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September 2014

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

1,2,3-Propanetricarboxylic acid, 2-(1-oxobutoxy)-, 1,2,3-trihexyl ester

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

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

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

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Director
NICNAS

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SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1507	Cintox Australia Pty Ltd	1,2,3-Propanetricarboxylic acid, 2-(1-oxobutoxy)-, 1,2,3-trihexyl ester	Yes	≤ 10 tonnes per annum	Component of inks, coatings and plastics

CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals* (GHS), as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

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

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

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

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

Environmental risk assessment
On the basis of the PEC/PNEC ratio and the reported use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

CONTROL MEASURES

Occupational Health and Safety

- No specific engineering controls, work practices or personal protective equipment are required for the safe use of the notified chemical itself. However, these should be selected on the basis of all ingredients in the formulation.

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

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

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Globally Harmonised System for the Classification and Labelling of Chemicals*

(GHS) as adopted for industrial chemicals in Australia, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation should be in operation.

Disposal

- Where reuse or recycling are unavailable or impracticable, dispose of the chemical in an environmentally sound manner in accordance with relevant Commonwealth, State, Territory and local government legislation.

Emergency procedures

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

Transport and Packaging

- The notified chemical is classified as UN 3082, environmentally hazardous substance, liquid, n.o.s./(n-butyryltri-n-hexyl citrate, 9, PG III. The transport and packaging of the notified chemical should be in accordance with State and Territory laws based on the requirements under the Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG Code) (NTC, 2007).

Regulatory Obligations

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

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

(1) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from component of inks, coatings and plastics (exclusive of plastics for food/potable water contact and children's toys), or is likely to change significantly;
- the amount of chemical being introduced has increased, or is likely to increase, significantly;
- the chemical has begun to be manufactured in Australia;
- additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

(Material) Safety Data Sheet
The (M)SDS of the notified chemical provided by the notifier was reviewed by NICNAS. The accuracy of the information on the (M)SDS remains the responsibility of the applicant.

ASSESSMENT DETAILS

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Cintox Australia Pty Ltd (ABN: 63 122 874 613)
Suite 1, Level 2
38-40 George Street
PARRAMATTA NSW 2150

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication: analytical data, degree of purity, impurities, use details, import volume and identity of manufacturer/recipients.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows: dissociation constant and acute inhalation toxicity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA (2014), Canada (1998), EU (2013) and Philippines (2000)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Citroflex B-6

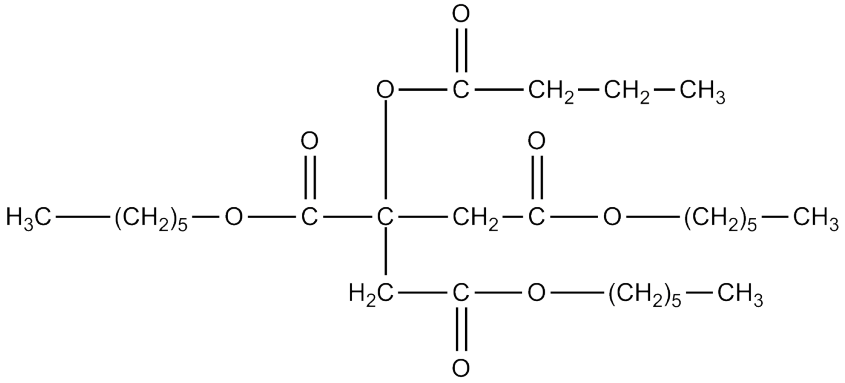
CAS NUMBER
82469-79-2

CHEMICAL NAME
1,2,3-Propanetricarboxylic acid, 2-(1-oxobutoxy)-, 1,2,3-trihexyl ester

OTHER NAME(S)
Butyryl tri-n-hexyl citrate
Butyryl trihexyl citrate
Citric acid, butanoyl-, trihexyl ester
Citroflex B 6
Trihexyl butyrylcitrate
Trihexyl citrate butyrate

MOLECULAR FORMULA
$C_{28}H_{50}O_8$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
514.69 Da

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

3. COMPOSITION

DEGREE OF PURITY
> 99%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: Clear oily liquid

Property	Value	Data Source/Justification
Freezing Point	< -20 °C	Measured
Boiling Point	247 °C at 103.3 kPa	Measured
Relative Density	0.994 at 21 °C	Measured
Vapour Pressure	2×10^{-12} kPa at 20 °C 6×10^{-12} kPa at 25 °C 1×10^{-9} kPa at 50 °C	Measured
Water Solubility	6.1×10^{-4} g/L at 20 °C	Measured
Fat Solubility	Miscible	Measured
Hydrolysis as a Function of pH	Conducted at 50°C 61% degradation (pH 7) 64% degradation (pH 9)	Measured
Partition Coefficient (n-octanol/water)	log Pow = > 4.11 at 21 °C	Measured
Surface Tension	56.0 mN/m at 20 °C	Measured
Adsorption/Desorption	log K_{oc} > 5.6	Measured
Dissociation Constant	Not determined	No dissociable functionality
Flash Point	234 ± 8 °C at 101.3 kPa	Measured
Flammability	Not flammable	Measured
Autoignition Temperature	384 ± 5 °C	Measured
Explosive Properties	Not explosive	Measured
Oxidising Properties	Predicted negative	Estimated

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

Reactivity
The notified chemical is expected to be stable under normal conditions of use. The notified chemical did not evolve gas on contact with water (ICI, 1991c).

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be imported in to Australia as a component of finished inks in writing instruments at ≤ 10% concentration.

The notified chemical may also be imported into Australia for use as a component of ink or coating products or as a component of plastic articles (exclusive of plastics for food/drinking water contact, children's toys or cosmetic/personal care products). The above uses may involve importing notified chemical in a neat form (> 99% concentration).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 2	< 3	< 4	< 5	< 10

PORT OF ENTRY
Melbourne and Sydney

TRANSPORTATION AND PACKAGING
The notified chemical is classified as UN 3082, environmentally hazardous substance, liquid, n.o.s./(n-butyryltri-n-hexyl citrate, 9, PG III. The transport and packaging of the notified chemical should be in accordance with State and Territory laws based on the requirements under the Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG Code) (NTC, 2007).

The notified chemical will be imported in writing instruments. If imported into Australia for use as a component of ink or coating products or as a component of plastic articles the notified chemical may be packaged in 1 – 10 L cans (coatings), 25 kg bags (resin compound pellets for moulding of plastic articles) or in 205 L drums when imported as the neat chemical.

USE
The notified chemical will be used as a component of finished inks in writing instruments at ≤ 10% concentration. It is anticipated by the notifier that in the future the notified chemical may be imported as a component of coatings at ≤ 10% concentration or in the neat form for reformulation in inks and coatings. The notified chemical may also be imported as a component of plastics (exclusive of plastics for food/potable water contact and children's toys) at ≤ 10% concentration (in final products) or ≤ 50% concentration (in masterbatches).

OPERATION DESCRIPTION

Imported as a component of finished inks and coatings
The notified chemical will be imported in finished ink products (writing instruments) which will be sold to end-users without repackaging.

