File No: STD/1524

July 2015

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

PUBLIC REPORT

Ethane, 1-ethoxy-2-(2-methoxyethoxy)-

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

TABLE OF CONTENTS

SUMMARY

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

ASSESSMENT REFERENCE	APPLICANT(S)	CHEMICAL OR TRADE NAME	HAZARDOUS CHEMICAL	INTRODUCTION VOLUME	USE
STD/1524	Epson Australia Pty Ltd	Ethane, 1-ethoxy-2-(2-methoxyethoxy)-	Yes	≤ 5 tonnes per annum	Solvent in printing inks

CONCLUSIONS AND REGULATORY OBLIGATIONS

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

Hazard classification	*Hazard statement*
Flammable Liquids Category 4	H227 – Combustible liquid.
Reproductive Toxicity Category 2 Suspected Human Reproductive Toxicant	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) as a substance toxic to reproduction Category 3 with the following risk phrase:

R62/63: Possible risk of impaired fertility/Possible risk of harm to the unborn child

Human health risk assessment
Provided that the recommended controls are being adhered to, under the conditions of the occupational settings described, the notified chemical is not considered to pose an unreasonable risk to the health of workers.

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

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

Recommendations

REGULATORY CONTROLS

- The notified chemical should be classified as follows:
  - Flammable Liquids Category 4: H227 – Combustible liquid.
  - Reproductive Toxicity Category 2 Suspected Human Reproductive Toxicant: 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.

- The (M)SDS provided by the notifier should be amended as follows:
  - Revise the information for the notified chemical in Sections 2 and 3 to include the hazard classification for reproductive toxicity.
  - Revise Section 8.2.2.2(c) *respiratory protection* to state:

"*Not required unless engineering controls are inadequate to control inhalation exposure (refer to Section 8.3 for ventilation recommendations).*"

- The notifier should comply with relevant State and Territory OHS labelling requirements.

- NICNAS will refer the notified chemical to Safe Work Australia, for their consideration.

CONTROL MEASURES

Occupational Health and Safety

- A person conducting a business or undertaking at a workplace should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced in the ink cartridges, during printing processes:
  - Local exhaust ventilation or other mechanical ventilation (as specified in Safe Work Australia Guidance Control guidance sheet *P39 Wide-format inkjet printing with solvent-borne inks*) if inhalation exposure may occur.

- 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 as introduced in the ink cartridges, during printing processes:
  - Avoid contact with skin and eyes
  - Avoid breathing in vapours
  - Compliance with Safe Work Australia Guidance Control guidance sheet *P39 Wide-format inkjet printing with solvent-borne inks*

- 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 as introduced in the cartridges:
  - Coveralls
  - Disposable gloves if dermal exposure to the ink may occur
  - Respiratory protection if engineering controls are inadequate to control inhalation exposure

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

Disposal

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

Emergency procedures

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

Regulatory Obligations

Secondary Notification
This risk assessment is based on the information available at the time of notification. The Director may call for the reassessment of the chemical under secondary notification provisions based on changes in certain

circumstances. Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act (1989)* the notifier, as well as any other importer or manufacturer of the notified chemical, have post-assessment regulatory obligations to notify NICNAS when any of these circumstances change. These obligations apply even when the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS).

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

(1) Under Section 64(1) of the Act; if
- the notified chemical is imported in any form other than as a component of printing ink at up to 25% concentration in sealed cartridges;
- the ink containing the notified chemical is used for printing in other than commercial facilities.

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from a solvent in printing inks, 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 and a product containing the notified chemical provided by the notifier were 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)
Epson Australia Pty Ltd (ABN: 91 002 625 783)
3 Talavera Rd
NORTH RYDE NSW 2113

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
No details are claimed exempt from publication.

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
USA

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Epson Ink Cartridge T6871 (product containing the notified chemical)

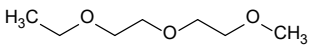
CAS NUMBER
1002-67-1

CHEMICAL NAME
Ethane, 1-ethoxy-2-(2-methoxyethoxy)-

OTHER NAME(S)
HISOLVE EDM
Diethylene glycol methyl ethyl ether
DEGMEE

MOLECULAR FORMULA
$C_7H_{16}O_3$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
148.2 Da

ANALYTICAL DATA

METHOD	FT-IR
Remarks	Measured with a NICOLET 6700 FT-IR equipped with F.S. Thunder Dome ATR (Thermo Fisher Scientific Inc, Waltham USA) and results consistent with structure of the notified chemical
TEST FACILITY	Unknown

METHOD	FT-IR (non-GLP)
Remarks	Measured with a FTIR 8400-S spectrophotometer quipped with a MKII Golden Gate Single

	Reflection ATR System (Shimadzu, Japan) and results consistent with structure of the notified chemical
TEST FACILITY	WIL (2014a)
METHOD	UV-Vis Absorption
Remarks	UV-Vis absorption spectra in water under neutral, acidic and alkaline conditions were obtained using a spectrophotometer. No absorbance maximum was observed.
TEST FACILITY	WIL Research (2014b)
METHOD	NMR
Remarks	Measured with a 400MHz Varian spectrometer (Varian, USA) and results consistent with structure of the notified chemical
TEST FACILITY	WIL Research (2013)

3. COMPOSITION

DEGREE OF PURITY
99.98%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS
None

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% BY WEIGHT)
None

ADDITIVES/ADJUVANTS
None

4. PHYSICAL AND CHEMICAL PROPERTIES

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

Property	Value	Data Source/Justification
Melting Point	< -80 °C	Measured
Boiling Point	177 °C at 101.3 kPa	Measured
Density	922 kg/m^3 at 20 °C	Measured
Vapour Pressure	0.21 kPa at 25 °C	Measured
Water Solubility	> 1 × 10^3 g/L at 20 °C	Measured
Hydrolysis as a Function of pH	$t_{½}$ >1 year at 25 °C at pH 4 – 9	Measured
Partition Coefficient (n-octanol/water)	log Pow = - 0.1 at 20 °C	Measured
Adsorption/Desorption	log K_{oc} <1.26	Measured
Dissociation Constant	Not determined	Does not contain dissociable functionalities
Flash Point (closed cup)	69 °C at 101.8 kPa	Measured
Flammability Limits	Lower limit: 2.5% volume. Upper limit: 33.0% volume	MSDS
Autoignition Temperature	175 °C	Measured
Explosive Properties	Not explosive	Contains no chemical groups associated with explosive properties.
Oxidising Properties	Not determined	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 recommended for hazard classification according to the *Globally Harmonised System of Classification and Labelling of Chemicals (GHS),* as adopted for industrial chemicals in Australia. The recommended hazard classification is presented in the following table.

