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April 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

KH-075

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

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/1547	Cintox Australia Pty Ltd	KH-075	Yes	≤ 20 tonnes per annum	Component of lubricant oil within sealed units

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Reproductive Toxicity (Category 2)	H361 – Suspected of damaging fertility or the unborn child

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 phrase:
R63: Possible risk of harm to the unborn child

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 assessed use pattern, the notified chemical is not considered to pose an unreasonable risk to the environment.

Recommendations

REGULATORY CONTROLS

Hazard Classification and Labelling

- The notified chemical/polymer should be classified as follows:
  - Reproductive Toxicity (Category 2): H361 – Suspected of damaging fertility or the unborn child

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

CONTROL MEASURES

Occupational Health and Safety

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

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

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

- A copy of the (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 not appropriate, dispose of the notified chemical in an environmentally sound manner in accordance with relevant Commonwealth, state territory and local government legislation.

Storage

- The handling and storage of the notified chemical should be in accordance with the Safe Work Australia Code of Practice for *Managing Risks of Hazardous Chemicals in the Workplace* (SWA, 2012) or relevant State or Territory Code of Practice.

Emergency procedures

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

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
  - the notified chemical is intended to be used in products directly available to the public;

or

(2) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from a component of lubricant oil, 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: chemical name, CAS number, molecular and structural formulae, molecular weight, analytical data, degree of purity, impurities, additives/adjuvants, use details and import volume.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule data requirements is claimed as follows: flammability limits, acute inhalation toxicity.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Korea (2012), China (2012)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
KH-075

MOLECULAR WEIGHT
> 400 Da

ANALYTICAL DATA
Reference NMR, IR, HPLC, GC-MS and UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY
> 95%

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20 °C AND 101.3 kPa: clear, slightly yellow liquid

Property	Value	Data Source/Justification
Melting Point/Freezing Point	< -25 °C	Measured
Boiling Point	Decomposition without boiling from ~180 °C at 101.3 kPa	Measured
Density	990 kg/m^3 at 20 °C	Measured
Vapour Pressure	2×10^{-7} kPa at 25 °C	Measured
Water Solubility	< 1-2.5 × 10^{-3} g/L at 20 °C	Measured
Hydrolysis as a Function of pH	Not determined	Notified chemical has limited solubility in water
Partition Coefficient (n-octanol/water)	log Pow ≥ 4.9 at 20 °C	Measured
Surface Tension	54.5 mN/m at 20 °C	Measured
Adsorption/Desorption	log K_{oc} ≥ 4 at 20 °C	Measured
Dissociation Constant	Not determined	Notified chemical contains no dissociable

		functionalities
Flash Point	216 °C at 101.4 kPa	Measured
Autoignition Temperature	> 400 °C	Measured
Explosive Properties	Predicted negative	Contains no functional groups that would imply explosive properties
Oxidising Properties	Predicted negative	Contains no functional groups that would imply oxidative properties

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

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

Physical hazard classification
Based on the submitted physico-chemical data depicted in the above table, the notified chemical is not recommended for hazard classification according to the *Globally Harmonised System 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 at ≤ 100% concentration.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	≤ 20	≤ 20	≤ 20	≤ 20	≤ 20

PORT OF ENTRY
Ports throughout Australia

IDENTITY OF MANUFACTURER/RECIPIENTS
Cintox Australia Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical (at ≤ 100% concentration) will be imported as oil pre-charged in manufactured articles, or in 18 L cans/205 L drums, and is expected to be distributed within Australia by road and/or rail.

USE
The notified chemical will be used as a component (≤ 100%) of lubricant oil within sealed units.

OPERATION DESCRIPTION
The majority of the notified chemical will be imported as oil contained within sealed manufacturing equipment that will ultimately be installed at end-use sites.

During servicing of the units, as required, trained technicians will manually drain the spent oil into a container for disposal and manually transfer or hand-pump replacement oil directly from the import container into the equipment. The unit will then be re-sealed prior to use. The equipment will not be running during servicing.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

CATEGORY OF WORKERS

Category of Worker	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage	0.5-2	12-24
Installation	2-8	200
Servicing	1	300

EXPOSURE DETAILS

Transport, storage and installation workers may come into contact with the notified chemical (at ≤ 100% concentration) only in the event of accidental rupture of containers or as a result of damage to the manufactured equipment.

During servicing of the equipment, dermal and ocular exposure of technicians to spillages of the notified chemical may occur. Spills are expected to be cleaned-up using rags and the notifier has indicated that technicians will wear personal protective equipment (PPE), such as overalls, gloves and eye protection to minimise exposure. Inhalation exposure is not expected.

6.1.2. Public Exposure

The notified chemical will not be directly available to the public, as it will be contained within manufactured equipment. Therefore, no direct exposure of the public to the notified chemical is expected.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, toxicokinetic	Gastrointestinal absorption was slow and incomplete; T_{max} = 3.4 to 7.2 hours Bioavailability = 4.8% to 13.1%
Rat, acute oral toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw; low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – Local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity – 14 days	NOAEL = 1000 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days	NOAEL = 100 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non-mutagenic
Genotoxicity – in vitro chromosome aberration	non-clastogenic
Genotoxicity – in vivo micronucleus test	non-clastogenic
Rat, reproductive and developmental toxicity screening study	NOAEL(paternal) = 1000 mg/kg bw/day NOAEL(maternal) = 1000 mg/kg bw/day NOAEL(reproductive) = 1000 mg/kg bw/day NOAEL(developmental) = 100 mg/kg bw/day
Developmental toxicity (rat)	NOAEL(maternal) = 1000 mg/kg bw/day NOAEL(foetal) = 1000 mg/kg bw/day
Two-generation reproductive toxicity (rat)	NOAEL(paternal) = 300 mg/kg bw/day NOAEL(maternal) = 300 mg/kg bw/day NOAEL(reproductive) = 300 mg/kg bw/day NOAEL(developmental) = 100 mg/kg bw/day

Toxicokinetics.

Toxicokinetic data in rats demonstrated that gastrointestinal absorption of the notified chemical is slow and incomplete, with 9.9%, 13.1% and 4.8% oral bioavailability when administered by gavage at doses of 150, 450

and 1000 mg/kg bw, respectively. Treatment related effects in various repeated dose oral toxicity studies in rats support the potential for systemic GI absorption.

Based on the molecular weight (> 400 Da), water solubility (< 1 – 2.5 x 10^{-3} g/L at 20 °C) and partition coefficient (log Pow ≥ 4.9 at 20 °C) of the notified chemical, absorption across the skin may occur, although the extent of absorption may be limited. The notified chemical may also be absorbed via the respiratory tract.

Acute toxicity.
The notified chemical was of low acute oral (LD50 > 2000 mg/kg bw) and dermal (LD50 > 2000 mg/kg bw) toxicity in rats. No acute inhalation toxicity data were provided for the notified chemical.

Irritation.
The notified chemical was non-irritating to the skin of rabbits but was a slight eye irritant to rabbits.

Skin sensitisation.
There was no evidence of skin sensitisation in a local lymph node assay (LLNA) in mice.

Repeated dose toxicity.
In a 14-day repeated dose oral gavage study, rats (3/sex/dose) were treated with the notified chemical at 100, 300 or 1000 mg/kg bw/day. The NOAEL was established as 1000 mg/kg bw/day, based on the lack of treatment related adverse effects.

In a 90-day repeated dose oral gavage study, rats (10/sex/dose) were treated with the notified chemical at 0, 100, 300 or 1000 mg/kg bw/day. A NOAEL of 100 mg/kg bw/day was established by the study authors based on adverse effects seen in the 300 or 1000 mg/kg bw/day treatment groups. Effects observed included organ weight increases along with changes in the clinical chemistry.

Mutagenicity/Genotoxicity.
The notified chemical was not mutagenic in a bacterial reverse mutation study. The notified chemical was not clastogenic in an *in vitro* chromosome aberration test or in an *in vivo* micronucleus study.

Reproductive/developmental toxicity.
In a reproductive/developmental screening study, rats (10/sex/dose) were administered the notified chemical by gavage at 0, 100, 300 or 1000 mg/kg bw/day for 15 days before mating and until completion of the study when the offspring were 7 days old. The NOAEL for paternal, maternal and reproductive toxicity was established as 1000 mg/kg bw/day, based on the lack of treatment related adverse effects. The NOAEL for developmental toxicity was established as 100 mg/kg bw/day, based on decreased offspring weights at 300 and 1000 mg/kg bw/day. There was evidence of an *in utero* effect in the absence of maternal toxicity based on the decreased offspring weights.

In a developmental toxicity study, mated female rats (20/dose) were administered the notified chemical by gavage on gestation day 6 to 19 at 0, 100, 300 or 1000 mg/kg bw/day. Effects noted during the study included decreased body weight gains in adult animals treated at 1000 mg/kg bw/day, along with decreased foetal weights in the male offspring of this group. The effects were not considered by the study authors to be biologically significant effects of treatment and therefore the NOAEL for both maternal and developmental toxicity was established as 1000 mg/kg bw/day.

In a two-generation reproductive toxicity study, P generation animals were administered the test substance by gavage for 10 weeks at 0, 30, 100 or 300 mg/kg bw/day (28/sex/dose) prior to mating. Dosing was continued throughout mating, pregnancy and lactation. Overall treatment of P generation animals with the test substance was approximately 18 weeks. Treatment in the offspring was initiated around the time of weaning and continued for 10 weeks during which the animals were mated and then allowed to produce another generation. The paternal NOAEL was established as 300 mg/kg bw/day, as although hyaline droplet nephropathy was present in the kidneys of F1 generation males, this was considered by the study authors to be a rat specific effects and therefore not relevant to humans. The maternal NOAEL was also set as 300 mg/kg bw/day with the study authors considering that no clear treatment related body weight, organ weight or histopathological changes present. The reproductive NOAEL was established as 300 mg/kg bw/day, based on the lack of treatment related adverse changes in reproductive performance. The developmental NOAEL was established as 100 mg/kg bw/day, based on a decrease in the viability index of the F1 offspring and body weight reductions in

the offspring of both generations. This finding is evidence of an *in utero* effect in the absence of maternal toxicity.