In the future, the notified chemical may also be imported in finished coating products which will be sold to end-users without repackaging.

Imported in the neat form for reformulation into inks/coatings and masterbatch pellets (potential future use)
The notified chemical in the neat form will be blended with other components to form finished ink/coating products or masterbatch pellets. The reformulation processes are expected to involve transfer between the imported drums and the blending tank, mixing in an enclosed system, QA testing, dispensing of finished products into 1-10 L cans, and routine cleaning and maintenance. In the case of formulation of masterbatches the mixture will be extruded into a waterbath before being chopped into pellets of the appropriate length. The

notifier states that local exhaust ventilation is expected to be in place during such operations. The finished products are expected to contain the notified chemical at up to 10% concentration.

End use of masterbatches for reformulation into plastic articles (potential future use)
The masterbatch pellets will be transferred into the feeding hopper on the injection moulding machine either manually or by vacuum. Inside the injection-moulding machine the masterbatch pellets will be melted and injected into a mould before being cooled and ejected into a suitable receptacle.

End-Use of coatings and inks (potential future use)
At a typical printing facility, the ink cartridge is expected be inserted into the printing machine or a pipe or hose will be connected to the containers holding the ink formulations and the ink containing the notified chemical (at up to 10% concentration) will be transferred to the printing machines via an automated and enclosed process. Any residual ink within printing equipment will be wiped clean using rags and solvents.

At coating facilities, the spray application of coatings containing the notified chemical (at up to 10% concentration) is expected to be largely automated and conducted within a spray booth.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

EXPOSURE DETAILS
Transport and storage workers may come into contact with the notified chemical at up to 100% concentration only in the event of an accidental rupture of containers.

Reformulation of inks/coating
Reformulation processes are expected to be largely enclosed and automated; however workers may experience dermal or ocular exposure to the notified chemical at up to 100% concentration during transfer from the imported drums to the blending tank, during quality control testing and maintenance and cleaning tasks. Dermal and ocular exposure to workers should be mitigated through the notifier anticipated use of personal protective equipment (PPE) including protective clothing, impervious gloves and goggles. Inhalation exposure is expected to be low as the notified chemical have a low vapour pressure at ambient temperatures. Inhalation exposure to the notified chemical should be further minimised through the use of local exhaust ventilation and enclosed processes.

Masterbatch production and injection moulding
Masterbatch production and injection moulding processes are expected to be largely enclosed and automated; however, workers may be exposed (dermal and ocular) to the notified chemical at up to 100% concentration when weighing and transferring it to the mixer or injection moulding machine, during quality control testing and maintenance and cleaning tasks. Dermal and ocular exposure to workers should be mitigated through the notifier anticipated use of personal protective equipment (PPE). Workers may be exposed to dust particles generated from the compounding of plastic pellets. Inhalation exposure of dust particles to workers is expected to be limited by notifier anticipated use of breathing protection as necessary. Workers may be exposed to plastic articles containing the notified chemical; however after curing the notified chemical will be bound within a polymer matrix and hence will not be bioavailable.

End-use
Printer operators are not expected to be exposed to ink containing the notified chemical at up to 10% concentration, as the process is expected to be mainly automated and enclosed. However, dermal exposure is possible to the notified chemical during connection and disconnection of lines from containers of ink to the printing machine and during printer maintenance. Exposure is expected to be limited by the notifier anticipated use of PPE. Inhalation exposure may occur if aerosols containing the notified chemical are generated during the operation of the printers. However, this is expected to be minimised by local exhaust ventilation employed in areas surrounding printing machines.

At coating facilities, exposure to the notified chemical at up to 10% concentration is not expected during the largely automated and isolated spray coating processes (within spray booth). However, dermal, ocular and inhalation exposure to the notified chemical at up to 10% concentration may occur during opening, decanting

and mixing processes, during charging the spray equipment and when cleaning and maintaining spray equipment. Exposure should be minimised through the notifier anticipated use of PPE including protective clothing, impervious gloves, goggles and safety boots.

Once the inks or coatings are cured and dried, the notified chemical will be bound within a solid matrix and will not be bioavailable.

6.1.2. Public Exposure

Products containing the notified chemical are only intended for use in industrial settings and will not be sold to the public. The public may come into contact with inks, coatings and plastic articles containing the notified chemical. However, once the inks or coatings are dried, the notified chemical will be bound within a solid matrix and will not be bioavailable.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Mouse, acute oral toxicity	LD50 > 48,000 mg/kg bw; low toxicity
Rat, acute oral toxicity	LD50 > 20,000 mg/kg bw; low toxicity
Rat, acute oral toxicity	LD50 > 5,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly-irritating
Guinea pig, skin sensitisation – non-adjuvant test	no evidence of sensitisation
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL > 1,000 mg/kg bw/day
Mutagenicity – bacterial reverse mutation test	non mutagenic
Genotoxicity – in vitro mammalian cell gene mutation test	non genotoxic
Genotoxicity – in vitro chromosome aberration study	non genotoxic
Genotoxicity – in vivo mammalian bone marrow chromosome aberration test	non genotoxic

Toxicokinetics.

For dermal absorption, molecular weights below 500 are favourable for absorption and molecular weights above 1000 do not favour absorption (ECHA, 2012). Dermal uptake is likely to be low if the water solubility is below 1 mg/l and the rate of penetration may be limited by the rate of transfer between the stratum corneum and the epidermis if log P values are above 4 (ECHA, 2012). Based on the water solubility (0.61 mg/L at 20 ^{o}C), partition coefficient (log P_{ow} > 4) and the molecular weight (519 Da), the notified chemical has limited potential for dermal absorption.

Acute toxicity.

In studies conducted in mice and rats the notified chemical was found to be of low toxicity via the oral route (LD50 > 48,000 and 5,000 mg/kg bw respectively) and in a study conducted on rats of low toxicity (LD50 > 2000 mg/kg bw) via the dermal route.

Irritation and sensitisation.

Based on studies conducted in rabbits the notified chemical was not irritating to the skin and slightly irritating to the eyes.

The notified chemical showed no evidence of skin sensitisation in guinea pigs at concentrations up to 100% (intradermal induction concentration of 5%, topical induction concentration of 100% and topical challenge concentration of 100%) in a Magnusson and Kligman test and at concentrations up to 100% (topical induction concentration of 100% and topical challenge concentration of 100%) in a Buehler test.

Repeated dose toxicity.

The no-observed-adverse-effect level (NOAEL) was established by the study authors as 1000 mg/kg bw/day in rats (the highest dose tested) based on the absence of test substance related toxicologically significant effects at any of the doses administered.

Mutagenicity/Genotoxicity.

The notified chemical was not mutagenic in a bacterial reverse mutation assay and not genotoxic in an in vitro mammalian cell gene mutation test, in an in vitro chromosome aberration study and in an in vivo mammalian bone marrow chromosome aberration test.

Health hazard classification
Based on the available information, the notified chemical is not recommended for classification according to the *Globally Harmonised System for the Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia, or the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Based on the toxicological investigations conducted on the notified chemical, the notified chemical is expected to be of low hazard to human health.