Hazard classification	*Hazard statement*
Flammable Liquids Category 4	H227 – Combustible liquid

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia. The notified chemical will be imported as a component (10 – 25% concentration) of inks for wide format ink-jet printers in sealed cartridges (maximum capacity of 700 mL). The neat form of the notified chemical will not be imported.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	0.7	1.5	3	4	5

PORT OF ENTRY
Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
The ink cartridges will be received in Australia by Epson Australia Pty Ltd.

TRANSPORTATION AND PACKAGING
The sealed ink cartridges containing the notified chemical will be transported by road throughout Australia.

USE
The notified chemical is a solvent in inks for wide format ink-jet printers for industrial and commercial use, and will be used at 10 – 25% concentration.

OPERATION DESCRIPTION
No reformulation or repackaging of the notified chemical will occur in Australia.

The cartridges containing the notified chemical at 10 – 25% concentration will be delivered to the end-user printing sites in the same packaging in which they are imported. Typical substrates that will be printed include posters, signboards and billboards. The sealed cartridges containing maximum 700 mL of ink will be handled by service technicians or workers in accordance with the instructions provided with the packages. Up to ten cartridges may be installed in each printer. Cleaning cartridges with a capacity of 350 mL, also containing the notified chemical, may be used by the service technicians and workers to clean the printing heads during maintenance. Workers will also carry out adjustments to the machines, including manual cleaning processes.

During printing, the ink containing the notified chemical will be transferred from the cartridges to the printing heads. The printing processes are expected to be fully automated, and the printers will have heaters as part of the equipment. During and immediately after the printing process, much of the notified chemical is expected to be volatilised. Small proportions of the chemical may be trapped in the printing substrates and volatilise slowly after printing.

6. HUMAN HEALTH IMPLICATIONS

6.1. Exposure Assessment

6.1.1. Occupational Exposure

EXPOSURE DETAILS

Transport and storage
Transport and storage workers are unlikely to be exposed to the notified chemical except in the event of an accidental cartridge rupture.

End-use
Under the proposed use scenario, print workers and service technicians may have the potential for dermal and ocular exposure to the inks containing the notified chemical at 10 – 25% concentration during ink cartridge replacement and printer maintenance and cleaning. As the ink cartridges are purposely designed to enclose the ink, and the printing processes are automated, the potential for dermal and ocular exposure to the notified chemical during printing is expected to be limited. Workers handling articles before the inks have completely dried may also come into minor dermal contact with the notified chemical in liquid form up to 25% concentration. The notifier stated that, if dermal exposure to the inks containing the notified chemical is likely to occur, service technicians and print workers are required to wear protective gloves to minimise the potential for exposure.

Repeated inhalation exposure of workers to the notified chemical may occur during and after the printing process, as a large proportion of the chemical is expected to be volatilised during printing. Further vapour may be released slowly from the print matrix, contributing to worker inhalation exposure in the printing and print article storage areas. Specific engineering controls or respiratory personal protective equipment (PPE) to reduce inhalation exposure have not been proposed by the notifier.

In a typical use scenario provided by the notifier, assuming an average office air space of 180 m^3 with an airflow rate of 2.2 changes/hour and with one printer carrying 10 ink cartridges operating in the office, the average air concentration of the notified chemical may reach 17 mg/m^3, if each ink cartridge is expected to be used for 30 days. Workers with an average body weight of 60 kg, assumed air inhalation rate of 23 m^3/day and exposure for 8 hours a day may inhale the notified chemical in a level of 2.17 mg/kg bw/day. It is acknowledged that there is a paucity of relevant exposure data for workers and that variables such as workshop dimensions and number of printers per site highly influence the estimated dose. The pattern of worker exposure is also highly variable and uncertain. For example, workers working in proximity of the printers while the printing processes are still occurring may be exposed to significantly higher than average level of the notified chemical, if local exhaust ventilation above the printing head is absent or insufficient.

Once the inks are dried, the notified chemical is expected to have evaporated and will not be available for further exposure.

6.1.2. Public Exposure
The ink cartridges containing the notified chemical at 10 – 25% concentration are intended for use in industrial and commercial settings and will not be sold to the public. The public may come into contact with dried inks after application to the substrates. However, once the inks are dried, the notified chemical is expected to be evaporated and will not be available for exposure to the public.

6.2. Human Health Effects Assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rat, acute dermal toxicity	LD50 > 2,000 mg/kg bw; low toxicity
Rabbit, skin irritation (2 studies)	Non-irritating to slightly irritating
Rabbit, eye irritation	Slightly irritating
Guinea pig, skin sensitisation – non-adjuvant test	No evidence of sensitisation

Rat, repeat dose oral toxicity – 28 days*	NOAEL = 250 mg/kg bw/day
Rat, repeat dose oral toxicity combined with reproductive/developmental toxicity screening – 42 days	NOAEL = 250 mg/kg bw/day for both repeat dose and reproductive/developmental toxicity
Mutagenicity – bacterial reverse mutation (2 studies)	Non mutagenic
Genotoxicity – simplified *in vitro* mammalian chromosome aberration	Non genotoxic
Genotoxicity – *in vitro* mammalian chromosome aberration	Non genotoxic
Genotoxicity – *in vivo* mammalian micronucleus test	Non genotoxic

* Details of the study are available in the NICNAS assessment report STD/1541 published on the NICNAS website.