There was evidence of decreased birth weights in offspring following repeated oral administration of the notified chemical to maternal animals before, during and after pregnancy, in both the reproductive/developmental screening study and the two generation reproductive toxicity study in rats. There was also evidence of a decrease in the viability index of the F2 animals in the two generation reproductive toxicity study in rats. The effects occurred in the absence of maternal toxicity in both studies and are likely due to *in utero* exposure to the notified chemical, as offspring had not been dosed directly with the notified chemical and because the decreased weights were recorded shortly after birth, before lactation had an appreciable effect. Recovery in the body weights was observed in the offspring as the affected animals had similar body weights to controls by the first week of age and there were no indications of lasting toxic effects in either study (although neither study conducted a detailed behavioural or functional assessment of the offspring). Additionally, the offspring were able to reproduce in the two-generation study, although the same body weight reduction was observed in the subsequent generation, but again recovery was observed. Although a statistically significant reduction in the viability index was not seen in the F1 animals it was seen in the F2 animals. The study authors suggest that this discrepancy in the viability index findings may be due to the treatment being initiated at a younger age in the F1 generation than the P generation and therefore the finding is still relevant. There was no evidence of an *in utero* effect on foetuses at doses that were not maternally toxic in a developmental toxicity study in rats.

The largest decrease in absolute offspring body weights was 18% in the reproductive/developmental screening study at 1000 mg/kg bw/day with a 14% decreases at 300 mg/kg bw/day. The decrease in offspring body weights was also observed in the two generation study at 100 and 300 mg/kg bw/day but the decreases in absolute body weight were 9% or less. The decrease seen in the viability index of F2 animals in the two generation study was 8%. The decreased birth weights are of concern because they occurred without maternal toxicity and in both the reproductive/developmental screening study and the two generation study where the animals were dosed throughout the pregnancy. Although the changes in bodyweight were low in the two generation study they were more significant in the reproductive/developmental screening study and combined with the decrease in the viability index seen in the F2 animals in the two generation study provide sufficient evidence of developmental toxicity in rats to justify classification.

Health hazard classification
Based on the available information, the notified chemical is 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. The recommended hazard classification is presented in the following table.

Hazard classification	***Hazard statement***
Reproductive Toxicity (Category 2)	H361 – Suspected of damaging fertility or the unborn child

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 phrase:

R63: Possible risk of harm to the unborn child

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety
Workers (particularly service technicians) may be exposed to the notified chemical at ≤ 100% concentration. The notified chemical may present a concern for effects following repeated exposure, therefore measures should be in place (e.g. use of PPE) to minimise any potential exposure of workers to the notified chemical. Overall, under the occupational settings described, the risk to the health of workers from use of the notified chemical is not considered to be unreasonable.

6.3.2. Public Health
As exposure of the public to the notified chemical is not expected, the risk to the public from use of the chemical is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will be manufactured, formulated, and the majority packaged into end-use sealed compressor units overseas, with a small volume of the notified chemical imported in containers for aftermarket repair and replacement. Therefore, there will be no environmental release in Australia from this stage of the notified chemical's life-cycle except in the unlikely event of accidental spills or leaks.

RELEASE OF CHEMICAL FROM USE

The notified chemical will be used as a component of lubricant oil in compressor units. Release during its use may arise from spills or leaks during equipment servicing by professional technicians. It is estimated by the notifier that these sources will account for 1-2% of the total import volume, or up to 400 kg/year (maximum 20 tonnes/year × 2%).

RELEASE OF CHEMICAL FROM DISPOSAL

After use, waste oil containing the notified chemical (estimated by the notifier to be 96-100% of the total import volume) will be collected by licensed waste management services and sent to waste oil depots or workshops for use as a fuel source. When used as fuel, the majority of the notified chemical will be consumed and thermally decomposed.

Residues of the notified chemical within empty import containers (estimated by the notifier to be 1-2% of the import volume) are expected to be disposed of to landfill. Assuming 2% of the notified chemical remains in empty containers after use, 400 kg/year (maximum 20 tonnes/year × 2%) of the notified chemical within empty import containers will be disposed of to landfill. In the event of disposal to landfill, the notified chemical is expected to be immobile and associate with the organic compartment of soil based on its low water solubility, and high P_{OW} and K_{OC}. Over time, the notified chemical is expected to degrade via abiotic and biotic processes to form water and oxides of carbon.

7.1.2. Environmental Fate

The notified chemical is not readily biodegradable, however, it is expected to eventually biodegrade in the environment (≥ 25% in 28 days). For details of the environmental fate studies, please refer to Appendix C. After use, the majority of the notified chemical will be reclaimed for use as fuel where it will be thermally decomposed.

Minor amounts of the notified chemical are expected to be disposed of to landfill as residues in containers or collected waste. Given the high soil adsorption/desorption coefficient (log $K_{OC} \geq 4$) and low water solubility (< 1 – 2.5 x 10^{-3} g/L), the notified chemical sent to landfill is expected to be immobile. The notified chemical is expected to associate strongly with the organic compartment in soil according to its high log K_{OC} and its potential to partition to organic phases (log $P_{OW} \geq 4.9$). The notified chemical is not readily biodegradable, however, bioaccumulation is not expected given the low bioconcentration factor (BCF = 0.648-3.611).

The notified chemical is expected to degrade by abiotic and biotic processes in landfill, or by thermal decomposition, to form water and oxides of carbon. For the details for the environmental fate studies, please refer to Appendix C.

7.1.3. Predicted Environmental Concentration (PEC)

The predicted environmental concentration (PEC) has not been calculated since no significant release of the notified chemical to the aquatic compartment is expected from the reported use pattern.

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 > 1.8 mg/L	Not harmful up to the limit of solubility (acute)
	30 d NOEC = 2.25 mg/L	Not harmful up to the limit of solubility

		(chronic)
Daphnia Toxicity	48 h EC50 > 1.8 mg/L 21 d NOEC = 0.518 mg/L	Not harmful up to the limit of solubility (acute) Not harmful up to the limit of solubility (chronic)
Algal Toxicity	72 h E_rC50 > 1.7 mg/L 72 h NOE_rC = 0.98 mg/L	Not harmful up to the limit of solubility (acute) Not harmful up to the limit of solubility (chronic)
Inhibition of Bacterial Respiration	3 h EC50 > 1000 mg/L	Not inhibitory to bacterial respiration
Earthworm Toxicity	28 d LC50 > 1000 mg/kg (dry wt)	Not harmful to earthworms (chronic)
Inhibition of Seed Germination/Root Development	EC50 > 1000 mg/L	Not inhibitory to seed germination/root development

Classification should be based only on toxic responses observed in the soluble range. The ecotoxicity endpoints for the notified chemical are higher than its solubility limit. No significant adverse effects were observed in any of the provided tests. It is concluded that the notified chemical is not expected to be harmful to organisms in either the aquatic or soil compartments up to the limit of its solubility in water. Therefore, the notified chemical is not formally classified under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) (United Nations, 2009) for acute and chronic effects.

7.2.1. Predicted No-Effect Concentration

A Predicted No-Effect Concentration (PNEC) for the aquatic compartment has not been calculated since the notified chemical is not considered to be harmful up to the limit of its solubility in water.

7.3. Environmental Risk Assessment

The Risk Quotient (RQ = PEC/PNEC) has not been calculated since the PEC and PNEC were not calculated. The notified chemical is not harmful up to the limit of its solubility in water and is not expected to bioaccumulate in the environment. Therefore, based on the assessed use pattern, the notified chemical is not expected to pose an unreasonable risk of the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point/Freezing Point < -25 °C

Method	OECD TG 102 Melting Point/Melting Range.
Remarks	The test substance remained in liquid form when the temperature was decreased to -25 °C.
Test Facility	Huntingdon (2012a)

Boiling Point Decomposition without boiling from ~180 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point.
Remarks	Determined by Differential Scanning Calorimetry. A series of exotherms and endotherms were noted from 180 °C, with a dark brown residue remaining at the end of the test.
Test Facility	Huntingdon (2012a)

Density 990 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	Determined using a pycnometer.
Test Facility	Huntingdon (2012a)

Vapour Pressure 2×10^{-7} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Determined using a vapour pressure balance.
Test Facility	Huntingdon (2012a)

Water Solubility < 1-2.5 × 10^{-3} g/L at 20 °C

Method	OECD TG 105 Water Solubility.
Remarks	Flask Method
Test Facility	Huntingdon (2012a)

Partition Coefficient (n-octanol/water) log Pow ≥ 4.9 at 20 °C

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	HPLC Method. The notified chemical eluted after the reference chemical benzylbenzoate.
Test Facility	Huntingdon (2012a)

Surface Tension 54.5 mN/m at 20 °C

Method	OECD TG 115 Surface Tension of Aqueous Solutions.
Remarks	Concentration: 90% saturated aqueous solution. Determined with a torsion balance using the ring method. The test substance was considered to be surface active.
Test Facility	Huntingdon (2012a)

Adsorption/Desorption log K_{oc} ≥ 4 at 20 °C

Method	OECD TG 121 Adsorption HPLC Screening Method.
Remarks	HPLC Screening Method. The notified chemical eluted after the reference chemical 2-methylnaphthlene.
Test Facility	Huntingdon (2012a)

Flash Point 216 °C at 101.4 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Determined using a Pensky-Martens closed cup apparatus.