During reformulation of inks, coatings and plastics there is potential for dermal, ocular and inhalation exposure to the notified chemical at up to 100% concentration. The expected enclosed and automated systems, local exhaust ventilation and use of PPE should minimise exposure and any potential risk.

During applications of inks and coatings containing the notified chemical there is potential for dermal, ocular and inhalation exposure to the notified chemical at up to 10% concentration. The expected use of PPE should minimise exposure and any potential risk.

Therefore, due to the low hazard and the use of engineering controls and PPE to limit exposure, the risk to the health of workers is not considered to be unreasonable.

6.3.2. Public Health
The notified chemical will be used in industrial settings only and will not be sold to the public. The public may come into contact with coatings and inks containing the notified chemical after application to surfaces. However, once the coatings and inks are cured and dried, the notified chemical will be bound to the surface to which it was applied and will not be bioavailable.

The formulation of the notified chemical into plastics will occur only in industrial settings. The public may come into contact the plastic products containing the notified chemical. However, the notified chemical will be bound within a polymer matrix and hence will not be bioavailable for exposure when used in the proposed manner.

Therefore, when used in the proposed manner, the risk to public health is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will not be manufactured within Australia. However, the notified chemical will be imported to Australia as a raw material for local reformulation of inks and coatings. During reformulation, spills and leaks are expected to be collected using suitable absorbent materials and placed in closed containers for disposal to landfill. The notified chemical is not expected to be released to sewers during reformulation. Empty containers are likely to be disposed of to landfill. Residues in the empty containers and waste water from equipment washings are expected to be collected and disposed of to waste facility.

The notified chemical is also expected to be used in plastics manufacture (injection moulding). During masterbatch plastic manufacture, release may result from residues in empty containers and spills and leaks during transfer operations. These will be collected using a suitable adsorbent material and will be disposed of to landfill. Once the notified chemical has been incorporated into the resin beads, releases are not expected to be significant. Waste resin beads will be swept or vacuumed and disposed of to landfill. No release to sewer is anticipated to occur. The release to landfill is expected to be < 0.5% of import volume.

RELEASE OF CHEMICAL FROM USE

When used as a component of inks (currently 100% of import volume), assuming that 50% of the ink and coating is applied to substrates and approximately 50% of the substrates enters the recycling stream, the amount of release to sewer from the recycling process is expected to be 2.5% of the total import volume (250 kg/year). The remainder of the notified chemical will be disposed of to landfill.

Injection moulding operations may result in releases to the environment from residue beads remaining in containers (0.1% or 10 kg of import volume). This amount of the notified chemical is expected to be disposed of to landfill with the containers. Spilled pellet would typically be collected and bagged, or could be melted and reprocessed or disposed of to landfill as normal industrial waste via a waste contractor. Similarly excess plastic residues remaining in the empty moulds would likely be either reused or discarded to landfill. There should be no release to sewer during this process.

RELEASE OF CHEMICAL FROM DISPOSAL

The notified chemical is expected to share the fate of the printed/coated articles which are expected to be disposed of to landfill. Empty containers containing residues of the notified chemical (up to 1% of the total import volume) are expected to be disposed of to landfill. Hence, the majority of the total import volume of the notified chemical is expected to be disposed of to landfill with a potential for some release to sewer. When used in plastic articles, the releases will not be significant as the notified chemical is expected to be trapped within the solid matrix.

7.1.2. Environmental Fate

A ready biodegradability study provided for the notified chemical indicated that in three of the four cultures tested with the notified chemical, a biodegradation level of 60% was reached. This test demonstrated that the notified chemical appears to have ultimately degraded to 60% in 55 days (half- life < 2 months) in the presence of a weak inoculum after an extended lag time. Based on this the notified chemical is not considered to be persistent in the aquatic environment. For the details of the environmental fate studies please refer to Appendix C. The notified chemical may have a potential for bioaccumulation due to its hydrophobic nature and low solubility in water. Available literature indicates that a chemical with ester functional group is expected to have low bioaccumulative potential (Van Den Berg, et al., 1995) through biotransformation in body. Therefore, the bioaccumulation potential of the notified chemical is not considered to be a concern.

Approximately half of the substrates to which the ink/coating containing the notified chemical is applied to is likely to be recycled. During recycling processes, waste substrates are repulped using a variety of chemical agents which, amongst other things, enhance detachment of ink/coating from the substrates. However, the notified chemical incorporated into the ink/coating matrix is unlikely to be released into the supernatant waters during recycling processes. The majority of the notified chemical is expected to sorb to sludge and sediment given the high *adsorption coefficient (log $K_{oc} \geq 5.6$)*. The majority of the notified chemical is expected to be disposed of to landfill where it is expected to degrade by biotic and abiotic processes to form water and oxides of carbon.

During plastic manufacture the notified chemical will be physically incorporated within the inert polymer matrix of moulded components and will share the fate of the articles. At the end of their useful life, articles containing the notified chemical are expected to be disposed of to landfill. In landfill, the notified chemical is bound within a polymer matrix and is not expected to be bioavailable or mobile due to its low solubility in water. It is expected to eventually degrade by biotic and abiotic processes in landfill to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

Considering the low water solubility of the notified chemical, and based on OECD Emission Scenario Documents on Pulp, Paper and Board Industry (ENV/JM/MONO(2009)25) for one individual paper recycling mill, the daily release of the notified chemical to waste water (E_{deink_water}) before any treatment plant, whether on-site or off-site, was calculated as follows:

$$E_{deink\_water} = C_{wastewater} \times Flow_{wastewater} \times Q_r$$
$$= 0.61 \text{mg/L} \times 12 \text{ m}^3\text{/t} \times 266 \text{ t/day}$$
$$= 1.95 \text{ kg/day}$$

E_{deink_water} (kg/day): Emission per day to waste water from de-inking or washing process during paper recycling; (OECD, ENV/JM/MONO(2009)25).

$C_{wastewater}$ (mg/L): Concentration of the notified chemical in waste water from paper recycling processes; 0.61 mg/L (i.e. the water solubility).

$Flow_{wastewater}$ (m^3/t recycled paper): Waste water generated from the whole plant; defaulted 12 m^3/day.

Q_r (t/day): Quantity of paper recycled at one site per day; defaulted 266 t/day.

Waste water from paper recycling processes is expected to be treated on-site before released to public sewer. Therefore, the daily release of the notified chemical to sewer ($E_{primary\_water}$) from one individual paper recycling mill was calculated as following:

$$E_{primary\_water} = E_{deink\_water} \times F_{primary\_water}$$
$$= 1.95 \text{ kg/day} \times 0.1$$
$$= 0.195 \text{ kg/day}$$

$E_{primary\_water}$ (kg/day): Emission to waste water after primary treatment of effluent;

$F_{primary\_water}$: Fraction of notified chemical remaining in waste water after primary treatment (0.1 for substance with water solubility of <1 mg/L).