Toxicokinetics, metabolism and distribution

The notified chemical has a molecular weight < 500 and is highly water soluble. Based on its chemical and physical characteristics and information on the similar chemical diethylene glycol dimethyl ether (CAS 111-96-6), it is expected that the notified chemical would be readily absorbed through biomembranes via all routes, distributed within the body and metabolised. It has been reported that dermal absorption of glycol ethers in both liquid and vapour form is very high (CICAD, 2002).

Acute toxicity

Acute toxicity studies on the notified chemical suggested that the chemical is of low toxicity via the oral and dermal routes with LD50 > 2,000 mg/kg bw. Although no mortality at the dose level of 2,000 mg/kg bw in the oral toxicity study was observed, clinical signs such as dorsal positions and inanimation were recorded in the test animals for the first day following the oral administration.

No acute inhalation toxicity information was provided for the notified chemical.

Irritation and sensitisation

Two skin irritation studies in rabbit were provided for the notified chemical. One of the studies showed no skin irritation properties for the notified chemical while the other showed reversible skin irritation scores below the GHS classification criteria. Based on the results, the notified chemical is likely to be slightly irritating to the skin.

An eye irritation study on the notified chemical showed that the chemical is slightly irritating to the eye with reversible effects.

A Buehler test on the notified chemical in guinea pigs did not reveal evidence of reactions indicative of skin sensitisation.

Repeated dose toxicity

Two repeated dose oral toxicity studies were made available for the notified chemical. A 42-day combined repeated dose oral toxicity study on the notified chemical with reproductive/developmental toxicity screening test was submitted by the notifier (Mitsubishi, 2014a). In this study, the dose levels were selected as 50, 250 and 1,000 mg/kg bw/day based on a 14-day range finding study. Two recovery groups, administered at 0 or 1,000 mg/kg bw/day, were also included in the study for a recovery period of 2 weeks.

A 28-day repeated dose toxicity study on the notified chemical conducted to OECD TG 407 was also available. Details of the study were included in the NICNAS assessment report STD/1541 published on the NICNAS website. Dose levels tested in this study were 250, 500 and 1,000 mg/kg bw/day. Two recovery groups (for a recovery period of 2 weeks) were administered at 0 or 1,000 mg/kg bw/day.

Both studies used a Sprague-Dawley strain of rat, with animals dosed by gavage. Combined, the 42-day and 28-day studies provide data for a dose response characterisation with dose levels of 0, 50, 250, 500 and 1,000 mg/kg bw/day. Additionally, a direct comparison can be made between the studies at 250 and 1,000 mg/kg bw/day and at 1,000 mg/kg bw/day following a 2 week recovery period.

Mortality

In the 42-day repeated dose oral toxicity study combined with reproductive/developmental screening test, no deaths occurred during the 6-week dosing period, including the highest dose level of 1,000 mg/kg bw/day. In the 28-day repeated dose oral toxicity study, at the dose level of 1,000 mg/kg bw/day, 2 of 10 males were found dead during the dosing period. The cause of deaths was not established by histopathology examination. The

clinical sign seen in these 2 animals was limited to a decrease in spontaneous motor activity on Day 9 only. An absence of treatment-related clinical signs of toxicity and effects on body weight in the animals of both studies, and the fact that no deaths were seen in the 42-day study suggest that the deaths in the 28-day study were unlikely to be related to the test material.

Clinical observations

Behavioural findings were not observed in the 42-day study. In the 28-day study, at dose levels of 500 or 1,000 mg/kg bw/day, the notified chemical induced a few sporadic behavioural changes in males during the treatment. Thus, an evaluation of all the available data does not provide robust evidence of treatment-related clinical signs of toxicity or a neurotoxicity potential for the notified chemical.

No treatment-related effect was seen on body weight or food consumption in either of the two available repeated dose studies up to the dose level of 1,000 mg/kg bw/day, including recovery groups.

Laboratory findings

Statistically significant decreases were seen in alkaline phosphatase, sodium and chloride in both the 42-day and 28-day studies at 1,000 mg/kg bw/day. The alkaline phosphatase changes were also seen in the 28-day study at the dose levels of 250 and 500 mg/kg bw/day, and may possibly be reflective of an adverse effect on metabolic function. These changes were considered to be treatment-related and potentially toxicologically significant at 500 and 1,000 mg/kg bw/day. The decreases in sodium and chloride were slight and absent in animals at the end of recovery period. Therefore, these findings are not considered toxicologically significant but potentially treatment-related. No treatment-related toxicologically significant changes in clinical chemistry parameters occurred at the next dose level of 250 mg/kg bw/day in either the 42-day or the 28-day study.

In the 42-day study, statistically significant changes were seen at 1,000 mg/kg bw/day: decrease in mean corpuscular haemoglobin concentration, eosinophil count and ratio, and increase in monocyte ratio. In the 28-day study, statistically significant changes were seen in haematology parameters: reduction in haemoglobin concentration and reticulocyte count at 500 and 1,000 mg/kg bw/day, and increase in monocytes at 1,000 mg/kg bw/day. An evaluation of all the available data therefore provides robust evidence of a treatment-related and toxicologically significant increase in monocytes, eosinophils and eosinophil ratio at 1,000 mg/kg bw/day. No treatment-related toxicologically significant changes in haematology parameters were considered to occur at the next dose level of 500 mg/kg bw/day.

No treatment-related effect was seen on urinalysis parameters in either study, up to the highest dose level of 1,000 mg/kg bw/day, including the recovery groups.