Test Facility Huntingdon (2012a)

Autoignition Temperature > 400 °C

Method EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks No ignition was observed within 5 minutes of addition of the test substance to a flask heated to 400 °C.
Test Facility Huntingdon (2012a)

Explosive Properties Predicted negative

Method EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks The chemical structure was observed for functional groups that may indicate explosive properties.
Test Facility Huntingdon (2012a)

Oxidizing Properties Predicted negative

Method EC Council Regulation No 440/2008 A.21 Oxidizing Properties (Liquids).
Remarks The chemical structure was observed for functional groups that may indicate oxidising properties.
Test Facility Huntingdon (2012a)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE Notified chemical

METHOD OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain Rat/CD
Vehicle Corn oil
Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 F	2000	0/3
2	3 F	2000	0/3

LD50 > 2000 mg/kg bw
Signs of Toxicity None observed.
Effects in Organs No gross abnormalities observed.

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

TEST FACILITY Huntingdon (2012b)

B.2. Acute toxicity – dermal

TEST SUBSTANCE Notified chemical

METHOD OECD TG 402 Acute Dermal Toxicity
Species/Strain Rat/CD
Vehicle None
Type of dressing Occlusive.
Remarks - Method No significant protocol deviations.

RESULTS

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

LD50 > 2000 mg/kg bw
Signs of Toxicity - Local No signs of dermal irritation were observed.
Signs of Toxicity - Systemic Body weight gains were lower in three female animals compared to the remaining animals, particularly in the first week following test substance administration. No other signs of toxicity were observed.
Effects in Organs No gross abnormalities observed.

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

TEST FACILITY Huntingdon (2012c)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain Rabbit/New Zealand White

Number of Animals	3 females
Vehicle	None
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks - Method	No significant protocol deviations.

RESULTS

Remarks - Results	Scores of zero for erythema and oedema were observed for all animals at all observations.

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

TEST FACILITY Huntingdon (2012d)

B.4. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 females
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	0.7	0	1	< 72 hours	0
Conjunctiva: chemosis	0	0	0	0	-	0
Conjunctiva: discharge	0	0	0	2	< 24 hours	0
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	Minimal conjunctival redness was observed in all animals but resolved by 24 hours in two animals and by 72 hours in the remaining animal. All animals had moderate conjunctival discharge at 1 hour with resolution by 24 hours.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY Huntingdon (2012e)

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

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay

Species/Strain	Mouse/ CBA/Ca (female)
Vehicle	Acetone:olive oil (4:1)
Remarks - Method	The study was conducted using 4 mice per dose, with the test substance administered at 25, 50 and 100%. Negative control groups either received the vehicle alone or a sham dose (tip of pipette passed over the surface of the ear). The vehicle negative control was used to calculate the stimulation index. A positive control group was also conducted using 25% hexylcinammaldehyde (HCA).

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (sham dose)	646	-
0 (vehicle control)	733	-
25	1153	1.6
50	1353	1.8
100	1030	1.4
Positive Control		
25% HCA	5328	7.3

Remarks - Results

No treatment related signs of systemic toxicity or irritation were observed.

The stimulation index values for the test substance groups were < 3, indicating the absence of a skin sensitisation response at the tested concentrations.

The positive control gave a satisfactory response confirming the validity of the test system.

CONCLUSION

There was no evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to the notified chemical.

TEST FACILITY

Huntingdon (2012f)

B.6. Repeat dose toxicity

TEST SUBSTANCE

Notified chemical

METHOD

Non-guideline study

Species/Strain: Rat/CD

Route of Administration: Oral – gavage

Exposure Information: Total exposure days: 14 days

Vehicle: Corn oil

Remarks - Method: In a 14 day repeated dose oral gavage study, rats (3/sex/dose) were treated with the notified chemical at 100, 300 or 1000 mg/kg bw/day. A vehicle control group was not conducted. Mortality, clinical signs of toxicity, body weight, food consumption and water consumption (by visual assessment) were recorded during the study. All animals were subject to gross necropsy. The kidneys, liver and spleen were weighed.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
low dose	3 M + 3 F	100	0/6
mid dose	3 M + 3 F	300	0/6
high dose	3 M + 3 F	1000	0/6

Clinical Observations

Chin rubbing was observed in one male treated at 1000 mg/kg bw/day on day 7 but was attributed to the palatability of the test substance. No other clinical signs were observed. All treatment groups had similar body weight gains, and food and water consumption.

Effects in Organs

Organ weights at all dose levels were similar in males. Females treated at 300 and 1000 mg/kg bw/day had increased liver weights. There were no treatment related macroscopic findings at necropsy.

Remarks – Results
The increased liver weights cannot be attributed to treatment as the small group sizes excluded a meaningful statistical analysis. Additionally, the toxicological significance is also unable to be determined in the absence of histopathological examination of the livers.

CONCLUSION
The NOAEL was established as 1000 mg/kg bw/day in this study, based on the lack of treatment related adverse effects.

TEST FACILITY Huntingdon (2012g)

B.7. Repeat dose toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
Species/Strain Rat/Crl:CD (SD)
Route of Administration Oral – gavage
Exposure Information Total exposure days: 90 days
Vehicle Corn oil
Remarks - Method No significant protocol deviations. Sensory reactivity and grip strength, and motor activity were assessed during week 12. Organ weights were also adjusted for terminal bodyweight, using the weight recorded before necropsy and statistical analyses conducted on these values.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10 M + 10 F	0	0/20
low dose	10 M + 10 F	100	0/20
mid dose	10 M + 10 F	300	0/20
high dose	10 M + 10 F	1000	0/20

Clinical Observations
Salivation and chin rubbing was observed most commonly in males and females treated at 1000 mg/kg bw/day, with observations also in the lower dose treatment groups. The study authors noted that these findings are likely due to the gavage dosing method and are not of toxicological concern. There were also slight increases in the incidence of hair loss and encrusted skin in females treated at 1000 mg/kg bw/day, but are of low toxicological concern due to the low incidence.

There were statistically significant decreases in forelimb grip strength during week 12 in males treated at 300 and 1000 mg/kg bw/day, but due to its isolated nature this finding is considered to be of low toxicological concern. Furthermore, these findings were reported as being within historical control ranges. There were no treatment related findings in the high (rearing) and low (cage floor activity) beam motor activity assessments.

There were slight non-statistically significant decreases in body weight gain in males treated at 300 and 1000 mg/kg bw/day (↓7% and ↓6%, respectively), and increases in females treated at 300 and 1000 mg/kg bw/day (↑5% and ↑3%, respectively). Due to the lack of statistical significance or dose response the study authors considered the findings to not be toxicologically significant. There were no treatment related changes in food or water consumption in males or females.

There were no treatment related ophthalmic lesions in males or females treated at 1000 mg/kg bw/day.

Laboratory Findings – Clinical Chemistry and Haematology
There were statistically significant decreases in haemoglobin concentration (↓4.6%), haematocrit (↓5.4%) and activated partial thromboplastin time (↓14.7%) in males treated at 1000 mg/kg bw/day. These changes were within the range of expected biological variability for this strain of rat and therefore unlikely to be treatment related.

There were statistically significant decreases in haemoglobin concentration (↓4.7%; ↓4.7%) and haematocrit (↓4.5%; ↓5.7%) in females treated at 300 and 1000 mg/kg bw/day respectively. There were statistically significant decreases in mean corpuscular haemoglobin (↓3.2%; ↓4.9%; ↓2.7%), mean corpuscular volume (↓2.9%; ↓4.9%; ↓4.2%), total leucocyte count (↓24%; ↓20%; ↓15%), lymphocyte count (↓23%; ↓25%; ↓27%), basophil count (↓33%; ↓33%; ↓33%) and eosinophil count (↓36%; ↓36%; ↓45%) in all groups (low; mid; high, respectively) of treated females. There was a statistically significant increase in mean corpuscular haemoglobin concentration (↑1.2%), and a statistically significant decrease in platelet count (↓18%) in females treated at 1000 mg/kg bw/day. Changes in haematological parameters in treated females were slight and considered by the study authors to be within the range of expected biological variability for this strain of rat. Neither was there any clear indication of a dose response in any of changes detected. Overall, the changes are unlikely to be of toxicological concern.

There were numerous treatment related changes in clinical chemistry parameters (see following Table). There were statistically significant increases in alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase in females treated at 300 and 1000 mg/kg bw/day. Urea and blood urea nitrogen were statistically significantly increased in males and females treated at 300 and 1000 mg/kg bw/day. There were statistically significant decreases in glucose in males treated at 1000 mg/kg bw/day and in females treated at 300 and 1000 mg/kg bw/day. There were statistically significant decreases in albumin/globulin ratio in females treated at 300 and 1000 mg/kg bw/day. Statistically significant increases in creatinine occurred in males in all dose groups and in females treated at 300 and 1000 mg/kg bw/day.

Clinical chemistry:

	Males (mg/kg bw/day)				*Females (mg/kg bw/day)*			
	0	*100*	*300*	*1000*	*0*	*100*	*300*	*1000*
Alkaline phosphatase (U/L)	103	96	92	85* (↓17%)	54	51	89** (↑65%)	79** (↑46%)
Alanine aminotransferase (U/L)	38	37	32	32	29	35	55** (↑90%)	93** (↑221%)
Aspartate aminotransferase (U/L)	59	68	61	57	58	59	79** (↑36%)	93** (↑60%)
Urea (mmol/L)	3.79	4.05	4.74* (↑25%)	5.03** (↑33%)	4.92	5.45	6.39** (↑30%)	6.82** (↑39%)
Blood urea nitrogen (mg/dL)	10.6	11.3	13.3* (↑25%)	14.1** (↑33%)	13.8	15.3	17.9** (↑30%)	19.1** (↑38%)
Creatinine (µmol/L)	32	38** (↑19%)	41** (↑28%)	38** (↑19%)	36	39	43** (↑19%)	41** (↑14%)
Glucose (mmol/L)	8.50	8.33	7.67	7.51* (↓12%)	7.06	6.89	5.81** (↓18%)	5.92** (↓16%)
Cholesterol (mmol/L)	1.57	1.87	1.84	1.84	2.07	1.76	1.77	1.52* (↓27%)
Albumin/globulin ratio	1.18	1.20	1.15	1.10	1.36	1.30	1.24* (↓9%)	1.19** (↓13%)

Statistically significant compared to control (*P < 0.05, **P < 0.01).