The waste water containing the notified chemical released to sewer is expected to be further treated at the public sewage treatment plant (STP). The provided study reported a log P_{OW} of ≥ 4.11. Using a log P_{OW} of 4.11, it was estimated by SimpleTreat (EC, 2003) that up to 79% of the notified chemical will remain in the water column in the STP with 21% removed in sludge. Therefore, the daily release of the notified chemical to surface water (E_{STP_water}) from an individual STP was calculated as following:

$$E_{STP\_water} = E_{primary\_water} \times F_{STP\_water}$$
$$= 0.195 \text{ kg/day} \times 0.79$$
$$= 0.15 \text{ kg/day}$$

E_{STP_water} (kg/day): Emission to surface water from STP effluent;
F_{STP_water}: Fraction of notified chemical remaining in water after STP treatment.

For a conservative scenario, it is assumed that waste water will be released to a moderately-sized STP and be diluted by the daily average water flow at the STP. The resultant Predicted Environmental Concentration (PEC) in river was calculated as following:

$$PEC_{river} = E_{STP\_water} \div W_{daily\_individual\ STP\_flow}$$
$$= 0.15 \text{ kg/day} \div 115 \text{ ML/day}$$
$$= 1.34 \text{ µg/L}$$

$F_{daily\text{-}individual\ STP\_flow}$ (ML): Individual STP daily average water flow (115ML, Brisbane water, QSL).

Based on the above calculated PEC of 1.34 µg/L for river water, the PEC for seawater can be calculated as 0.13 µg/L by dividing by a factor of 10.

7.2. Environmental Effects Assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	96 h EC50 > 120 mg/L	Not harmful to fish (acute)
Fish Toxicity (Early-life)*	28 d LC50 ≥ 0.539 mg/L	Potentially harmful to fish (chronic)
	28 d NOEC = 0.252 mg/L	
Daphnia Toxicity	48 h EC50 = 0.38 mg/L	Very toxic to *Daphnia (acute)*
Daphnia Toxicity (Reproduction)	21 d EC50 > 0.416 mg/L	Very toxic to *Daphnia (chronic)*
	21 d NOEC = 0.0742 mg/L	
Algal Toxicity	96 h EC50 > 1.04 mg/L	Not harmful to alga (acute)
Earthworm**	14 d LC50 > 1000 mg/kg soil	Very slightly toxic to earthworm (acute)
	14 d NOEC = 1000 mg/kg soil	

* Less chronic toxicity for fish than for *Daphnia*, therefore the study was not summarised (Huntingdon, 2009a).
** Endpoints not used for risk assessment purposes, therefore the study was not summarised (Huntingdon, 2009b).

The notified chemical is considered to be very toxic to aquatic organisms based on the reported acute and chronic endpoints to *Daphnia* under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009). Therefore, the notified chemical is formally classified as "Acute Category 1; Very toxic to aquatic life" under the GHS. Based on the acute toxicity and potential for the notified

chemical to persist in the environment, the chronic hazard of the notified chemical has been formally classified as "Chronic Category 1; Very toxic to aquatic life with long lasting effects" under the GHS.

7.2.1. Predicted No-Effect Concentration

The Predicted No-Effect Concentration (PNEC) has been calculated using the most sensitive chronic endpoint for *Daphnia* (21 d NOEC = 0.0742 mg/L). An assessment factor of 50 was used considering acute endpoints for three trophic levels and chronic endpoints for two trophic levels are available.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Daphnia (NOEC)	0.0742	mg/L
Assessment Factor	50	
PNEC:	1.48	µg/L

7.3. Environmental Risk Assessment

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	1.34	1.48	**0.90**
Q - Ocean	0.13	1.48	**0.1**

The risk quotient (RQ = PEC/PNEC) has been calculated to be 0.9, which is close to 1.0. This may indicate a potential concern to the aquatic organisms. However, this estimate has been calculated based on the conservative case consideration. The RQ value is expected to be lower considering the following aspects:

- The notified chemical is also expected to be used for printing to other substrates in addition to paper. The notified chemical associated with these substrates is not expected to be released to water compartment.
- The notified chemical may be degraded via biodegradation in water which results in a lower PEC and a lower RQ.
- The $logP_{OW}$ of 4.11 was used for removal percentage calculation in STPs. The actual $logP_{OW}$ is expected to be higher. US EPA (2011) predicted a $logP_{OW}$ of 8.2, SimpleTreat predicted a removal of 85% using a $logP_{OW}$ of 6, indicating a four times lower of the RQ value.

Therefore, the release of the notified chemical to the aquatic environment is unlikely to reach ecotoxicologically significant concentrations based on its annual importation quantity.

On the basis of the PEC/PNEC ratio and the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < 20 °C

Method In house method.
Remarks Determined by visual interpretation.
Test Facility ICI (1991a)

Boiling Point 247 °C at 101.3 kPa

Method Directive 84/449/EEC A.2.
Remarks The study authors noted that due to the viscosity of the test substance the test method likely underestimated the boiling point, with visual interpretation of the experiment suggesting a boiling point of 270 ± 10 °C.
Test Facility ICI (1991a)

Relative Density 0.994 at 21 °C

Method In house method.
Remarks Determined using a capillary stoppered density bottle method.
Test Facility ICI (1991a)

Vapour Pressure 2×10^{-12} kPa at 20 °C; 6×10^{-12} kPa at 25 °C; 1×10^{-9} kPa at 50 °C

Method Directive 84/449/EEC.
Remarks Determined using weight-loss effusion manometry.
Test Facility ICI (1991b)

Water Solubility 6.1×10^{-4} g/L at 20 °C

Method OECD TG 105 Water Solubility.
EC Council Regulation No 440/2008 A.6 Water Solubility.
Remarks Flask Method
Test Facility ICI (1991a)

Fat (or n-octanol) Solubility Miscible

Method Similar to OECD TG 116 Fat Solubility of Solid and Liquid Substances.
Remarks Analytical Method: HPLC
The test substance was dissolved at a 1:1 ratio in the standard fat HB307.
Test Facility ICI (1991a)

Hydrolysis as a Function of pH 61% degradation at pH 7
64% degradation at pH 9

Method Described in EEC (1984) Official Journal of the European Communities, L251 Vol

pH	*T (°C)*	*120 hours*
7	50	61
9	50	64

Remarks A full study could not be conducted as the concentration of the test substance in the study needed to be less than 0.6 mg/L. The ability of the analytical method to include small changes in the concentration was not possible at an initial concentration of less than 0.6 mg/L.
Test Facility ICI (1991a)

Partition Coefficient (n-octanol/water) log Pow > 4.11

Method OECD TG 117 Partition Coefficient (n-octanol/water).
EC Council Regulation No 440/2008 A.8 Partition Coefficient.
Remarks HPLC Method
Test Facility ICI (1991a)

Surface Tension 56.0 mN/m at 20 °C

Method Directive 84/449/EEC A.5.
Remarks Concentration: saturated
Test Facility ICI (1991a)

Adsorption/Desorption log K_{oc} > 5.6

Method OECD TG 121 Adsorption Coefficient on Soil and Sewage sludge using High Performance Liquid Chromatography.
Remarks HPLC Method
Test Facility Huntingdon (2006)