Effects on non-reproductive organs

In the 42-day study, statistically significant changes in liver (increase) and thymus (decrease) weight were reported at the dose level of 1,000 mg/kg bw/day. In the 28-day study changes in spleen and liver (increase), adrenal and thymus (decrease) weight were consistently seen at the dose level of 1,000 mg/kg bw/day. Liver weight increase was also seen in animals treated at 500 mg/kg bw/day. While the liver weight changes were associated with microscopic changes, the thymus weight changes were associated with macroscopic and microscopic changes. The liver and thymus weight changes are considered potentially treatment-related and toxicologically significant. The adrenal weight findings in the 28-day study were seen in the absence of macroscopic and microscopic changes and are not considered toxicologically significant. The spleen weight findings in the 28-day study were seen in the presence of macroscopic and microscopic changes, but the findings were absent in the 42-day study, suggesting that the findings were likely not related to the test material. No treatment-related toxicologically significant changes in organ weights were considered to occur at the next dose level of 250 mg/kg bw/day.

The limited finding of minimal periacinar hepatocyte hypertrophy in the liver of 1 animal of the recovery group administered at 1,000 mg/kg bw/day in the 28-day study was not seen in the 42-day study. Thus, it is not considered to be toxicologically significant but it may potentially be treatment-related.

At the end of the recovery period, no adverse treatment effects on the non-reproductive organs were seen in males administered at 1,000 mg/kg bw/day.

Reproductive/developmental toxicity

Reproductive toxicity
In both the 42-day and 28-day studies, reproductive/developmental toxicity-related findings were observed in the high dose treatment group of 1,000 mg/kg bw/day. Statistically significant reductions in epididymis and testis weights of the males were associated with histopathological changes in the reproductive organs including degeneration/necrosis of spermatocyte/spermatid, decrease of sperm and appearance of cell debris in the duct of the epididymides, some of which were of increased degree and incidence at the end of the recovery period. Reversibility of organ weight reductions was not recorded in either study, following a 2 week recovery period. These changes are considered treatment-related and toxicologically significant.

No treatment-related macroscopic effect was seen on male sex organs in either study at the end of the dosing period or at the end of the recovery period, up to and including 1,000 mg/kg bw/day.

Sperm analysis was carried out in the 28-day study at the end of the dosing period. The following effects seen in males administered at 1,000 mg/kg bw/day were considered treatment-related and toxicologically significant:

- Motility and count: a decrease in motility of spermatozoa and an increase in immobile spermatozoa which were associated with a decrease in percentage mobile spermatozoa.

- Morphology: a statistically significant ($p < 0.05$) decrease in the percentage of normal spermatozoa and a statistically significant ($p < 0.05$) increase in percentage spermatozoa with head anomaly which were associated with an increase (not statistically significant) in percentage of isolated head in the sample.

- Numeration in epididymis: a statistically significant ($p < 0.01$) lower epididymis tail weight and a decrease (not statistically significant) in the number of spermatozoa in the tail of the left epididymis.

Overall, a comparison of the data between the two available studies shows no significant qualitative differences in effects on male reproductive organs of the test material. Both studies provide no evidence of treatment-related macroscopic changes in male sex organs. However, both studies demonstrated a reduction in testis and epididymis weight along with microscopic changes in these organs at the dose level of 1,000 mg/kg bw/day. Additionally, in the study where sperm analysis was carried out, toxicologically significant changes were seen.

There were no effects of reproductive toxicity seen at the next dose levels of 250 or 500 mg/kg bw/day in the 42-day or the 28-day study, respectively.

Developmental toxicity
In the 42-day study, combined with reproductive/developmental toxicity screening test, prolongation of gestation period and decrease of delivery index were noted in females treated at the dose level of 1,000 mg/kg bw/day. In offspring, a decrease of litter number and birth index, and increase of number of stillborn were observed that were significantly different from the parameters of the vehicle control. Other adverse effects seen in the high dose group were total litter loss in 5 females and at post-natal Day 4 a reduced viability index and low body weights of offspring. The No Observed Adverse Effect Level (NOAEL) was established as 250 mg/kg bw/day in this study for both the repeated dose toxicity and the reproductive/developmental toxicity, based on the effects observed at the dose level of 1,000 mg/kg bw/day.

Further considerations
Based on the evaluation of the two available studies, it can be concluded that the observed findings in male reproductive organs at the dose level of 1,000 mg/kg bw/day cannot be considered as a secondary, non-specific consequence of other toxic effects. The observed deaths in the 28-day study, sporadic clinical signs, limited changes in haematology parameters, change in a single clinical chemistry parameter, organ weight changes in the liver and thymus, macroscopic changes in the thymus, and microscopic changes in the liver and thymus, are not considered to provide evidence of significant generalized toxicity for which the observed findings in male reproductive organs can be considered as secondary, non-specific consequence.

The 42-day study provided by the notifier produced the same findings as in the 28-day study regarding the male reproductive organs at the dose level of 1,000 mg/kg bw/day, such as decreases in absolute and relative testis and epididymis weight and microscopic changes in these organs. These effects on the male reproductive organs in both studies did not reverse after a 2 week recovery period and were consistent with the

reproductive/developmental hazards seen with some other short chain glycol ethers of this chemical class. Therefore, the concern that the notified chemical is a potential hazard for reproductive toxicity cannot be currently dismissed based on the available data. Additionally, this concern is supported by the fact that certain glycol ethers of this chemical class are considered as reproductive toxicants. *Safe Work Australia* (SWA) has listed a structurally very similar chemical, diethylene glycol dimethyl ether (CAS No. 111-96-6), as a reproductive Category 2 toxicant in the *Hazardous Substances Information System* (HSIS, web link - http://hsis.safeworkaustralia.gov.au/).

Recently, the US EPA has issued a Significant New Use Rule (SNUR, US EPA, 2014) on 7 commercially available ethylene glycol ethers regarding reproductive hazard concerns for this group of chemicals. According to the US EPA, based on both toxicity data and structure-activity relationships, ethylene glycol ethers that consist of 1, 2 or 3 glycol ether groups and terminal alkyl groups of 1 to 4 carbons can be anticipated to cause developmental and reproductive toxicity and/or haemolytic toxicity. Based on the structure of the notified chemical, it characteristically falls into the same category of ethylene glycol ethers for which the US EPA raised concerns. According to the US EPA SNUR documents, ethylene glycol ethers have been shown to cause damage to reproductive organs as well as toxicity to blood and blood forming organs. Exposure to this group of chemicals can pose risks to consumers, workers and children because of potential birth defects due to damage of reproductive organs.