Effects in Organs

There were macroscopic observations of pale liver in all groups treated with the test substance, with increased incidence compared to control groups in all groups of treated females treated and males treated at 300 and 1000 mg/kg bw/day. The incidence of this finding in males treated at the 100 mg/kg bw/day was similar to the control group. Relative liver weights showed a statistically significant increase in males and females treated at 300 and 1000 mg/kg bw/day. There was an increased incidence of periportal hepatocellular vacuolation in all female treatment groups and in males treated at 1000 mg/kg bw/day. The intracytoplasmic vacuolation was stated by the study authors to represent accumulation of fat droplets and decreased cytoplasmic glycogen, based on Oil Red O and Period Acid Schiff staining in selected animals. There was minimal to slight centrilobular hepatocellular hypertrophy in males treated at 300 and 1000 mg/kg bw/day and in females treated at 1000 mg/kg bw/day, considered by the study authors to be an adaptive response due to an increased activity of hepatic enzymes.

There were treatment related macroscopic findings of irregular surface of the kidneys and pale kidneys in all male treatment groups, with enlarged kidneys at a low incidence in males treated at 300 and 1000 mg/kg bw/day. Females treated at 300 and 1000 mg/kg bw/day had a low incidence of pale kidneys. Relative kidney

weights were statistically increased in all treated male dose groups. There were treatment related histopathological findings in males of all treatment groups including hyaline droplets in the cortical tubules, granular casts at the corticomedullary junction and chronic progressive nephropathy. The study authors noted that hyaline droplet nephropathy is a consequence of droplet accumulation in the cortical tubules, accompanied by the accumulation of granular casts in the corticomedullary junction. The study authors noted that this mechanism is a rat specific effect, due to the complexing of the test substance with α-2-microglobulin, a rat specific protein.

Despite a statistically significant increase in the relative kidney weights in females treated at 1000 mg/kg bw/day, there were no associated histopathological findings. Thus, the increased kidney weights in females are not considered to represent a toxicologically adverse effect.

Organ weights:

	Males (mg/kg bw/day)				*Females (mg/kg bw/day)*			
	0	*100*	*300*	*1000*	*0*	*100*	*300*	*1000*
Liver								
absolute (g)	19.39	20.71	21.02	23.08	10.81	10.78	13.69	15.13
relative	19.02	20.27	21.56** (↑13%)	23.36** (↑23%)	10.89	11.06	13.49** (↑24%)	14.96** (↑37%)
Kidneys								
absolute (g)	3.36	3.71	4.21	4.51	1.90	1.97	2.05	2.09
relative	3.30	3.64* (↑10%)	4.30** (↑30%)	4.55** (↑38%)	1.90	2.00	2.03	2.07* (↑9%)
Adrenals								
absolute (g)	0.057	0.056	0.056	0.058	0.061	0.064	0.065	0.076
relative	0.057	0.055	0.056	0.058	0.061	0.064	0.064	0.076** (↑25%)
Spleen								
absolute (g)	0.69	0.80	0.76	0.83	0.61	0.51	0.57	0.61
relative	0.68	0.79* (↑15%)	0.77* (↑13%)	0.84** (↑22%)	0.62	0.52** (↓16%)	0.56	0.61
Heart								
absolute (g)	1.56	1.52	1.50	1.61	0.96	1.03	1.10	1.12
relative	1.54	1.49	1.53	1.62	0.97	1.05** (↑8%)	1.08** (↑12%)	1.11** (↑15%)

Statistically significant compared to control (*P < 0.05, **P < 0.01). Statistical testing not conducted on absolute organ weights. Relative weights adjusted for terminal body weights.

Histopathological findings:

	Males (mg/kg bw/day)				*Females (mg/kg bw/day)*			
	0	*100*	*300*	*1000*	*0*	*100*	*300*	*1000*
Liver (10/sex/dose)								
hepatocyte vacuolation, periportal	0	1 (1.0)	0	4 (1.3)	1 (1.0)	7 (1.3)	7 (1.9)	10 (1.8)
hepatocyte hypertrophy, centrilobular	0	0	4 (1.3)	10 (1.6)	0	0	0	6 (1.0)
Kidneys (10/sex/dose)								
hyaline droplets, cortical tubules	0	10 (1.8)	10 (2.8)	10 (2.9)	0	0	0	0
granular casts, corticomedullary junction	0	8 (1.4)	9 (1.8)	10 (1.3)	0	0	0	0
chronic progressive nephropathy	0	8 (1.6)	10 (1.7)	10 (2.2)	0	0	0	0
Thyroid (10/sex/dose)								
follicular cell hypertrophy	1 (1.0)	0	4 (1.0)	10 (1.5)	0	0	1 (1.0)	5 (1.2)

( ), Average severity of affected animals: 1=minimal, 2=slight, 3=moderate.

There was a treatment related increased incidence of follicular cell hypertrophy in the thyroid in males treated at 300 and 1000 mg/kg bw/day and females treated at 1000 mg/kg bw/day, with an observation in a single female

treated at 300 mg/kg bw/day. The study authors note that the hypertrophy seen in the thyroids could be the result of increased circulating hepatic enzymes.

Adrenal inflammatory cell infiltration in the zona reticularis was only marginally increased compared to controls in females treated at 1000 mg/kg bw/day. Additionally, adjusted adrenal weights were statistically significantly increased in this dose group. The study authors noted that the inflammatory cell infiltration was unlikely to account for the increased adrenal weights. Given that the inflammatory infiltration was observed only at a minimally increased incidence and because there were observations in the control group, it was considered by the study authors to be a background change.

There were statistically significant increases in adjusted spleen weights in all male treatment groups. Based on the lack of associated histopathological findings, the increased spleen weights were considered to be of low toxicological concern by the study authors.

The relevance of a dose related trend of statistically significant increased heart weights in all treated groups of females is unclear in the absence of histopathological findings. However, this effect cannot be excluded as a toxicologically adverse finding.

Remarks – Results

The study authors propose that the effects seen in the liver were not adverse in females treated at 100 mg/kg bw/day, on the basis that the fatty change was not observed in males and because there were no clinical chemistry changes in females at this dose. However, liver toxicity may occur in the absence of changes in circulating enzyme levels, thus the changes in females treated at 100 mg/kg bw/day cannot be excluded as toxicologically significant findings. It is recognised that effects observed in the kidney may be rat specific and therefore not relevant to the risk assessment of humans.

CONCLUSION

The NOAEL was established by the study authors as 100 mg/kg bw/day,based on adverse effects in the organs along with associated changes at the higher doses of 300 and 1000 mg/kg bw/day .

TEST FACILITY Huntingdon (2012h)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical

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

Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA (pKM101)
Metabolic Activation System	Phenobarbital/5,6-benzoflavone induced rat liver (S9 homogenate)
Concentration Range in Main Test	a) With metabolic activation: 0, 5, 15, 50, 150, 500, 1500, 5000 µg/plate b) Without metabolic activation: 0, 5, 15, 50, 150, 500, 1500, 5000 µg/plate
Vehicle	Acetone
Remarks - Method	No significant protocol deviations. In Test 2, the S9 content was increased from 10% to 20%.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	> 5000	none reported	negative
Test 2	-	> 5000	none reported	negative
Present				
Test 1	-	> 5000	none reported	negative
Test 2	-	> 5000	none reported	negative

Remarks - Results	No statistically or biologically significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains up to and including the maximum dose, either with or without metabolic activation. The positive controls gave satisfactory responses, confirming the validity of the test system.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Huntingdon (2011a)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test
Cell Type/Cell Line	Human peripheral lymphocytes
Metabolic Activation System	Phenobarbital/5,6-benzoflavone induced rat liver (S9 homogenate)
Vehicle	Acetone
Remarks - Method	No significant protocol deviations. The maximum tested concentration was 4000 µg/mL, as fluctuations in osmolality > 50 mOsm/kg were observed at higher concentrations.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 40.31*, 67.18, 111.97, 186.62, 311.04, 518.4, 864*, 1440, 2400, 4000*, MMC 0.2*	3 h	21 h
Test 2	0*, 25, 100, 250, 500, 1000, 1500, 2000, 2500, 3000*, 3500*, 4000*, MMC 0.1*	21 h	21 h
Present			
Test 1	0*, 40.31, 67.18, 111.97, 186.62*, 311.04, 518.4, 864*, 1440, 2400, 4000*, CP 5*	3 h	21 h
Test 2	0*, 100, 250, 500, 1000, 2000*, 3000*, 4000*, CP 5*	3 h	21 h

*Cultures selected for metaphase analysis.
MMC, Mitomycin C. CP, Cyclophosphamide.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*		
	*Cytotoxicity**	*Precipitation*	*Genotoxic Effect*
Absent			
Test 1	> 4000	none reported	negative
Test 2	> 4000	none reported	negative
Present			
Test 1	> 4000	none reported	negative
Test 2	> 4000	none reported	negative

*Reduction in mitotic index of ≥ 50%.

Remarks - Results	Under all experimental conditions, there was no evidence of an increase in the proportion of cells with chromosomal aberrations. No statistically significant increases in polyploidy metaphases were observed. The positive and vehicle controls gave satisfactory responses confirming the validity of the test system.
CONCLUSION	The notified chemical was not clastogenic to human peripheral blood

lymphocytes treated *in vitro* under the conditions of the test.

TEST FACILITY Huntingdon (2011b)

B.10. Genotoxicity – in vivo

TEST SUBSTANCE Notified chemical

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test
Species/Strain Mouse/CD-1
Route of Administration Oral – gavage
Vehicle Corn oil
Remarks - Method In a preliminary toxicity study, two male and two females rats were treated with the test substance at 2000 mg/kg bw/day for two consecutive days and observed for a further day. No clinical signs of toxicity were observed. Body weight losses were noted on Day 2, with animals gaining weight by termination (Day 3).