Flash Point 234 ± 8 °C

Method BS4689:1980 Method for Determination of Flash and Fire Points of Petroleum Products: Cleveland Open Cup Method.
Test Facility ICI (1991c)

Flammability Not flammable

Method Directive 84/449/EEC A.13.
Remarks The test substance was determined to be not flammable as it did not spontaneously ignite on contact with air at ambient temperature and the flash point is not within the range of 21-55 °C.
Test Facility ICI (1991c)

Autoignition Temperature 384 ± 5°C

Method Directive 84/449/EEC A.15.
Test Facility ICI (1991c)

Explosive Properties Not explosive

Method Directive 84/449/EEC A.14.
Remarks Tested by BAM fall hammer and Koenen steel tube.
Test Facility ICI (1991c)

Oxidizing Properties Predicted negative

Method Directive 84/449/EEC.
Remarks The test substance was predicted to be not oxidising based on the chemical structure.
Test Facility ICI (1991c)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 401 Acute Oral Toxicity.
- Species/Strain: Rat/Crl:COBS CD (SD)BR and Mouse/Crl:COBS CD-1(ICR)BR
- Vehicle: The test substance was administered as supplied.
- Remarks - Method: The maximum concentration in mice was 48 g/kg bw and in rats it was 20 g/kg bw. Different volumes of the test substance were administered by gavage undiluted to achieve the required dose.

RESULTS

Mice

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	4 M	5,000	0/4
2	4 M	20,000	0/4
3	5 M	48,000	0/5

Rats

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 M	3,000	0/3
2	4 M	5,000	0/4
3	5 M	20,000	0/5

- LD50: Mice > 48,000 mg/kg bw, Rats > 20,000 mg/kg bw
- Signs of Toxicity: There were no mortalities at any dose in either mice or rats. There were no signs of systemic toxicity observed.
- Effects in Organs: There were no signs of gross pathological changes at necropsy.
- Remarks - Results: There were no adverse effects on bodyweight gain.

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

TEST FACILITY: Pfizer (1982)

B.2. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 401 Acute Oral Toxicity – Limit Test.
- Species/Strain: Rat/Sprague-Dawley (HSD:SD)
- Vehicle: Corn oil

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
5000 mg/kg	5 females and 5 males	5,000	0/10

- LD50: > 5,000 mg/kg bw
- Signs of Toxicity: No sign of systemic toxicity.
- Effects in Organs: No abnormalities noted at necropsy.

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

TEST FACILITY MAI (1991a)

B.3. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 402 Acute Dermal Toxicity – Limit Test.
Species/Strain Rabbit/Albino
Vehicle Test substance administered as supplied
Type of dressing Occlusive
Remarks - Method No significant protocol deviations.

RESULTS

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

LD50 > 2,000 mg/kg bw
Signs of Toxicity - Local Very slight erythema was noted at one abraded site at 24- and 48-hour observations. Very slight to slight desquamation of epidermis began within 6 or 7 days of dosing at 4 intact and 2 abraded sites which became normal by Day 9.
Signs of Toxicity - Systemic No treatment-related systemic toxicity was observed.
Effects in Organs No treatment-related gross pathological changes were apparent.
Remarks - Results All animals were alert and active and exhibited essentially normal body weight gains and food consumption with one exception. The study authors noted that reduced food consumption, soft faeces and/or diarrhoea and a progressive overall weight loss in one animal which was attributed to coccidiosis and was not considered to be treatment-related.

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

TEST FACILITY Pfizer (1991)

B.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
Species/Strain Rabbit/Albino
Number of Animals 6
Vehicle None
Observation Period 7 days
Type of Dressing Occlusive
Remarks - Method Abraded skin and intact skin sites on each animal were tested using a 24 hour exposure period. Observations were recorded at 24 and 72 hours after patch removal only.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Intact sites				
Erythema/Eschar	0	0	-	0
Oedema	0	0	-	0
Abraded sites				
Erythema/Eschar	0.08	1	< 48 hours	0
Oedema	0	0	-	0

*Calculated on the basis of the scores at 24 and 72 hours for ALL animals.

Remarks - Results	At 24 hours, barely perceptible erythema was noted at 1 abraded skin site and disappeared at 48 hours. At 7 days, slight desquamation of the epidermis was noted at another abraded skin site.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	Pfizer (1991)

B.5. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion.
Species/Strain	Rabbit/ Albino
Number of Animals	6
Observation Period	7 days
Remarks - Method	0.1 mL of test substance was instilled into a single eye of the test animals. The treated eyes were not rinsed after dosing and were observed for 7 days.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Conjunctiva: redness	0.11	2	< 48 hours	0
Conjunctiva: chemosis	0	0	-	0
Conjunctiva: discharge	0	0	-	0
Corneal opacity	0	0	-	0
Iridial inflammation	0	0	-	0

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

Remarks - Results	At 2.5 hours, mind reddening was noted in 3/6 eyes and only in 1 eye at 24 hours, which had subsided by 48 hours.
CONCLUSION	The notified chemical is slightly-irritating to the eye.
TEST FACILITY	Pfizer (1991)

B.6. Skin sensitisation

TEST SUBSTANCE	Notified chemical
METHOD	Similar to OECD TG 406 Skin Sensitisation - Buehler Test.
Species/Strain	Guinea pig/albino Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 10
INDUCTION PHASE	Induction Concentration: topical: 100%
Signs of Irritation	Very faint erythema was seen in 2 animals in the third induction. During the range finding test reactions were noted at 50% and 25% v/v but not for the neat material. The study authors speculated that this may be due to the chemical reacting to the alcohol it was prepared in.
CHALLENGE PHASE	Induction Concentration: topical: 100%
Remarks - Method	There was no vehicle only control (negative control) group in the main study as no vehicle was used. Two positive control groups received induction and challenge and challenge only, respectively. The positive

control was 2,4-dinitrochlorobenzene.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: challenge*	
		24 h	*48 h*
Test Group (induced)	100%	0/10	0/10
Test Group (non-induced)	100%	0/10	0/10
Positive Control Group (induced)	0.05%	4/5	2/5
Positive Control Group (non-induced)	0.05%	0/5	0/5

Remarks - Results: No skin reactions were noted in groups treated with the test substance for either induced or non-induced animals. In the positive control groups, progressing erythema was noted for the induced animals and no skin reactions were noted for non-induced animals.

CONCLUSION: There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: MAI (1991b)

B.7. Skin sensitisation

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 406 Skin Sensitisation - Magnusson and Kligman.

Species/Strain: Guinea pig/ albino Hartley

PRELIMINARY STUDY: Maximum Non-irritating Concentration:
intradermal: 0.5 - 5% (v/v) in mineral oil
topical: 75 - 100% (v/v) in ethyl alcohol

MAIN STUDY

Number of Animals: Test Group: 24 Control Group: 20

INDUCTION PHASE: Induction Concentration:
intradermal: 5% (v/v) in mineral oil
topical: 100%

Signs of Irritation: Not reported (creation of a local irritation prior to topical induction was not reported)

CHALLENGE PHASE: Induction Concentration:
topical: 100%

Remarks - Method: There was no additional satellite group in the control and in the top dose group for observation of reversibility, persistence, or delayed occurrence of toxic effects.