Mutagenicity/Genotoxicity
The notified chemical is not expected to be mutagenic or genotoxic, as two bacterial reverse mutation assays and two *in vitro* mammalian chromosome aberration tests did not reveal evidence of genotoxicity. One *in vivo* mammalian erythrocyte micronucleus test also did not show evidence of clastogenicity for the notified chemical. However, as no clinical effects of toxicity were observed during the study, evidence of the test substance reaching bone marrow to produce clastogenicity could not be verified. Overall, based on the information available there is not a strong concern for genotoxicity.

Health hazard classification
Evaluation of the 42-day repeated dose toxicity study provided by the notifier concluded that the observed findings in male reproductive organs at 1,000 mg/kg bw/day were toxicologically significant and not considered a secondary non-specific consequence of other toxic effects. The study also raised concerns for developmental toxicity at the highest dose tested of 1,000 mg/kg bw/day. According to the GHS (Section 3.7.2.5.3), findings on male reproductive organs in repeat dose studies can be considered sufficient to justify classification for reproductive toxicity in the absence of a one or two generation test.

The systemic findings in the 28-day repeated dose toxicity study, excluding effects on the male reproductive organs, are also not considered to constitute marked toxicity of the test substance such that the observed effects on male reproductive organs may be considered a secondary, non-specific consequence of such. Supportive evidence includes observed deaths at 1,000 mg/kg bw/day being unlikely to be related to the test material; no significant changes in bodyweight and food consumption; sporadic clinical signs of toxicity; limited (and generally non-reproducible) changes in haematology parameters; change in a single clinical chemistry parameter; and limited macroscopic changes and changes to organ weight. Furthermore, there were observed changes in male reproductive organs, including histopathological changes, which were still evident after a 2 week recovery period.

The 42-day and 28-day studies produced the same findings at 1,000 mg/kg bw/day: decreases in absolute and relative (to bw) testis and epididymis weight, and microscopic changes in these organs. Both studies also showed no reversibility of effects on testis and epididymis weight and microscopic changes in these organs after a 2-week recovery period. Additionally, sperm analysis in the epididymis was undertaken in the 28-day study with treatment-related effects being noted on motility, count, morphology and numeration in the epididymis at 1,000 mg/kg bw/day.

Overall, based on the findings observed in the two repeated dose studies, which are not considered as a secondary non-specific consequence of other toxic effects, it is concluded that the full safety of the notified chemical has not currently been established, with respect to reproduction and development. Classification as a Category 2 reproductive toxicant under the GHS is therefore justified in this instance, for the notified chemical.

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

Hazard classification	*Hazard statement*
Reproductive Toxicity Category 2 Suspected Human Reproductive Toxicant	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 phrases:

R62/63: Possible risk of impaired fertility/Possible risk of harm to the unborn child

6.3. Human Health Risk Characterisation

6.3.1. Occupational Health and Safety

According to the study reports provided, the notified chemical may be slightly irritating to the skin and eye. However, the enclosed nature of the packaging containing the notified chemical at a concentration ≤ 25% and the provision of handling instructions would limit the irritation effects and dermal/ocular exposure. Dermal exposure could also occur to vapour released during and after printing. The notifier stated in the submission that, if dermal exposure to the inks containing the notified chemical is likely to occur, service technicians and workers are required to wear protective gloves to minimise the potential for exposure.

The major concern for long-term exposure to the notified chemical is the possibility of adverse reproductive and/or developmental outcomes to workers carrying out printing and associated processes. As the notified chemical is expected to volatilise during printing and drying, inhalation exposure to workers during and after printing is expected to be the largest contributor to systemic exposure. Based on the NOAEL of 250 mg/kg bw/day established in the repeated oral toxicity study combined with reproductive/developmental toxicity screening for the notified chemical and the daily average inhalation uptake of 2.17 mg/kg bw/day in a typical use scenario (see Section 6.1.1), a margin of exposure (MoE) can then be calculated as approximately 115. A MoE value ≥ 100 is considered to be acceptable for the proposed use scenario. However, as mentioned in Section 6.1.1, there is a paucity of relevant exposure data for workers. The worker inhalation exposure scenario is also uncertain. It is acknowledged that these factors highly influence the calculated MoE. Therefore, given the hazard profile of the notified chemical, risk controls (i.e., engineering, work practices and PPE) should be implemented and their effectiveness monitored.

Under the conditions of use provided by the notifier regarding the product composition, usage and scenarios of use, the risk to printing workers from the use of the notified chemical is not expected to be unreasonable. However changes in use parameters such as higher usage of the ink containing the notified chemical, higher concentrations of the notified chemical in the inks, or printing in poorly ventilated or small areas may increase the inhalation exposure and thus the risk. Therefore controls to reduce inhalation exposure during printing and while the printed media are drying would further reduce exposure and risk. These could include enhanced ventilation controls and safe work practices. The Safe Work Australia (SWA) guidance document, *P39 –Wide-format inkjet printing with solvent-borne inks*, recommends providing a good standard of general ventilation, and that ventilation equipment is maintained and working effectively. In order to provide the fresh air, powered wall- or window-mounted fans, with five to ten air changes per hour and a through draught, are recommended in this guidance document that is higher than the expected ventilation under the scenario provided by the notifier. Safe work practices and use of appropriate PPE would further reduce exposure. The notifier has advised that gloves will be worn if contact with the liquid ink is expected.