Animals treated with the test substance and vehicle control were sacrificed 24 hours after the second dose. Positive control animals were sacrificed 24 hours after a single dose.

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Sacrifice Time hours*
I (vehicle control)	6 M	0	72
II (low dose)	6 M	500	72
III (mid dose)	6 M	1000	72
IV (high dose)	6 M	2000	72
V (positive control, MMC)	5 M	12	48

MMC, Mitomycin C.

RESULTS
Doses Producing Toxicity No clinical signs of toxicity were noted. Sporadic body weight losses were observed in animals of the treated and vehicle control groups.

There were no statistically significant decreases in the proportion of polychromatic erythrocytes.
Genotoxic Effects There was no statistically significant increase in the frequency of the detected micronuclei at any concentration. The positive control gave a satisfactory response, confirming the validity of the test system.

CONCLUSION The notified chemical was not genotoxic under the conditions of the *in vivo* micronucleus test.

TEST FACILITY Huntingdon (2011c)

B.11. Reproduction/Developmental toxicity

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 421 Reproduction/Developmental Toxicity Screening Test.
Species/Strain Rat/Crl:CD (SD)
Route of Administration Oral – gavage
Exposure Information Exposure days: up to 46 days
Vehicle Corn oil
Remarks - Method No significant protocol deviations. Males and females were treated with the test substance for 15 days before mating and until completion of the study when the offspring were 7 days old. Offspring were not dosed directly with the test substance.

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	10 M + 10 F	0	0/20
low dose	10 M + 10 F	100	0/20
mid dose	10 M + 10 F	300	2/20
high dose	10 M + 10 F	1000	1/20

Mortality and Time to Death

Three animals were killed *in extremis*. One female treated at 300 mg/kg bw/day was killed on lactation day 2 and another was killed around the time of parturition, 23 days after mating. One female treated at 1000 mg/kg bw/day was also killed around the time of parturition, 21 days after mating. Most of the offspring of these animals were found dead. Necropsy findings in these females included altered or decreased gastrointestinal tract content, pale or inactive mammary tissue, small spleen, and placenta and amniotic sac lodged in the vagina. These mortalities are unlikely to be treatment related based on their low incidence and the lack of a dose response.

Effects on Parental Animals

Absolute body weights and body weight gains were unaffected in treated males. There was no clear evidence of an effect on maternal body weights, despite statistically significant decreases in absolute body weights in females treated at 300 and 1000 mg/kg bw/day before mating and statistically significant decreases in body weight gain in the group treated at 1000 mg/kg bw/day from gestation day 17 to 20. The study authors noted that the decrease in body weight gain towards the end of gestation could have resulted in the lower observed birth weights. Food consumption was similar in treated and control groups.

Although there was no treatment related effect on gestation length, the study authors noted that an increase in the number of animals in the control group compared to the treatment groups that had a gestation length of 23 days could have resulted in this group having slightly higher pup birth weights. There were no treatment related changes in pre-coital interval, gestation length, gestation index, conception rate or fertility index.

There were no treatment related macroscopic findings or organ weight changes. Histopathological examination of the ovaries revealed prominent corpora lutea of pregnancy at increased incidence in all treatment groups but there was no dose response. The study authors noted that in the absence of a clear effect on reproductive performance and the lack of a dose response, this finding is unlikely to be of toxicological significance. There were no treatment related histopathological findings in the male reproductive organs.

Effects on Pups

Clinical observations included cold to touch, bruising and dark abdomen but with no dose response, these effects are not considered to be treatment related. There was an isolated statistically significant decrease in viability index in the group treated at 300 mg/kg bw/day but was not considered treatment related due to the lack of an effect at 1000 mg/kg bw/day. There were no treatment related changes in the number of implantations, live litter size, post implantation survival, live birth index or male to female ratio.

There were statistically significant decreases in absolute male pup weights in the groups treated at 300 (↓10% to 14%) and 1000 mg/kg bw/day (↓12% to 18%) on days 1, 4 and 7. However, there were no changes in male pup body weight gains. A statistically significant decrease in male pup body weight in the group treated at 100 mg/kg bw/day (↓12%) on day 7 is likely to be incidental as there were no statistically significant changes in absolute body weights at earlier observations or body weight gain. In females, there were statistically significant decreases in absolute female pup weights in the groups treated at 300 (↓12%) and 1000 mg/kg bw/day (↓17% to 19%) on days 1 and 4, but there were no decreases in female pup body weight gain. As the pups were not treated directly with the test substance after birth, the decreased absolute pup weights is likely attributable to an *in utero* effect of treatment, given that pups gained weight at similar rates after birth, thus making exposure via lactation unlikely.

CONCLUSION

The NOAEL for paternal, maternal and reproductive toxicity was established as 1000 mg/kg bw/day, based on the lack of treatment related adverse effects. The NOAEL for developmental toxicity was established as 100 mg/kg bw/day, based on decreased pup weights at 300 and 1000 mg/kg bw/day. There was evidence of an *in utero* effect in the absence of maternal toxicity under the conditions of the study.

TEST FACILITY Huntingdon (2012i)

B.12. Developmental toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 414 Prenatal Developmental Toxicity Study
Species/Strain Rat/Crl:CD (SD)
Route of Administration Oral – gavage
Exposure Information Exposure days: gestation days 6-19
Post-exposure observation period: none (sacrificed on gestation day 20)
Vehicle Corn oil
Remarks - Method No significant protocol deviations.

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
control	20	0	0/20
low dose	20	100	0/20
mid dose	20	300	0/20
high dose	20	1000	0/20

Effects on Dams

There were no treatment related toxicologically significant clinical signs of toxicity. Chin rubbing was observed in females treated at 300 and 1000 mg/kg bw/day but was associated with the dosing method.

There were statistically significant decreases in body weight gains in females treated at 1000 mg/kg bw/day from gestation days 6 to 11 (↓22%), gestation days 6 to 20 (↓9%). Females treated at 300 mg/kg bw/day showed a statistically significant mean 1 g loss in bodyweight over the first day of dosing. Absolute body weights adjusted for gravid uterine weight were similar in treated and control groups but there was a statistically significant decrease in the adjusted body weight gain over gestation days 6 to 20 (↓21%) in females treated at 1000 mg/kg bw/day. This may be considered to indicate maternal toxicity in the group treated at 1000 mg/kg bw/day, although the study authors did not consider the changes to be biologically adverse. There was a statistically significant reduction in food consumption in females treated at 1000 mg/kg bw/day on gestation days 18 to 19 (↓13%). There were no toxicologically adverse macroscopic observations at necropsy.

Reproductive performance parameters were similar in treated and control groups, including the number of corpora lutea, implantations, early and late resorptions, litter size, number of live young, total number of foetuses, male to female ratio, and pre- and post-implantation loss.

Effects on Foetus

There were statistically significant decreases in foetal weights for males (↓6%) and the combined total for males and females (↓5%) in the group treated at 1000 mg/kg bw/day. There were slight but non-statistically significant decreases in female foetal weights in the group treated at 1000 mg/kg bw/day (↓5%).

There were slightly increased incidences of incompletely ossified or unossified cranial centres in the groups treated at 300 and 1000 mg/kg bw/day, and incompletely ossified or unossified hyoid bone and pelvic bones in the group treated at 1000 mg/kg bw/day. These changes were considered by the study authors to be within historical control ranges. Together with their low incidence, these changes are unlikely to be of toxicological concern. There was also an increased incidence of folded retinas (2/280) in the group treated at 1000 mg/kg bw/day. The relevance of this finding is unclear but was considered by the study authors to be of low toxicological concern based on the low incidence.

CONCLUSION

The effects noted were not considered by the study authors to be biologically significant effects of treatment. Therefore, the NOAEL was established by the study authors as 1000 mg/kg bw/day, based on the absence of treatment related adverse effects at all doses.

TEST FACILITY Huntingdon (2012j)

B.13. Reproductive toxicity – two generation study

TEST SUBSTANCE Notified chemical

METHOD OECD TG 416 Two-Generation Reproductive Toxicity Study.
Species/Strain Rat/Crl:CD (SD)
Route of Administration Oral – gavage
Vehicle Corn oil
Remarks - Method In a two-generation reproductive study, P generation animals were administered the test substance by gavage for 10 weeks at 0, 30, 100 or 300 mg/kg bw/day (28/sex/dose) prior to mating. Dosing was continued throughout mating, pregnancy and lactation. The P generation males were sacrificed after 18 weeks of treatment and the females were sacrificed on day 28 post partum.

The F1 generation offspring were culled on post partum day 4 (5/sex/litter). Animals were selected to form the F1 adult generation (24/sex/dose) by selecting males and females on day 20 with the lowest identifier in each litter. Unselected animals were sacrificed on day 21. Dosing of the F1 generation was commenced when the animals were 21 to 28 days old. The F1 generation adults were sacrificed identically to the P generation. All P and F1 generation adults were subject to macroscopic examination, with microscopic examination of any macroscopic abnormalities. Sperm analysis was conducted. The male and female reproductive organs were examined histologically.

The F1 generation offspring that were culled on day 4 were subject to macroscopic examination only when considered to be externally abnormal. One male and female was randomly selected from each litter from animals sacrificed on day 21 and subject to macroscopic examination and body and organ weight analysis. The F2 generation were not treated directly with the test substance.