The negative control was mineral oil for intradermal injection and ethyl alcohol for topical application. The positive control was 1-chloro-2,4-dinitrobenzene in mineral oil for intradermal injection and 1-chloro-2,4-dinitrobenzene in petrolatum for topical application.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after: challenge*	
		24 h	*48 h*
Test Group	100%	2/24	0/24

Negative Control Group	100%	0/10	0/10
Positive Control Group	5%	10/10	10/10

Remarks - Results: Slight patchy erythema was noted in a single male and a single female in the treatment group following the challenge application. These observations were present at the 24 hour interval only. No reactions were noted in the negative control group and moderate to severe erythema were noted in all animals in the positive control group.

CONCLUSION: There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.

TEST FACILITY: IRDC (1992)

B.8. Repeat dose toxicity

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.

Species/Strain: Rats/Sprague-Dawley
Route of Administration: Oral – gavage
Exposure Information: Total exposure days: 28 days
Dose regimen: 7 days per week
Post-exposure observation period: 0 (all animals were sacrificed within 24 h after the last treatment)
Vehicle: Corn oil
Remarks - Method: No significant protocol deviations.

A range finding test was conducted at doses up to 5,000 mg/kg bw/day for four days with no signs of toxicity observed.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	5 per sex	0	0/10
low dose	5 per sex	250	0/10
mid dose	5 per sex	500	0/10
high dose	5 per sex	1000	0/10

Mortality and Time to Death
No test substance related deaths occurred during the study.

Clinical Observations
One female animal in the 500 mg/kg bw/day group appeared thin on days 13-18. All other animals appeared normal. No notable differences in body weight gain were noted in males or females. Significantly higher food consumption was noted in female high dose animals during week three but at no other time.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Significantly lower aspartate aminotransferase (AST) (male) and blood albumin (female) and significantly higher creatinine (male) and blood calcium (female) were noted in 1000 mg/kg bw/day group. Significantly decreased blood albumin (female) was noted in 500 mg/kg bw/day group. Significantly lower AST (male) and blood albumin (female) were noted in 250 mg/kg bw/day group.

There were no significant differences in haematology for males and females.

Significantly lower pH was noted in the female 500 mg/kg bw/day group and both male and female 1000 mg/kg

bw/day groups. Extremely high urinary protein was noted in two male animals of 1000 mg/kg bw/day group.

Effects in Organs
Statistically significant increases in relative liver weight were noted in male animals of 500 mg/kg bw/day and 1000 mg/kg bw/day groups. No differences were noted in absolute liver weight.

No significant effects noted in the organs at necropsy.

Remarks – Results
No systemic toxicity was observed in body weight and food consumption. The changes in clinical pathology were not considered by the study authors to be biologically significant. A male animal in high dose group having excessive urinary protein was considered by the study authors to be an isolated incident. The liver weight changes were not considered by the study authors to be biologically significant.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 1000mg/kg bw/day in this study, based on the absence of test substance related toxicological significant effects at any of the doses administered.

TEST FACILITY MAI (1991c)

B.9. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100, *E. coli*: WP2uvrA
Metabolic Activation System	Rat S9 fraction from Aroclor 1254 induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 667-10,000 µg/plate b) Without metabolic activation: 667-10,000 µg/plate
Vehicle	Ethanol
Remarks - Method	A dose range finding study (10-10,000 µg/plate) was performed on some strains (TA100 and WP2uvrA) in both the presence and absence of metabolic activation system. In the main tests, aliquots of 0.05 mL of either test substance, positive, or negative control solution was used at five concentrations up to 10,000 µg/plate. The negative control was ethanol and positive controls were methanesulfonic acid, methyl ester, 2-nitrofluorene, ICR-191, sodium azide, in the absence of S9 mix and 2-aminoanthracene in the presence of S9 mix.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 10,000	> 10,000	≥ 667	Negative
Test 2		> 10,000	≥ 667	Negative
Present				
Test 1	> 10,000	> 10,000	≥ 667	Negative
Test 2		> 10,000	≥ 667	Negative

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

All the positive control chemicals used in the test induced marked

increases in the frequency of revertant colonies thus confirming 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 MAI (1991d)

B.10. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

METHOD Similar to OECD TG 471 Bacterial Reverse Mutation Test.
Plate incorporation procedure

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100
Metabolic Activation System	Rat S9 fraction from Aroclor 1254 induced rat liver
Concentration Range in Main Test	a) With metabolic activation: 20 – 2,000 µg/plate b) Without metabolic activation: 20 – 10,000 µg/plate c) In vivo metabolic activation (mouse urine): 0.05 – 1 mL/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	The test substance was tested without metabolic activation on the TA 1537, TA 100 and TA 98 strains. It was then tested with metabolic activation on all four strains. In addition the urine of mice treated at concentrations of 50, 500 and 1000 mg/kg bw with the test substance was tested against all four strains of bacteria.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	> 10,000	≥ 500	Negative
Test 2				
Present				
Test 1	-	> 2,000	≥ 500	Negative
Test 2		> 2,000	≥ 500	Negative
In vivo		*(mL/plate)*	*(mL/plate)*	
Test 1	-	> 1	> 1	Negative
Test 2		> 1	> 1	Negative

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

All the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies thus confirming 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 Pfizer (1983)

B.11. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical

METHOD	Similar to OECD TG 476 In vitro Mammalian Cell Gene Mutation Test.
Species/Strain	Mouse
Cell Type/Cell Line	Lymphoma/L5178Y
Metabolic Activation System	Rat S9 fraction from Aroclor 1254 induced rat liver
Vehicle	Dimethyl sulfoxide
Remarks - Method	The preliminary toxicity data indicated approximate LD50 value for 3 hours exposure of 5-10 × 10^{-4} M.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Expression Time*	*Selection Time*
Absent				
Test 1	168*, 224*, 299*, 398*, 531*, 709*, 946*	3 hours	48 hours	10 days
Test 2	53*, 71*, 94*, 126*, 168*, 224*, 299*, 398*, 531*, 709*	3 hours	48 hours	10 days
Present				
Test 1	126*, 168*, 224*, 298*, 398*, 531*, 709*, 946*	3 hours	48 hours	10 days

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	≥ 168	Not specified	Positive
Test 2		> 709	Not specified	Negative
Present				
Test 1	-	> 946	Not specified	Negative

Remarks - Results	In the absence of metabolic activation, the notified chemical produced a slight but statistically significant increase in mutation frequency at dose levels permitting acceptable cell survival. However, the notified chemical did not produce and increase in the mutation frequency in a second test in the absence of metabolic activation, the study authors considered the slight increase in the first test was spurious. It should be noted that the cytotoxicity seen in the first test without metabolic activation was not replicated in the other two tests in this study.
CONCLUSION	The notified chemical was not clastogenic to L5178Y mouse lymphoma cells treated in vitro under the conditions of the test.
TEST FACILITY	Pfizer (1983)