While the notified chemical is classified as a flammable liquid Class 4, under the proposed use scenario it is not likely that the air concentration of the notified chemical would reach the lower explosion limit of 2.5% if effective engineering controls (ventilation) are in place to reduce the inhalation exposure of workers. Therefore, if these controls are in place, the notified chemical is not expected to pose a flammability hazard in the workplace.

Provided that adequate workplace controls are in place to reduce exposure to the inks containing the notified chemical, the risk to workers is not considered unreasonable.

6.3.2. Public Health

The products containing the notified chemical will not be sold to the public. The public may have contact with dry printed materials. However, as the notified chemical is used as a solvent of the ink, it is expected to be

evaporated during the printing and not to be available for exposure after drying. Therefore, based on the use scenario, the risk of the notified chemical to the health of the public is not considered to be unreasonable.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1. Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical will not be manufactured or reformulated in Australia. It will be imported in sealed cartridges. The ink cartridges are designed to prevent leakage and will not be opened during transport. Therefore there will be no release of the notified chemical to the environment from these activities.

RELEASE OF CHEMICAL FROM USE

The ink cartridges are designed to prevent leakage and will not be opened during use, installation or replacement. Therefore there will be no release of the notified chemical to the environment from these activities under normal conditions. However, if leakage or spillage occurs, the ink containing the notified chemical is expected to be contained with absorbent materials and sent to licensed waste disposal contractors. The residual ink containing the notified chemical (2% of the total import volume) is expected to be disposed of to landfill. The majority of the notified chemical is expected to be evaporated during the printing process.

RELEASE OF CHEMICAL FROM DISPOSAL

Empty cartridges containing the notified chemical are expected to be disposed of to landfill.

7.1.2. Environmental Fate

As the majority of the notified chemical is expected to be released to the atmosphere, the potential for the notified chemical to persist and experience long range transport was assessed (AOP Program v1.92; US EPA, 2011). The notified chemical is predicted to experience a half-life of 3.7 hours (assuming a 12 hour day). As such, it is expected that the notified chemical will undergo rapid degradation via reactions with OH-radicals, and will not experience long-range transport.

The notified chemical trapped in the ink matrices is expected to be disposed of to landfill with the substrate to which the ink is applied. The notified chemical is not readily biodegradable. Given the high water solubility and low log Koc, the notified chemical may leach from landfill and enter surface waters. A small proportion of the notified chemical may be released to sewer during paper recycling. Given the high water solubility and low log Koc, the notified chemical is not expected to partition to sludge during waste water treatment processes in sewage treatment plants (STPs). Therefore, the notified chemical is expected to remain in waste water and be released to aquatic environments.

Based on its high water solubility and low log Pow, the notified chemical is not expected to bioaccumulate. Ultimately, the notified chemical is expected to degrade via biotic and abiotic processes in the atmosphere and surface waters to form water and oxides of carbon.

7.1.3. Predicted Environmental Concentration (PEC)

Based on its use in printing, it is conservatively assumed that 100% of the total import volume of the notified chemical was used in paper printing. Using a worst-case scenario, it is assumed that 50% of the paper products containing the notified chemical will be recycled and will be released to the sewer with no removal during recycling or STP processes. As the notified chemical is to be processed at paper recycling facilities located throughout Australia, it is anticipated that such releases will occur on 260 days into the Australian effluent volume. The resultant estimate for the predicted environmental concentration (PEC) in sewage effluent nationwide is summarised in the table below.

Predicted Environmental Concentration (PEC) for the Aquatic Compartment		
Total Annual Import/Manufactured Volume	5,000	kg/year
Proportion expected to be released to sewer	50%	
Annual quantity of chemical released to sewer	2,500	kg/year
Days per year where release occurs	260	days/year
Daily chemical release:	9.62	kg/day

Water use	200.0	L/person/day
Population of Australia (Millions)	22.613	million
Removal within STP	0%	
Daily effluent production:	4,523	ML
Dilution Factor - River	1.0	
Dilution Factor - Ocean	10.0	
PEC - River:	2.13	µg/L
PEC - Ocean:	0.21	µg/L

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1,000 L/m^2/year (10 ML/ha/year). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 10 cm of soil (density 1500 kg/m^3). Using these assumptions, irrigation with a concentration of 2.1 µg/L may potentially result in a soil concentration of approximately 14.2 µg/kg from each year of irrigation. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 70.9 µg/kg and 141.7 µg/kg, respectively.

7.2. Environmental Effects Assessment

Ecotoxicological data were submitted for the notified chemical. Details of the studies can be found in Appendix C.

Endpoint	*Result*	*Assessment Conclusion*
Fish	LC50 (96 h) > 90.8 mg/L	Not harmful to fish at the tested concentration
Daphnia	LC50 (48 h) > 93.6 mg/L	Not harmful to aquatic invertebrates at the tested concentration
Algae	EC50 (96 h) > 89.5 mg/L	Not harmful to algae at the tested concentration

The notified chemical is not harmful to fish, aquatic invertebrates and algae at the tested concentrations. Therefore, under the *Globally Harmonised System of Classification and Labelling of Chemicals* (GHS; United Nations, 2009), the notified chemical has not been formally classified for acute and chronic toxicities.