Generation	*Group*	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
P	control	28M + 28F	0	0/56
P	low dose	28M + 28F	30	0/56
P	mid dose	28M + 28F	100	3/56
P	high dose	28M + 28F	300	2/56
F1	control	24M + 24F	0	0/48
F1	low dose	24M + 24F	30	1/48
F1	mid dose	24M + 24F	100	3/48
F1	high dose	24M + 24F	300	1/48

RESULTS

Mortality and Time to Death

There were no treatment related mortalities in the P generation. A male treated at 300 mg/kg bw/day was found dead on day 82 with no clinical signs of toxicity observed before death. A cause of death could not be determined following macro and microscopic examination. A female treated at 300 mg/kg bw/day was killed *in extremis* due to clinical signs of toxicity observed around the time of parturition on gestation day 22. Microscopic examination revealed that uterine inflammation and haemorrhage contributed to morbidity in this animal. Three females treated at 100 mg/kg bw/day were killed *in extremis* around the time of parturition. Two deaths were attributed to uterine haemorrhage, with the other death likely due to septicaemia from endometritis.

There were no treatment related mortalities in the F1 generation. A single male treated at 100 mg/kg bw/day was found dead on day 52 with no clinical signs of toxicity before death. A cause of death could not be determined following macro and microscopic examination. Four females were killed *in extremis*. The death of a female treated at 300 mg/kg bw/day on lactation day 2 was attributed to endometritis. The cause of death of one

female treated at 100 mg/kg bw/day on lactation day 7 could not be determined, with the death of another female at this dose on gestation day 14 attributed to a mammary adenocarcinoma. The death of the female treated at 30 mg/kg bw/day on gestation day 17 was due to uterine haemorrhage.

Effects on Parental (P) animals

There were no treatment related clinical signs of toxicity observed in P generation adults. There were no treatment related changes in absolute body weights or body weight gains in males or females. There were sporadic statistically significant decreases in food consumption before mating in all groups of treated females but these were not considered by the study authors to be toxicologically significant based on the low magnitude of the decreases, the sporadic nature of the effect and the lack of any associated change in body weight. There were no treatment related changes in females in food consumption during gestation or lactation. There were no treatment related changes in food consumption in males. Food conversion efficiency was unaffected in males and females treated with the test substance.

There were no treatment related changes in the oestrous cycle, pre-coital interval, mating and fertility performance, and gestation length or gestation index. There were no treatment related changes in the number of implantations, total litter size, post implantation survival, live birth index, viability index, lactation index on day 21, or sex ratio. There were no treatment related changes in sperm motility, concentration or morphology.

There were statistically significant increases in relative liver weights in males and females treated at 300 mg/kg bw/day. A statistically significant increase in absolute liver weights in males treated at 100 mg/kg bw/day is not considered to be treatment related in the absence of an associated increase in relative liver weight. There were statistically significant increases in relative kidney weights in males treated at 100 and 300 mg/kg bw/day and in females treated at 300 mg/kg bw/day. There were statistically significant increases in relative spleen weights in males treated at 100 and 300 mg/kg bw/day. A statistically significant increase in absolute epididymides weight in males treated at 300 mg/kg bw/day is not considered to be of toxicological significance with no associated increase in relative epididymides weights.

	Males (mg/kg bw/day)				*Females (mg/kg bw/day)*			
	0	*30*	*100*	*300*	*0*	*30*	*100*	*300*
Organ weights								
Liver								
absolute (g)	24.43	25.36	26.71* (↑9%)	28.12** (↑15%)	14.26	13.69	14.56	15.31* (↑7%)
relative	3.87	4.03	4.00	4.40** (↑14%)	4.55	4.44	4.67	4.91** (↑8%)
Kidneys								
absolute (g)	4.04	4.16	4.78** (↑18%)	5.05** (↑25%)	2.35	2.33	2.42	2.44
relative	0.642	0.665	0.722** (↑12%)	0.791** (↑23%)	0.750	0.754	0.774	0.780* (↑4%)
Spleen								
absolute (g)	0.774	0.781	0.900** (↑16%)	0.870** (↑12%)	0.646	0.710	0.745	0.770
relative	0.123	0.125	0.135* (↑10%)	0.136** (↑11%)	0.193	0.198	0.191	0.200

Statistically significant compared to control (*P < 0.05, **P < 0.01). Relative weights adjusted for terminal body weights.

There were no treatment related macroscopic findings in the P generation. There were no microscopic changes in the reproductive tissues or in the pituitary or adrenal glands of P generation males or females. Histopathology was only conducted on other organs when there were macroscopic abnormalities, thus microscopic findings in the P generation were not a thorough investigation of the systemic target organ toxicity following administration of the test substance, i.e., microscopic effects indicative of toxicologically adverse effects would only have been detected in the presence of an associated macroscopic change. The main finding was hyaline droplets in the cortical tubules in males treated at 100 and 300 mg/kg bw/day (4/4 and 2/2 animals examined, respectively), with associated chronic progressive nephropathy (4/4 and 2/2, respectively) and granular casts at the corticomedullary junction (1/4 and 2/2 animals examined, respectively). These findings were not observed in controls and were therefore considered to represent a treatment related effect, however, the study authors considered this to be a male rat specific finding which is of no relevance to humans.

Effects on 1st Filial Generation (F1)

There were no treatment related clinical signs of toxicity in F1 offspring during the first week of the study and separation of the parents and offspring at weaning was well tolerated in all groups. There was a statistically significant decrease in absolute body weights in male F1 offspring at day 1 of age in the group treated at 300 mg/kg bw/day (↓6%). There were no other decreases in absolute body weights of F1 males at any observation up to weaning on day 21, or on body weight gain. There were also statistically significant decreases in absolute body weights in female offspring treated at 100 and 300 mg/kg bw/day at day 1 of age (↓6% and ↓8%, respectively) and on day 7 of age (↓7% and ↓6%, respectively) but there were no decreases in body weight gains in females. There were no treatment related toxicologically significant changes in organ weights or macroscopic findings in the F1 generation offspring sacrificed on day 21 of age.

There were no treatment related clinical signs of toxicity in F1 generation adults. There were no treatment related changes in absolute body weight or body weight gains in F1 generation males. A statistically increase in body weight gain of gestation day 0 to 20 in the females treated at 300 mg/kg bw/day (↑11%) was considered to be of low toxicological significance. Absolute body weights and body weight gains in females were otherwise unaffected. There were no treatment related changes in food consumption or food conversion efficiency in males or females. Statistically significant increases in food consumption in females treated at 100 and 300 mg/kg bw/day during week 9 of the pre-pairing treatment was considered incidental by the study authors based on the isolated nature of the findings.

There was no effect on sexual maturation in any treatment group, based on similar observations in control and treated groups in the time of completion of balano preputial separation in males and the time of completion of vaginal opening for females. There were no treatment related changes in the oestrous cycle, pre-coital interval, gestation length or gestation index. There were no treatment related changes in the number of implantations, total litter size, post implantation survival, live birth index, lactation index on day 21 or sex ratio. There were no treatment related changes in sperm motility, concentration or morphology.

There was a statistically significant decrease in viability index (number of live offspring on day 4 before culling ÷ number of live offspring on day 1) in the group treated at 300 mg/kg bw/day (↓8%). The study authors note that this finding is possibly treatment related, as treatment in the F1 generation was initiated at an earlier age at which they were possibly more susceptible.

There was a statistically significant decrease in fertility index in the groups treated at 100 and 300 mg/kg bw/day. These decreases were attributed by the study authors by two pairs failing to mate and two females found not to be pregnant in the group treated at 100 mg/kg bw/day, and another two females found not be pregnant in the group treated at 300 mg/kg bw/day. The study authors then noted that the non-pregnant females are a common occurrence in control groups. Together with the lack of a dose response, these findings are not considered to be related to treatment with the test substance, thus mating and fertility performance were unaffected by treatment.

There were statistically significant increases in relative liver weights in males treated at 300 mg/kg bw/day and in females treated at 100 and 300 mg/kg bw/day. There were statistically significant increases in relative kidney weights in males treated at 100 and 300 mg/kg bw/day, and ovary weights in females treated at 300 mg/kg bw/day. Statistically significant increases in absolute spleen and adrenal weights in males treated at 300 mg/kg bw/day are considered incidental findings as there were no changes in the relative organ weights.

	Males (mg/kg bw/day)				*Females (mg/kg bw/day)*			
	0	*30*	*100*	*300*	*0*	*30*	*100*	*300*
Organ weights								
Liver								
absolute (g)	22.92	23.71	24.92	25.66** (↑12%)	15.32	16.06	16.02	16.86** (↑10%)
relative	3.70	3.78	3.86	4.15** (↑12%)	4.72	4.84	4.94* (↑5%)	5.06** (↑7%)
Kidneys								
absolute (g)	4.05	4.16	4.56** (↑13%)	4.94** (↑22%)	2.32	2.38	2.44	2.45
relative	0.654	0.664	0.711** (↑9%)	0.800** (↑22%)	0.717	0.716	0.754	0.737
Ovaries								
absolute (g)	-	-	-	-	0.118	0.131	0.124	0.136** (↑15%)
relative	-	-	-	-	0.0365	0.0395	0.0383	0.0407* (↑12%)

Statistically significant compared to control (*P < 0.05, **P < 0.01). Relative weights adjusted for terminal body weights.

There were no treatment related macroscopic findings in F1 generation adults. There were no microscopic changes in the reproductive tissues or in the pituitary or adrenal glands of P generation males or females. Like the previous generation, the main finding in the F1 generation was hyaline droplets in the cortical tubules in males treated at 100 and 300 mg/kg bw/day (3/3 and 10/10 animals examined, respectively), with associated chronic progressive nephropathy (2/3 and 10/10, respectively) and granular casts at the corticomedullary junction (2/3 and 9/10 animals examined, respectively). The chronic progressive nephropathy was also observed in males treated at 30 mg/kg bw/day (2/6 animals examined). These findings in the kidney were not observed in controls and are therefore considered to be treatment related, however, the study authors considered this to be a male rat specific finding which is of no relevance to humans. There were no treatment related changes in primordial ovarian follicle counts in females treated 300 mg/kg bw/day.