B.12. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Strain	Human
Cell Type/Cell Line	Peripheral blood lymphocytes
Metabolic Activation System	Rat S9 fraction from Aroclor 1254 induced rat liver
Vehicle	Ethanol
Remarks - Method	Doses up to 1.5 µg/mL were chosen in a dose-finding study (using continuous treatment method)) on the basis that the percentage of cells with structural aberrations was not significantly increased above that of the solvent control at either 20 or 44 hour harvest in the absence of metabolic activation. The negative control was ethanol and positive controls were mitomycin C in the absence of S9 mix and cyclophosphamide in the presence of S9 mix.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0.2*, 0.4*, 0.8*, 1.5*	20	20
Test 2	0.2*, 0.4*, 0.8*, 1.5*	44	44
Present			
Test 1	0.2*, 0.4*, 0.8*, 1.5*	4	20
Test 2	0.2*, 0.4*, 0.8*, 1.5*	4	44

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	> 1.5	> 1.5	≥ 1.5	Negative
Test 2	> 1.5	> 1.5	≥ 1.5	Negative
Present				
Test 1		> 1.5	≥ 1.5	Negative
Test 2		> 1.5	≥ 1.5	Negative

Remarks - Results: The test substance did not induce any statistically significant increases in the frequency of cells with aberrations in any of the exposure groups.

CONCLUSION: The notified chemical was not clastogenic to human peripheral blood lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY: MAI (1991e)

B.13. Genotoxicity – in vivo

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 475 Mammalian Bone Marrow Chromosome Aberration Test.

Species/Strain: Mouse/CD-1

Route of Administration: Oral

Vehicle: Distilled water

Remarks - Method: Brief protocol was reported.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	Not reported	Not reported	6, 12, 24
II (low dose)	5	500	6
III (high dose)	5	1000	6, 12, 24

RESULTS

Doses Producing Toxicity: Not stated

Genotoxic Effects: Genotoxic effects were similar in treated groups and the control and within historical control values.

Remarks - Results: There was no evidence provided within the study report to confirm that the test substance was transported to the bone marrow.

CONCLUSION: The notified chemical was not clastogenic under the conditions of this in vivo mammalian bone marrow chromosome aberration test.

TEST FACILITY: Pfizer (1983)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 310 Ready Biodegradability CO_2 in Sealed vessels (Headspace Test) and Modified Sturm Test, Procedure C.4-C of the Annex to Directive 92/69/EEC, OECD Procedure 301B (adopted 1992).

Inoculum	Activated sludge
Exposure Period	57 days
Auxiliary Solvent	Acetone
Analytical Monitoring	Theoretical Inorganic Carbon (ThIC)
Remarks - Method	The test was conducted according to the guidelines above. No significant deviations from the test guidelines were reported. Control substances employed in both test systems were hexadecane in the sealed vessel CO_2 evolution test and sodium benzoate and hexadecane in the Modified Sturm test. As the test substance was poorly soluble in water, a stock solution in acetone was prepared. An aliquot (10 mL containing 45.9 mg of test substance) were added to clear empty bottles. Acetone was evaporated using stream of nitrogen to deposit the test substance in the vessels. The test and reference substances were employed at nominal concentrations of 10.3 and 10 mg/L respectively. A dispersing agent (Tween 85) was employed in two of the Modified Sturm test cultures.

RESULTS

Sealed Vessel CO_2 Evolution Test

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
3	0.5	3	21.5
7	0	7	35.4
14	0	14	65.9
21	06	21	74.9
28	3.6	28	80.4
42	28.9	42	87.7
56	37.6	56	85.7

Modified Sturm Test

Day	Culture 1	Culture 2	Culture 3 + Tween 85	Culture 4 + Tween 85
	% Degradation			
4	0	0	0	0
8	0	0	0	0
14	nt	nt	2	2
28	3	5	7	15
43	29	43	nt	nt
57	42	65	8	66

nt = not tested

Remarks - Results: All validity criteria for the test were satisfied.

Air flow in the Modified Sturm test culture fell below the minimum recommended rate (30ml/minute) on one occasion in two cultures. However, this was not considered to be significant, nor to have affected the integrity of the test.

In the Sealed Vessel CO_2 evolution test, 3.6% degradation was observed at the end of day 28. However, the degradation increased to a range of 21-63.8% at the end of day 56 demonstrating that the test substance is ultimately degradable under stringent test conditions. .

In the Modified Sturm test, a lag period of 20 days occurred in test mixtures containing Tween 85 and between 28-34 days in test mixture without Tween 85. Degradation proceeded to 11% on day 22, 24% on day 28, 62% on day 50 and 66% on day 57. This demonstrated that the test substance is ultimately degradable under stringent test conditions.

CONCLUSION The notified chemical cannot be considered readily biodegradable. However, it is ultimately biodegraded in the presence of weak inoculum at a concentration above its limit of water solubility following extended incubation.

TEST FACILITY Huntingdon (2008)

C.1.2. Ready biodegradability

TEST SUBSTANCE Notified chemical

METHOD OECD TG 301 C Ready Biodegradability: Modified MITI Test (I).

Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	Biochemical Oxygen demand (BOD)
Remarks - Method	The test was conducted according to the guidelines above. No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Sodium acetate*	
Day	*% Degradation*	*Day*	*% Degradation*
5	0	5	64
10	0	10	69
15	0	15	70
20	0	20	72
25	0	25	69
28	<1	28	71

Remarks - Results All validity criteria for the test were satisfied. The toxicity control exceeded 70% and 71% biodegradation after 14 and 28 days respectively, implying that the test substance was not toxic to micro-organisms. Since biodegradation reached > 1%, the test substance can be classed as readily biodegradable.

CONCLUSION The notified chemical is not readily biodegradable.

TEST FACILITY ICI (1991d)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD
- Species: Rainbow trout (*Oncorhynchus mykiss*)
- Exposure Period: 96 hours
- Auxiliary Solvent: Dimethylformamide (≤ 0.24 mL/L)
- Water Hardness: 182-186 mg $CaCO_3$/L
- Analytical Monitoring: Analysis of the test concentration was attempted using HPLC/UV method at start and end of the test period.
- Remarks – Method: The test was conducted following the above test guideline and good practice laboratory practice (GLP).
  Rainbow trout were exposed to a geometric series of five test concentrations, a solvent control, and a blank well water control, all in duplicates. The nominal loading rates used in the study were 15.6, 25.9, 43.2, 72.0, and 120 mg/L.

RESULTS

Nominal loading rate (mg/L)	*Number of Fish*	*Mortality*				
		1 h	*24 h*	*48 h*	*72 h*	*96 h*
Blank control	20	0	0	0	0	0
Solvent control	20	0	0	0	0	0
15.6	20	0	0	0	0	0
25.9	20	0	0	0	0	0
43.2	20	0	0	0	0	0
72.0	20	0	0	0	0	0
120	20	0	0	0	0	0

- LC50: > 120 mg/L at 96 hours (nominal)
- NOEC: 120 mg/L at 96 hours (nominal)
- Remarks – Results: All the test validity criteria were met. Due to the low water solubility, the analysis of test concentration varies significantly at two different loading rates. The test concentration did not show clear decline in the concentration. Therefore, the endpoints were present on the basis of nominal loading rates. Since no mortality and adverse effects were observed at all the test levels, the notified chemical is considered to be not harmful to fish up to the limit of water solubility.