7.2.1. Predicted No-Effect Concentration

The predicted no-effect concentration (PNEC) for the notified chemical has been calculated and is presented in the table below. The PNEC is calculated based on the endpoint for the most sensitive species (Algae, E_rC50) for the notified chemical. Acute ecotoxicity endpoints for aquatic species from three trophic levels are available. Therefore, an assessment factor of 100 has been used.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment		
Endpoint (Lower Limit)	89.5	mg/L
Assessment Factor	100	
PNEC:	895.0	µg/L

7.3. Environmental Risk Assessment

The Risk Quotient values have been calculated as follows:

Risk Assessment	PEC µg/L	PNEC µg/L	Q
Q - River	2.13	895	0.002
Q - Ocean	0.21	895	0.0002

The Risk Quotients (Q = PEC/PNEC) for a conservative discharge scenario have been calculated to be << 1 for the river and ocean compartments. The notified chemical is not expected to be bioaccumulative and is expected to slowly degrade in the environment. Based on the short half-life of the notified chemical in air, it is not expected to pose an unacceptable risk in this compartment. Based on the assumed low hazard and the assessed use pattern of the notified chemical, it is not expected to pose an unreasonable risk to the environment.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point < -80 °C

Method	OECD TG 102 Melting Point/Melting Range. EC Council Regulation No 440/2008 A.1 Melting/Freezing Temperature.
Remarks	DSC method. No significant protocol deviations. The chemical remained in liquid form at the lowest temperature tested (-80 °C).
Test Facility	WIL Research (2014)

Boiling Point 177 °C at 101.3 kPa

Method	OECD TG 103 Boiling Point. EC Council Regulation No 440/2008 A.2 Boiling Temperature.
Remarks	DSC method. No significant protocol deviations. An endothermic peak below the boiling temperature was attributed to evaporation.
Test Facility	WIL Research (2014)

Density 0.922×10^3 kg/m^3 at 20 °C

Method	OECD TG 109 Density of Liquids and Solids. EC Council Regulation No 440/2008 A.3 Relative Density.
Remarks	Pycnometer method. No significant protocol deviations.
Test Facility	WIL Research (2014)

Vapour Pressure 0.21 kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Council Regulation No 440/2008 A.4 Vapour Pressure.
Remarks	Isothermal thermogravimetric effusion method. No significant protocol deviations.
Test Facility	WIL Research (2014)

Solubility > 1×10^3 g/L at 20 °C

Method	OECD TG 105 Water Solubility
Remarks	After the stirring period, the test substance was clear and no undissolved test substance was observed. The solubility of the test substance was determined by visual observations.
Test Facility	WIL Research (2014)

Hydrolysis as a Function of pH Hydrolytically stable

Method OECD TG 111 Hydrolysis as a Function of pH.

pH	*T (°C)*	*t½*
4	25	> 1 year
7	25	> 1 year
9	25	> 1 year

Remarks	The mean concentration of the test substance after 5 days at 50 °C had not decreased by more than 10%. The test substance is considered hydrolytically stable according to the criterion in data reporting guidelines for hydrolysis studies according to this test.
Test Facility	WIL Research (2014)

Partition Coefficient (n-octanol/water) log Pow = -0.1 at 20 °C

Method	OECD TG 107: Partition Coefficient (n-octanol/water), Shake Flask Method
Remarks	The Shake flask method at neutral pH was applied for the determination of the partition coefficient of the test substance.
Test Facility	WIL Research (2014)

Adsorption/Desorption log K_{oc} < 1.26

Method	OECD TG 121 Adsorption – Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks	The HPLC analysis was performed at neutral pH. The HPLC method using soil-adsorption-reference data was applied for the determination of the adsorption coefficient (K_{oc}) of the test substance.
Test Facility	WIL Research (2014)

Flash Point 69 °C at 101.8 kPa

Method	EC Council Regulation No 440/2008 A.9 Flash Point.
Remarks	Determined using the Pensky Martens Closed Cup method. No significant protocol deviations.
Test Facility	WIL Research (2014)

Autoignition Temperature 175 °C

Method	EC Council Regulation No 440/2008 A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	No significant protocol deviations.
Test Facility	WIL Research (2014)

Explosive Properties No explosive properties

Method	EC Council Regulation No 440/2008 A.14 Explosive Properties.
Remarks	The test substance does not contain chemical groups which are associated with explosive properties.
Test Facility	WIL Research (2014)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical (99.98% in purity)
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method
Species/Strain	Rat/Crl:CD (SD), females
Vehicle	Sterile distilled water
Remarks - Method	No significant deviations of the protocol were noted.

RESULTS

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

LD50	> 2,000 mg/kg bw
Signs of Toxicity	At the observations from 1 to 4 hours after dosing, clinical signs described as dorsal positions and inanimation were observed in all test animals dosed at 2,000 mg/kg bw. The signs were recovered 1 day after the administration.
Effects in Organs	No necropsy findings caused by the administration of the test substance were noted.
Remarks - Results	No mortality of the test animals was noted during the study.
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	KTR (2013a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical (99.98% in purity)
METHOD	OECD TG 402 Acute Dermal Toxicity (Limit Test)
Species/Strain	Rat/Crl:CD (SD), SPF
Vehicle	Sterile distilled water
Type of dressing	Semi-occlusive
Remarks - Method	No significant deviations of the protocol were noted. A control group was included.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	10 (5 F/5 M)	0	0/10
2	10 (5 F/5 M)	2,000	0/10

LD50	> 2,000 mg/kg bw
Signs of Toxicity - Local	No local clinical signs related to the administration of the test substance were noted.
Signs of Toxicity - Systemic	No systemic clinical signs related to the administration of the test substance were noted.
Effects in Organs	No necropsy findings related to the administrations of the test substance were noted.
Remarks - Results	No mortality of the test animals was noted during the study.
CONCLUSION	The notified chemical is of low toxicity via the dermal route.
TEST FACILITY	KTR (2013b)

B.3. Irritation – skin (1)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation)
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	None
Observation Period	4 hours exposure, 7 days observation after removal of treatment
Type of Dressing	Semi-occlusive
Remarks - Method	The purity of the test substance was not specified. After the 4 h application period, any residual test material was removed by gentle swabbing with 74% industrial methylated spirits.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	*2*	*3*			
Erythema/Eschar	2	1.7	1.3	2	< 7 days	0
Oedema	1	1	0.3	2	> 72 hours	0

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

Remarks - Results	Well defined erythema and slight oedema was noted at all treated skin sites after 1 hour after the patch removal. After 7 days, the irritation effects were recovered; however, slight desquamation was observed on all treatment sites.
CONCLUSION	The notified chemical is slightly irritating to the skin.
TEST FACILITY	Safepharm (1997a)

B.4. Irritation – skin (2)

TEST SUBSTANCE	Notified chemical (99.98% in purity)
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White, females
Number of Animals	3
Vehicle	None
Observation Period	4 hours exposure, 72 hours observation after removal of treatment
Type of Dressing	Semi-occlusive
Remarks - Method	No significant deviations of the protocol were noted. The animals were treated sequentially, to check for any serious effects. Observations were taken for 72 h after patch removal.