Effects on 2nd Filial Generation (F2)

There were no treatment related clinical signs of toxicity in F2 offspring during the first week of the study and separation of the parents and offspring at weaning was well tolerated in all groups. Similar to the effects seen in the offspring of the previous generation, there were statistically significant decreases in absolute body weights in male and female F2 generation offspring (↓9% and ↓6%, respectively) in the groups treated at 300 mg/kg bw/day at day 1 of age, but with no decreases in offspring body weight gain. There were no toxicologically significant changes in organ weights in the F2 generation sacrificed on day 21 of age.

Remarks – Results

There were no clear indicators of treatment related effects on body weights of adult animals. There were no clear histopathological findings in females, and effects in males were deemed by the study authors to be rat specific findings which are of no relevance to humans. Increased organ weights in the adult animals were not considered to be adverse treatment related effects by the study authors. The were no adverse effects on the reproductive performance of treated animals, however, the decrease in the viability index of the F2 animals and body weight reductions in the offspring of both generations were treated as adverse developmental effects by the study authors.

CONCLUSION

The NOAEL for reproductive and general toxicity was established as 300 mg/kg bw/day, based on an absence of treatment related adverse changes at any dose. The developmental NOAEL was established was established by the study authors as 100 mg/kg bw/day, based on decreased offspring birth weights and a decrease in the viability index of the F2 animals. This finding is evidence of an *in utero* effect in the absence of maternal toxicity under the conditions of the study.

TEST FACILITY Huntingdon (2013)

B.14. Toxicokinetics

TEST SUBSTANCE Notified chemical

METHOD Non-guideline study
Species/Strain Rat/Sprague-Dawley
Vehicle Olive oil

STUDY DESIGN AND OBJECTIVE
This study involved the determination of plasma toxicokinetic parameters of the test substance in rats, including bioavailability (oral and intravenous injection exposure). Male test animals were 6-8 weeks old and were acclimatised for 7 days prior to dosing. Animals were housed 5 per cage with food and water available ad libitum. The room was kept at 20-26 °C, 40-70% humidity, > 15 air exchanges per hour and lighting period between 0800 and 2000 hrs. The test substance was formulated with olive oil at concentrations of 15, 45 or 100 mg/mL for oral administration to deliver oral doses of 150, 450 or 1000 mg/kg bw (5 males/dose). Another group of 5 males were treated intravenously with the test substance at 20 mg/kg bw (vehicle not specified). Animals were fasted before dosing (duration not specified) but water was available. Blood was collected from the orbital venous sinus at 5, 15, 30, 45 minutes, 1, 2, 4, 6, 8, 10, 24 and 48 hours (0.5 mL/collection).

Detection of the test substance was based on the assumption that it rapidly hydrolyses to various metabolites. A single commonly available metabolite was used as a marker of serum concentrations of the test substance. Plasma samples were treated with base prior to analysis. A HPLC-MS/MS detection method for this metabolite was assessed and its recovery in plasma was 80.5-85.8%, the intraday precision was 9.6-12.7% and the intraday accuracy was 95.1-103.0%, the standard curve r^2 value was 0.998 and the limit of quantitation was 20 ng/mL.

RESULTS

	Plasma concentration (ng/mL)			
	Dose mg/kg bw (route)			
	150 (oral)	*450 (oral)*	*1000 (oral)*	*20 (iv)*
Collection time				
5 min	293	664	602	577
15 min	370	561	1153	942
30 min	377	1202	2033	4298
45 min	511	2018	2892	1429
1 hr	477	2348	3523	1052
2 hr	716	4340	5831	1328
4 hr	683	2862	3526	918
6 hr	896	4362	2729	1007
8 hr	879	5130	1902	1019
10 hr	1172	4122	2909	1080
24 hr	210	1548	1485	539
48 hr	312	1006	591	630
Toxicokinetic parameters				
AUC_{0-48} (μg.h.L^{-1})	27413	108152	87389	36755
$t_{1/2}$ (hr)	29.65	20.91	20.03	41.06
C_{max} (μg.L^{-1})	1344	6376	6673	4672
T_{max} (hr)	7.20	6.00	3.40	-
F (%)	9.9	13.1	4.8	-

AUC, area under the curve; $t_{1/2}$, half-life; C_{max}, maximum concentration; T_{max}, time at C_{max}; F, bioavailability.

DISCUSSION
The bioavailability was determined using the following formula: $F = (AUC^{oral}/AUC^{iv}) \times (dose^{iv}/dose^{oral}) \times 100$. The study authors noted that there was a non-linear relationship between dose and bioavailability. Overall, these toxicokinetic data suggest that oral bioavailability was incomplete and absorption was relatively slow.

A limitation of this study is that it assumes there is no pre-systemic metabolism of the test substance to the metabolite with subsequent absorption and bioavailability of just the metabolite, in which case the test substance itself would not be bioavailable.

CONCLUSION
Under the conditions of this non-guideline toxicokinetic study, absorption of the notified chemical across the gastrointestinal tract was slow and incomplete.

TEST FACILITY CDSERZU (2014)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sludge from a local domestic wastewater treatment plant (Worlingworth, UK).
Exposure Period	28 days.
Auxiliary Solvent	None.
Analytical Monitoring	Theoretical Oxygen Demand (ThOD).
Remarks - Method	No significant deviations in protocol.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
4	3	4	67
7	6	7	75
14	13	14	84
21	20	21	82
28	25	28	95

Remarks - Results	All validity criteria for the test were satisfied. The percentage degradation of the reference compound, sodium benzoate (84%), surpassed the threshold level of 60% by 14 days. Therefore, the test indicates the suitability of the inoculums. The toxicity control exceeded 40% biodegradation after 3 days, showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical after 28 days was 25%. Therefore, the test substance cannot be classified as readily biodegradable according to the OECD (301 F) guideline.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Huntingdon (2012k)

C.1.2. Bioaccumulation

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 305 Bioaccumulation: Semi-static Fish Test.
Species	*Brachydanio rerio* (zebra fish).
Exposure Period	28 days.
Auxiliary Solvent	None.
Concentration Range	Nominal: 0.15 mg/L (low), 1.5 mg/L (high). Actual: 0.12-0.168 mg/L (low), 0.999-1.46 mg/L (high).
Analytical Monitoring	LC-MS
Remarks - Method	The two acetone standard solutions of the notified chemical were prepared 9 days apart, outside the 7 days stated in the protocol. The deviation was not deemed to have had a significant impact on the validity or integrity of the study. All other validity criteria for the test were met and satisfied. The notified chemical is a mixture of components, for which the BCF of only 1 component was measured. During the exposure period, the concentration of the notified chemical in water and fish were measured on days 0, 22, 23, 24, 25, 26, 27, and 28

within the 28-day test period. The bioconcentration factor (BCF) was determined by comparing the concentration of the notified chemical in the fish to the mean concentration of the notified chemical in the test water. The test conditions were: 22.3-23.7 °C, pH 6.90-8.18 and > 60.2% dissolved oxygen.

RESULTS

Bioconcentration Factor	BCF (low concentration) = 0.648 (0.179-1.453). BCF (high concentration) = 3.611 (0.947-14.45).
CT50	Not determined.
Remarks - Results	All validity criteria for the test were satisfied. During the exposure period of 28 days, the mortalities in both control and treated fish were 0% at the end of the test. There were no abnormalities in shape of the body or in swimming and eating behaviour during the test period. The test is considered reliable.

CONCLUSION Under the study conditions, one component of the notified chemical is not considered to be bioaccumulative.

TEST FACILITY Safety Evaluation Center (2013a)

C.1.3. Inherent biodegradability

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 302 C Inherent Biodegradability: Modified MITI Test (II).

Inoculum	Activated sludge samples from ten sites around Guangzhou, China where various chemicals were used and discharged, including wastewater treatment plants, natural bodies of water and surface soils.
Exposure Period	28 days.
Auxiliary Solvent	None.
Analytical Monitoring	Theoretical Oxygen Demand (ThOD).
Remarks – Method	No significant deviations in protocol.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
4	9.5	4	84.2
7	19.7	7	88.1
14	16.4	14	94.6
21	31.3		
28	35.9		

Remarks – Results

During the test period the temperature variation range was 23.6-26.9 °C, outside the 25 ± 1 °C stated in the protocol. In some chromatographic runs the 5th component of the notified chemical was not detected as the flow rate was lower than that stated in the protocol. Neither deviation from protocol was deemed to have had a significant impact on the validity or integrity of the study. All other validity criteria for the test were met and satisfied.

The percentage degradation of the reference compound, sodium benzoate (70.8%), surpassed the threshold level of 60% by 2 days. Therefore, the test indicates the suitability of the inoculums. The toxicity control exceeded 40% biodegradation after 2 days, showing that toxicity was not a factor inhibiting the biodegradability of the test substance. The degree of degradation of the notified chemical after 28 days was 35.9%. Therefore, the test substance cannot be classified as readily biodegradable according to the OECD (302 C) guideline.

CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	Guangdong Detection Center of Microbiology (2012a)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 203 Fish, Acute Toxicity Test – Semi-static.
Species	*Oryzias latipes* (medaka).
Exposure Period	96 hours.
Auxiliary Solvent	None.
Water Hardness	44 mg $CaCO_3$/L.
Analytical Monitoring	GC.
Remarks – Method	Following the range finding test (conducted at a nominal concentration of 110 mg/L of the notified chemical), the definitive test was conducted at 1.8 mg/L of the notified chemical due to its low water solubility. No significant deviations in protocol.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality (%)*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	8	0	0	0	0	0
110	1.8	8	0	0	0	0	0

EC50	> 1.8 mg/L at 96 hours.
NOEC	Not determined.
Remarks – Results	All validity criteria for the test were satisfied. The test solutions were renewed after 48 hours during the 96 h test period. No abnormalities in behaviour or appearance were observed. The 96 h EC50 for fish was determined to be > 1.8 mg/L, based on measured concentrations.
CONCLUSION	Under the study conditions, the notified chemical is not harmful to fish up to the limit of its water solubility.
TEST FACILITY	CERI (2011a)

C.2.2. Chronic toxicity to fish

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 210 Fish, Early-life Stage Toxicity Test – Semi-static.
Species	*Danio rerio* (zebra fish).
Exposure Period	30 days (post-hatch).
Auxiliary Solvent	Acetone.
Water Hardness	96-104 mg $CaCO_3$/L.
Analytical Monitoring	LC-MS/MS.
Remarks – Method	No significant deviations in protocol.

