicle and test substance groups were increased to ten/group. The preliminary toxicity test was conducted using only male animals at doses of 320 and 400 mg/kg/day, based on data from the Mouse Micronucleus test for the analogue.

Dose mg/kg bw	*Number and sex of animals*	*Sacrifice time hours*
0 (vehicle control)	10 male	48
0 (vehicle control)	10 male	24
80	10 male	24
160	10 male	24
320	10 male	48
320	10 male	24
25 (Positive control, CP)	5 male	24

CP = cyclophosphamide

RESULTS

Doses producing toxicity: No premature deaths occurred in the preliminary toxicity test. However, the clinical signs observed at 400 mg/kg after 24-hours exceeded acceptable limits permitted by the Home Office for this type of study and, therefore, the animals were killed in *extremis*. The clinical signs observed at 400 mg/kg were as follows: hunched posture, ataxia, lethargy, ptosis, pilo-erection, decreased respiratory rate and laboured respiration. In animals dosed orally at 320 mg/kg, clinical signs observed were acceptable and as follows: pilo-erection and diuresis. 320 mg/kg was therefore chosen as the maximum tolerated dose.

No premature deaths occurred in any of the treatment groups. Clinical signs (hunched posture, ataxia, lethargy and diuresis) were observed in all treated animals.

Genotoxic effects: The test substance did not induce any significant or dose-related increases in the frequency of aberrations in any of the treatment groups. The test substance did not induce a significant increase in the numbers of polyploidy cells in any of the treatment groups.

No statistically significant reductions in the mean mitotic index were observed in any of the treatment groups, when compared to their concurrent vehicle control groups. The mean mitotic index of the positive control group was statistically significantly lower than that of the 24-hour vehicle control group, indicating a cytotoxic response in the bone marrow.

All vehicle control animals gave values of chromosome aberrations within the expected range. The mean frequency of aberrations was consistent between the two vehicle control groups, the highest frequency (0.3% cells with aberrations excluding gaps) being seen in

	the 48-hour group.
	The positive control group animals showed highly significant increases in the frequency of aberrations, indicating that the test method itself was operating as expected.
Remarks - Results	Although there was no indication of cytotoxicity to the bone marrow, the observation of clinical signs of toxicity indicated that systemic absorption had occurred. Therefore, it is assumed that the target organ was reached.
CONCLUSION	The analogue chemical was not clastogenic to rat bone marrow cells *in vivo* under the conditions of the test.
TEST FACILITY	Safepharm Laboratories (2005d)

A2.9. Genotoxicity - in vivo micronucleus

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
	EC Directive 2000/32/EC B.12 Mutagenicity Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Albino mice/Crl:CD-1™ (ICR)BR
Route of administration	Oral - gavage
Vehicle	Arachis oil
Remarks - Method	No significant protocol deviations. In the preliminary toxicity test male and female rats were treated with 500 mg/kg of the test substance. The test substance showed no marked difference in its toxicity to male or female rats; therefore only male rats were used in the main test. In the main test animals were treated with the test substance once.

Dose mg/kg bw	*Number and sex of animals*	*Sacrifice time hours*
First experiment		
0 (vehicle control)	7	48
0 (vehicle control)	7	24
125	7	24
250	7	24
500	7	24
500	7	48
50 (Positive control, CP)	5	24

CP = cyclophosphamide

RESULTS

Doses producing toxicity	Clinical signs were observed in animals dosed at 250 mg/kg and above as follows: hunched posture, ptosis and ataxia. The maximum tolerated dose (MTD) of the test substance was therefore selected as 500 mg/kg for use in the main test.

In the main test, no premature deaths were observed in any treatment group. Clinical signs were observed in both the 24 and 48-hour groups of animals dosed at and above 250 mg/kg ,as follows: hunched posture, ptosis and ataxia.

Genotoxic effects

There were no statistically significant decreases in the polychromatic erythrocytes/ normochromatic erythrocytes (PCE/NCE) ratio in the 24 or 48-hour treatment groups when compared to their concurrent vehicle control groups. However, the observation of clinical signs of toxicity was taken to indicate that systemic absorption had occurred.

A summary of the results for the micronuclei count is shown in the table below.

Dose	*Number of PCE with micronuclei per 2000 PCE*	
mg/kg bw	*Group mean*	*SD*
First experiment		
0 (vehicle control) - 48 h	1.1	1.5
0 (vehicle control) - 24 h	1.4	2.6
125	0.9	1.2
250	1.0	1.0
500 - 48 h	1.3	1.0
500 - 24 h	1.7	2.4
50 (Positive control, CP)	43.8*	17.3

* = $p < 0.001$

Remarks - Results

The positive control showed a marked increase in the incidence of micronucleated polychromatic erythrocytes, confirming the sensitivity of the system to the known mutagenic activity of cyclophosphamide under the conditions of the test.

The notified chemical did not induce a significant increase in the frequency of the micronuclei at any dose level.