CONCLUSION: The notified chemical is not harmful to fish.

TEST FACILITY: Wildlife (1991a)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE: Notified chemical

METHOD
- Species: *Daphnia magna*
- Exposure Period: 48 hours
- Auxiliary Solvent: Dimethylformamide (≤ 0.10 mL/L)
- Water Hardness: 150 mg $CaCO_3$/L
- Analytical Monitoring: Analysis of the test concentration was conducted using HPLC/UV method at start and end of the test period.
- Remarks - Method: The test was conducted following the above test guideline and good practice laboratory practice (GLP).

Rainbow trout were exposed to a geometric series of five test concentrations, a solvent control, and a blank well water control, all in duplicates. The nominal test concentrations used in the study were 0.07, 0.12, 0.2, 0.34, and 0.56 mg/L.
EC50 value and 95% confidence limits (CL) were calculated using the computer program of Stephen (1978). The binomial method was used to evaluate mortality at 48 hours. The no effect concentration (NOEC) was determined by visual examination of the mortality and effects data.

RESULTS

Nominal Concentration (mg/L)	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
Blank control	20	0	5*
Solvent control	20	0	1**
0.07	20	0	0
0.12	20	1**	3**
0.20	20	0	0
0.34	20	1**	2**
0.56	20	0	15

* Three of five dead animals were stuck to the beaker wall above the water level.

** Dead animals were stuck to the beaker wall above the water level.

LC50	0.38 mg/L (95% CL 0.20-0.56 mg/L) at 48 hours (nominal)
NOEC	0.2 mg/L at 48 hours (nominal)
Remarks - Results	All the test validity criteria were met. The analysis of test concentration at two different loading rates indicated declines of 21% to 14% at the end of the test. Therefore, the endpoints were present on the basis of nominal loading rates. Since no mortality and adverse effects were observed at all the test levels, the notified chemical is considered to be not harmful to fish up to the limit of water solubility. The notified chemical is considered to be very toxic to *Daphnia* based on the test outcome.

CONCLUSION The notified chemical is very toxic to *Daphnia.*

TEST FACILITY Wildlife (1991b)

C.2.3. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 211 *Daphnia magna*, Reproduction Test.

Species	*Daphnia magna*
Exposure Period	21 d
Auxiliary Solvent	Tetrahydrofuran (0.1 mL/L)
Water Hardness	Total hardness 254-270 mg $CaCO_3$/L
Analytical Monitoring	The test concentrations were measured by gas chromatography using mass spectrometric detection (GC-MS) method.
Remarks - Method	The test was conducted following the above test guideline and good practice laboratory practice (GLP). Groups of ten, individually-housed *Daphnia* were exposed for 21 days to the test substance prepared at nominal concentrations of 0.0128, 0.032, 0.08, 0.2, and 0.5 mg/L (highest concentration limited ·by the solubility of the test substance in the media). The overall geometric mean measured concentration was 0.0114, 0.0294, 0.0742; 0.196 and 0.416 mg/L, respectively. On the days of preparation, the test solutions were clear and colourless. The test media were renewed daily and the solvent stocks on a weekly basis during the definitive test. There were two control groups, one of

ten *Daphnia* exposed to dilution medium alone and the other of twenty *Daphnia* exposed to dilution medium containing tetrahydrofuran (0.1 mL/L).

Mean measured concentration, cumulative mean number of offspring released per adult daphnid (*Daphnia magna*), standard deviations (SD) and survival of parental daphnids.

	Nominal loading Rate (mg/L)						
Test Day 21	*Blank control*	*Solvent control*	*0.0114*	*0.0294*	*0.0742*	*0.196*	*0.416*
Mean no. of live offspring (SD)	77.1 (5.9)	78.1 (7.07)	75.2 (7.41)	78.2 (5.61)	76.1 (4.53)	74.6 (4.95)	63.3 (14.0)
Mean no. of live offspring excluding floaters (SD)	77.1 (5.9)	78.1 (7.07)	75.2 (7.41)	78.2 (5.61)	75.8 (4.34)	70.6 (8.87)	39.1 (14.8)
Mean length of survival parent daphnids (mm)	3.7	3.7	3.6	3.7	3.7	3.7	3.6
% Survival of adult *Daphnids*	100	95	90	100	100	100	80

21 day EC50 (Immobilization)	> 0.416 mg/L (top test mean concentration)
21 day EC50 (Reproduction)	> 0.416 mg/L (top test mean concentration)
21 day NOEC	0.0742 mg/L

Remarks - Results

The geometric mean measured concentration was used to express the endpoints. Based on parental mortality, the no observed effect concentration (NOEC) was > 0.416 mg/L. Based on floating, the NOEC was 0.0742 mg/L.

Statistical analysis of the body lengths of surviving adults after 21 days of exposure to the notified chemical indicated that growth was adversely affected at 0.416 mg/L, giving a NOEC of 0.196 mg/L.

Statistical analysis of the total number of live neonates produced by each surviving adult in the test groups compared to the solvent control group indicated that reproduction was significantly reduced at a concentration of 0.4 16 mg/L (-1 9.5%; $p < 0.001$), giving a NOEC of 0.196 mg/L.

Based on the low NOEC for floating, the notified chemical is considered to be very toxic to *Daphnia* on a chronic basis.

CONCLUSION

The notified chemical is chronically very toxic to *Daphnia.*

TEST FACILITY

Huntingdon (2009c)

C.2.4. Algal growth inhibition test

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 201 Alga, Growth Inhibition Test

Species: Green alga (*Selenastrum capricornutum)*

Exposure Period: 96 hours

Concentration Range: Nominal: 1 mg/L; Actual: 1.04 mg/L (0 hour)

Auxiliary Solvent: Dimethylformaide (0.1 mL/L)

Water Hardness: Not provided

Analytical Monitoring: The test concentration was analysed at test start and end using HPLC method.

Remarks - Method: The study was conducted following the above test guideline and good practice laboratory practice (GLP). Following two range-finding tests, a definitive test was conducted at a nominal concentration of 1 mg/L in six replicates.

RESULTS

Biomass		*Growth*	
E_bC50	*NOEC*	*E_rC50*	*NOEC*
mg/L at 96 h	*mg/L*	*mg/L at 96 h*	*mg/L*
> 1.04	1.04	> 1.04	1.04

Remarks - Results	The test concentration at start was determined to be 1.04 mg/L at test start and below the limit of detection at test end. The endpoints were present based on the initial measured concentration. No inhibition of the alga growth was detected at the range-finding test and the definitive test. Therefore, the 96-hour EC50 was reported as >1.04 mg/L. The no-observed-effect concentration (NOEC) was reported as 1.04 mg/L, which is above the reported water solubility. Considering no effects were detected at the concentration above the water solubility, the notified chemical is considered to be not harmful to green alga (*Selenastrum capricornutum)* up to the limit of water solubility.
CONCLUSION	The notified chemical is considered to be not harmful to green alga.
TEST FACILITY	Huntingdon (2005)

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