RESULTS

Concentration mg/L		*Number of Eggs*	*Mortality Post-hatch (%)*					
Nominal	*Actual*		*0 d*	*6 d*	*12 d*	*18 d*	*24 d*	*30 d*
Control	Control	60	0	0	11.7	18.3	18.3	18.3
Solvent control	Solvent control	60	0	0	13.3	20.0	20.0	20.0
0.65	0.537	60	0	0	11.7	20.0	20.0	20.0
1.3	1.24	60	0	0	13.3	21.7	21.7	21.7

2.6	2.25	60	0	0	16.7	26.7	26.7	26.7

NOEC 2.25 mg/L.

Remarks – Results All validity criteria for the test were satisfied. The test solutions were renewed every 24 hours during the test period. With the exception of immobility before death, no other abnormalities in behaviour or appearance were observed. The 30 d post-hatch NOEC for fish was determined to be 2.25 mg/L, based on measured concentrations.

CONCLUSION Under the study conditions, the notified chemical is not harmful to fish on a chronic basis up to the limit of its water solubility.

TEST FACILITY Safety Evaluation Center (2013b)

C.2.3. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Semi-static.

Species *Daphnia magna.*

Exposure Period 48 hours.

Auxiliary Solvent None.

Water Hardness 44 mg $CaCO_3$/L.

Analytical Monitoring GC.

Remarks - Method Following the range finding test (conducted at a nominal concentration of 110 mg/L of the notified chemical), the definitive test was conducted at 1.8 mg/L of the notified chemical due to its low water solubility. No significant deviations in protocol.

RESULTS

Concentration mg/L		*Number of D. magna*	*Cumulative Immobilised (%)*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
110	1.8	20	0	0

EC50 > 1.8 mg/L at 48 hours.

NOEC Not determined.

Remarks - Results All validity criteria for the test were satisfied. The test solutions were not renewed during the 48 h test period. No immobilisation or abnormalities in behaviour or appearance were observed. The 48 h EC50 was determined to be > 1.8 mg/L, based on measured concentrations.

CONCLUSION Under the study conditions, the notified chemical is not harmful to daphnids up to the limit of its water solubility.

TEST FACILITY CERI (2011b)

C.2.4. Chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 211 *Daphnia magna* Reproduction Test – Semi-static.

Species *Daphnia magna.*

Exposure Period 21 days.

Auxiliary Solvent Tetrahydrofuran.

Water Hardness 226-259 mg $CaCO_3$/L.

Analytical Monitoring LC-MS/MS.

Remarks - Method Following the range finding test (conducted at nominal concentrations of 0.01-10 mg/L of the notified chemical), the definitive test was conducted

at 0.00427, 0.0138, 0.0573, 0.195, and 0.518 mg/L of the notified chemical due to its low water solubility.

Four daphnids were accidentally killed during preparation, resulting in 18 daphnids being used in the control group (not 20 as stated in the protocol) and 8 daphnids being used in the nominal concentration test (not 10 as stated in the protocol). The deviation was not deemed to have had a significant impact on the validity or integrity of the study. All other validity criteria for the test were met and satisfied.

RESULTS

	Test Concentration mg/L		
	Control	*Solvent Control*	*0.518*
Total No. of Offspring Released by Survived *Daphnia*	108 ± 15	117 ± 15	112 ± 15
Body Lengths of Surviving Adults (mm)	3.84	3.98	3.91
Survival (%)	100	100	87.5*

* Two daphnids were accidentally killed during preparation and therefore excluded from the data calculations.

NOEC 0.518 mg/L.

Remarks - Results All validity criteria for the test were satisfied. The test solutions were renewed every 24 h during the 21 d test period. No sub-lethal effects as determined by body lengths of the surviving adults were observed. The EC50 was not determined due to insufficient parent mortality. The 21 d NOEC was determined to be 0.518 mg/L, based on measured concentrations.

CONCLUSION Under the conditions of the study, the notified chemical is not harmful to daphnids on a chronic basis up to the limit of its water solubility.

TEST FACILITY Huntingdon (2012l)

C.2.5. Algal growth inhibition test

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 201 Freshwater Alga, Growth Inhibition Test.

Species *Pseudokirchneriella subcapitata* (green alga).

Exposure Period 72 hours.

Concentration Range Nominal: 6.8-110 mg/L (loading rate).
Actual: 0.32-1.7 mg/L.

Auxiliary Solvent None.

Water Hardness Not reported.

Analytical Monitoring GD.

Remarks - Method Following the range finding test (conducted at nominal concentrations of 6.8-110 mg/L of the notified chemical), the definitive test was conducted at 0.32, 0.63, 0.98, 1.2, and 1.7 mg/L of the notified chemical due to its low water solubility. No significant deviations in protocol.

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 72 h	*NOE_bC mg/L*	*E_rC50 mg/L at 72h*	*NOE_rC mg/L*
> 1.7	Not determined	> 1.7	0.98

Remarks - Results All validity criteria for the test were satisfied. The actual concentrations of the test substance in water accommodated fractions were measured at 0 and 72 hours within the 72 h test period. No effects were observed.

CONCLUSION Under the conditions of the study, the notified chemical is not harmful to alga up to the limit of its water solubility.

TEST FACILITY	CERI (2011c)

C.2.6. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test – Carbon and Ammonium Oxidation.
Inoculum	Aerated activated sludge from a synthetic sewage feed.
Exposure Period	3 hours.
Concentration Range	Nominal: 10-1000 mg/L (loading rate). Actual: Not determined.
Remarks – Method	The test was conducted at nominal concentrations of 10, 30, 100, 300, and 1000 mg/L of the notified chemical due to its low water solubility. No significant deviations in protocol.
RESULTS	
EC50	> 1000 mg/L at 3 hours.
NOEC	1000 mg/L at 3 hours.
Remarks – Results	All validity criteria for the test were satisfied. No significant effects were observed. Consequently, the EC50 could not be calculated and was determined to be > 1000 mg/L, the highest concentration in the study. The NOEC was determined to be 1000 mg/L.
CONCLUSION	Under the conditions of the study, the notified chemical is not inhibitory to microbial activity up to the limit of its water solubility.
TEST FACILITY	Huntingdon (2012m)

C.2.7. Chronic toxicity to earthworms

TEST SUBSTANCE	Notified chemical.
METHOD	OECD TG 222 Earthworm Reproduction Toxicity Test. US EPA OPPTS 850.6200: Earthworm Subchronic Toxicity Test.
Species	*Eisenia foetida* (earthworm).
Exposure Period	56 days (28 days exposure, 28 days hatching).
Auxiliary Solvent	Acetone.
Remarks - Method	No significant deviation in protocol.

RESULTS

	Test Concentration (mg/kg dry soil weight)	
	Control	*1000*
Adult survival (%)	100	100
Increase in body weight (mg)	12	7
No. hatched juveniles	51.8 ± 14.6	42.1 ± 7.2

LC50	> 1000 mg/kg (dry wt) at 28 days.
NOEC	> 1000 mg/kg (dry wt) at 28 days
Remarks - Results	All validity criteria for the test were satisfied. No significant mortality effects were observed. Some cocoons in the cohort exposed to the notified chemical appeared smaller than those in the control cohort. The 28 d LC50 was out of the tested concentration range (> 1000 mg/kg dry soil weight).
CONCLUSION	Under the conditions of the study, the notified chemical is not harmful to earthworms on a chronic basis.
TEST FACILITY	Safety Evaluation Center (2012)

C.2.8. Seed germination toxicity test

TEST SUBSTANCE	Notified chemical.
METHOD	US EPA OPPTS 850.4200: Seed Germination/Root Elongation Toxicity Test.
Species	*Lycopersicon esculentum* (tomato), *Cucumis sativis* (cucumber), *Lactuca sativa* (lettuce), *Phaseolus radiates* L. (mung bean), *Brassica oleracea* (cabbage), *Citrullus lanatus* (watermelon), *Brassicaceae brassica* (mustard leaf), *Oryza sativa* (rice), *Daucus carota* (carrot), *Zea mays* (corn).
Exposure Period	Test terminated once 65% of the control cohort had germinated and developed roots ≥ 20 mm long.
Concentration Range	Nominal: 5-1000 mg/L. Actual: Not determined.
Auxiliary Solvent	Ethanol.
Analytical Monitoring	GC.
Remarks - Method	No significant deviations in protocol.
RESULTS	
EC50	> 1000 mg/L for germination and root elongation inhibition.
Remarks - Results	During the test period the temperature variation range was 23.9-25.6 °C, outside the 25 ± 1 °C stated in the protocol. The deviation from protocol was deemed not to have had a significant impact on the validity or integrity of the study. All other validity criteria for the test were met and satisfied. At least 65% of test seeds in the control and solvent control treatments had germinated, with a mean root development of ≥ 20 mm long. No significant differences in germination rate and root elongation inhibition rates between the control and solvent control treatments were detected. Germination rates at the nominal concentration of 1000 mg/L were ≥ 60% in all ten seed types tested. The root development inhibition rate ranged from < 0-28.1%. Therefore, the EC50 of both seed germination and root development inhibition are > 1000 mg/L.
CONCLUSION	Under the conditions of the study, the notified chemical is not inhibitory of seed germination or root development.
TEST FACILITY	Guangdong Detection Center of Microbiology (2012b)

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