CONCLUSION

The notified chemical was not clastogenic to mouse bone marrow under the conditions of the test.

TEST FACILITY

Safepharm Laboratories (2006b)

A3 ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

The robust summaries of the ecotoxicological studies analysed for the assessment of the notified chemical as a new chemical are reproduced here without modification.

A3.1. Environmental fate

A3.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: CO2 Evolution Test EC Directive 92/69/EEC C.4-C Biodegradation: Determination of the "Ready" Biodegradability: Carbon Dioxide Evolution Test
Inoculum	Mixed population of activated sewage sludge micro-organisms
Exposure period	28 Days
Auxiliary solvent	Sodium benzoate
Remarks - Method	The test substance, at a concentration of 10 mg Carbon/L, was exposed to activated sewage sludge micro-organisms with culture medium in sealed culture vessels in the dark at 21°C for 28 days. The degradation of the test substance was assessed by the determination of carbon dioxide produced. Control solutions with inoculum and the standard material, sodium benzoate, together with a toxicity control were used for validation purposes.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
6	13	6	51
14	25	14	66
22	34	22	69
28	46	28	80

Remarks - Results	The study is considered valid since all validation criteria have been satisfied. On Days 0, 6 and 13 the contents of both the test substance and the toxicity control vessels were observed to be cloudy brown dispersions with fine particles of test substance on the surface. On Days 20 and 27 no undissolved test substance was visible. The test substance attained 46% degradation after 28 days and therefore cannot be considered to be readily biodegradable under OECD Guideline No. 301B.
CONCLUSION	The notified chemical cannot be considered readily biodegradable.
TEST FACILITY	Safepharm Laboratories (2008d)

A3.1.2. Bioaccumulation

Remarks	The physico-chemical properties (log P_{OW} = 4.09 and water solubility of 2.58 x 10^{-3} g/L), and the nature of being not readily biodegradable, indicate that the notified chemical has potential for bioaccumulation. The risk of bioaccumulation is mitigated by the expected low exposure to natural waters.

A3.2. Ecotoxicological Investigations

A3.2.1. Acute toxicity to fish

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test - 96 hour, Semi-Static Limit Test
Species	Rainbow trout (*Oncorhynchus mykiss*)
Exposure period	96 hours
Auxiliary solvent	Dimethylformamide (DMF)
Water hardness	100 mg $CaCO_3$/L
Analytical monitoring	HPLC
Remarks - Method	No significant protocol deviations
	1.0 mg/L was the highest attainable test concentration due to the limited solubility of the test substance and auxiliary solvent, and having due regard for the amount of auxiliary solvent permitted in the test under the OECD Guidelines. During preliminary solubility work, fine particles of test substance were observed dispersed throughout the test media at concentrations in excess of 1.0 mg/L indicating this to be the maximum limit of water solubility under these conditions.

RESULTS

Concentration mg/L		*Number of fish*	*Mortality*						*% Mortality*
Nominal	*Actual*		*3 h*	*6 h*	*24 h*	*48 h*	*72 h*	*96 h*	*96 h*
Control		10	0	0	0	0	0	0	0
Solvent control		10	0	0	0	0	0	0	0
1.0 R1	0.78	10	0	0	0	0	0	0	0
1.0 R2	0.78	10	0	0	0	0	0	0	0

LC50	> 0.78 mg/L at 96 hours
NOEC	0.78 mg/L at 96 hours
Remarks - Results	In the range-finding test there was no sub-lethal effects of exposure. The results showed no mortalities at the 1.0 mg/L test concentration. A concentration of 1.0 mg/L was selected for the definitive test. This experimental design conforms to a "Limit Test" and confirms that at the highest attainable test concentration (1.0 mg/L) no mortalities or sub-lethal effects of exposure were observed.
	There were no mortalities in 20 fish exposed to a test concentration of 1.0 mg/L for a period of 96 hours. The results of the definitive test

showed the highest concentration resulting in 0% mortality to be ≥ 1.0 mg/L. The no-observed effect concentration (NOEC) was 1.0 mg/L as zero mortalities, and no sub-lethal effects of exposure, were observed at this concentration.

A reduction of concentration was observed after analysis of fresh and old media, and therefore, it was considered justifiable to base the results on the time-weighted mean measured test concentrations of the centrifuged test media to give a "worst case" analysis of the data.

The test result is considered applicable to the notified chemical based on the formula similarity.

CONCLUSION	The analogue substance is not toxic up to the limit of its solubility.
TEST FACILITY	Safepharm Laboratories (2005e)

A3.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - 48 hour static
Species	*Daphnia magna*
Exposure period	48 hours
Auxiliary solvent	DMF
Water hardness	250 mg $CaCO_3$/L
Analytical monitoring	HPLC
Remarks - Method	Following a preliminary range-finding test, 20 daphnids (4 replicates of 5 animals) were exposed to an aqueous solution of the test substance at a concentration of 1.0 mg/L for 48 hours at a temperature of 21.3º to 21.9ºC under static conditions. Immobilisation, and any adverse reactions to exposure, were recorded after 24 and 48 hours. A positive control was analysed approximately every 6 months using potassium dichromate as the reference material.

RESULTS

Concentration mg/L	*Number of D. magna*	*Number immobilised*	
Nominal		*24 h*	*48 h*
Control	10	0	0
Solvent control	10	0	0
1.0	20	0	0

LC50	> 1.0 mg/L at 48 hours
NOEC	1.0 mg/L at 48 hours
Remarks - Results	Analysis of the centrifuged test preparations at 0 and 48 hours showed measured test concentrations of 81% to 85% of nominal value. Therefore, it was considered justifiable to estimate the EC50 values in terms of nominal test concentration only. The test substance preparations were observed to be clear, colourless solutions

	throughout the duration of the test.
	The test result is considered applicable to the notified chemical based on the formula similarity.
CONCLUSION	The analogue substance is not toxic to *Daphnia magna* up to the limit of its solubility.
TEST FACILITY	Safepharm Laboratories (2005f)

A3.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified substance
METHOD	OECD TG 201 Alga, Growth Inhibition Test
	EC Directive 92/69/EEC C.3 Algal Inhibition Test
Species	Green alga (*Desmodesmus subspicatus*)
Exposure period	72 hours
Concentration range	Nominal: 0.015, 0.048, 0.15, 0.48 and 1.5 mg/L
	Actual: 0.0018, 0.0045, 0.010, 0.43 and 1.4 mg/L (Geometric mean measured test concentration)
Auxiliary solvent	None
Water hardness	Not reported
Analytical monitoring	HPLC for determination of test substance concentrations
Remarks - Method	No significant deviations from standard protocol

*Biomass**		*Growth**	
E_bC50	*NOEC*	*E_rC50*	*NOEC*
mg/L at 72 h	*mg/L*	*mg/L 0 -72 h*	*mg/L*
0.014	0.0018	0.15	0.0018

* Based on geometric mean measured test concentrations.

Remarks - Results	Analysis of the test preparations at 72 hours showed a marked decline in measured test concentrations in the range of less than 1% to 70% of the nominal. These results were in-line with the preliminary stability analyses that indicated the test substance was unstable in culture medium over the test period, particularly at the lower test concentrations employed.
	Given this decline in measured concentrations it was considered justifiable to base the results on the geometric mean measured test concentrations of the centrifuged test media in order to give a "worst case" analysis of the data.
	At the start of the test all control and test cultures were observed to be clear colourless solutions. After the 72-hour test period all control, 0.0018, 0.0045 and 0.010 mg/L test cultures were observed to be green dispersions whilst the 0.48 mg/L and 1.5 mg/L test cultures were observed to be clear colourless solutions.
	Based on the geometric mean measured test concentrations the E_rC50 (0–72 h) value was 0.15 mg/L; 95% confidence limits 0.10– 0.23

	mg/L, the E_yC50 (0–72 h) value was 0.010 mg/L; 95% confidence limits 0.0070– 0.014 mg/L and the E_bC50 (0–72) value was 0.014 mg/L; 95% confidence limits 0.010–0.021 mg/L. The lowest observed effect concentration (LOEC) based on growth rate, yield and biomass integral was 0.0045 mg/L and the NOEC was 0.0018 mg/L.
CONCLUSION	The notified chemical is very toxic to algae.
TEST FACILITY	Safepharm Laboratories (2008e)

A3.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Analogue chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test
	EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated sewage sludge microorganisms
Exposure period	3 hours
Concentration range	56, 100, 180, 320, 560 and 1000 mg/L
Remarks - Method	Following preliminary range-finding tests, activated sewage sludge was exposed to an aqueous dispersion of the test substance at the concentrations listed above for a period of 3 hours at a temperature of approximately 21°C, with the addition of a synthetic sewage as a respiratory substrate. The rate of respiration was determined after 30 minutes and 3 hours contact time, and compared to data for the control and a reference material 3,5-dichlorophenol.
RESULTS	
EC50	240 mg/L (95% confidence limits 200–290 mg/L)
NOEC	56 mg/L
Remarks - Results	It was not possible to obtain an EC50 and an EC80 value (at 30 minutes) for the test substance, as no concentration tested resulted in greater than 50% inhibition after 30 minutes contact time. It was not possible to obtain a 95% confidence limit for the test substance after 30 minutes contact time, as the data generated did not fit the models available for the calculation of this limit. The reference had an EC50 of 8.7 mg/L (95% CL 7.1–11), which is within the accepted range of 5-30 mg/L. The test result is considered applicable to the notified chemical based on the formula similarity.
CONCLUSION	The analogue is not harmful to sewage sludge microorganisms.
TEST FACILITY	Safepharm Laboratories (2007b)

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