RESULTS

Remarks - Results	No dermal irritation (including erythema/eschar and oedema) scores above zero for the test substance were recorded in the study. No test substance-related clinical signs and mortality were noted during the study. Body weight gains were as expected.
CONCLUSION	The notified chemical is non-irritating to the skin.
TEST FACILITY	KTR (2014a)

B.5. Irritation – eye

TEST SUBSTANCE	Notified chemical (99.98% in purity)
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion
Species/Strain	Rabbit/New Zealand White
Number of Animals	3 (Females)
Observation Period	6 days
Remarks - Method	No significant deviations of the protocol were noted. Five minutes prior to treatment, two drops of a topical ocular anaesthetic (0.5% proparacaine hydrochloride) were applied to each test eye. The test substance in the amount of 0.1 mL per treatment was then applied.

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	1.67	1.67	1.67	2	< 6 days	0
Conjunctiva: chemosis	1	1	0.67	2	< 72 hours	0
Conjunctiva: discharge	0.33	1	0.33	2	< 72 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	After the treatment with the test substance, eye irritation signs such as conjunctiva redness, discharge and chemosis were observed. These signs were recovered within 6 days.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	KTR (2014b)

B.6. Skin sensitisation

TEST SUBSTANCE	Notified chemical (99.98% in purity)
METHOD	OECD TG 406 Skin Sensitisation – Buehler Test Method
Species/Strain	Guinea pig/ElmSam:HA, males
PRELIMINARY STUDY	Maximum Non-irritating Concentration: topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 20 Control Groups: 10 positive/10 negative
INDUCTION PHASE	Induction Concentration: topical: 100% Inductions were applied on Days 0, 7 and 14 on the same induction area for each test animal.
Signs of Irritation	Not noted
CHALLENGE PHASE	Challenge Concentration topical: 100% Challenge was applied on Day 28 on a new challenge area for each test animal.
Remarks - Method	Sterile distilled water was used as a vehicle for the test substance and as a negative control. DNCB (1-chloro-2,4-dinitrobenzene) at 1% in corn oil was used as a positive control.

RESULTS

Animals	*Challenge Concentration*	*Skin Reactions after Challenge*			
		24 h		*48 h*	
		S.I.	*F.I.*	*S.I.*	*F.I.*
Test Group (with induction exposure)	100% (test substance)	0	0	0	0
Negative Control Group	100% (test substance)	0	0	0	0
Positive Control Group	1% (DNCB)	1.6	100	0.6	60

S.I: sensitisation index (mean score of skin reaction in the group)
F.I: frequency index (percentage of animals with skin reaction in the group)

Remarks - Results: One animal in the treatment group in the main study was accidentally injured 1 day after first induction and was euthanized. No treatment-related mortality or clinical signs were observed in any treated animals. A normal increase in body weight was seen in all surviving animals.

No skin reactions were seen in treated or negative control animals. The positive controls behaved as expected, confirming the validity of the test system.

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

TEST FACILITY: KTR (2014c)

B.7. Repeat dose toxicity – 14 day range-finding

TEST SUBSTANCE: Notified chemical

METHOD: Range-finding study to select doses for combined repeated dose and reproductive/developmental toxicity screening test (see Appendix B.8.)

Observations and examinations: clinical signs, body weight, food consumption, haematology, blood chemistry, necropsy and organ weight

Species/Strain: Rat/Crl:CD (SD)
Route of Administration: Oral – gavage
Exposure Information: Total exposure days: 14 days
Dose regimen: 7 days per week
Post-exposure observation period: none
Vehicle: Water
Remarks - Method: The purity of the test substance was not specified. No GLP statement was provided.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	10 (5 F/5 M)	0	0/10
Low dose	10 (5 F/5 M)	110	0/10
Mid dose	10 (5 F/5 M)	330	0/10
High dose	10 (5 F/5 M)	1,000	0/10

Mortality and Time to Death
No unscheduled deaths of test animals were recorded.

Clinical Observations
No test substance related abnormality was noted in the test animals.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Low values of mean corpuscular haemoglobin concentration (MCHC) were noted in males treated at dose levels ≥ 330 mg/kg bw/day. Low values of platelets, reticulocyte ratio and reticulocytes were noted in males treated at

a dose level of 1,000 mg/kg bw/day.

Effects in Organs
Increase of liver weight was noted in males treated at 1,000 mg/kg bw/day. Decrease of ovaries weight was noted in females treated at 1,000 mg/kg bw/day.

Remarks – Results
Decrease of relative testes weight in males treated at 110 and 1,000 mg/kg bw/day was also noted but considered as incidental by the study authors due to the lack of dose-dependency.

CONCLUSION
A high dose level of 1,000 mg/kg bw/day for the test substance was selected for the subsequent combined repeat dose toxicity study with reproductive/developmental toxicity screening test (see Appendix B.8.)

TEST FACILITY Mitsubishi (2013)

B.8. Repeat dose toxicity – 42-day study, combined with reproductive/developmental toxicity screening

TEST SUBSTANCE Notified chemical (99.98% in purity)

METHOD OECD TG 422 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test

Species/Strain	Rat/Crl:CD (SD)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 42 days for males and satellite females (without mating); until Day 4 of lactation for females Dose regimen: 7 days per week Post-exposure observation period: 14 days
Vehicle	Water
Remarks - Method	Each group consisted of 12 males and 12 females. Five satellite females each were added to the high dose (1,000 mg/kg bw/day) group and the control group. Ten animals (5 males and 5 satellite females) from the high dose group were examined for recovery along with ten animals (5 males and 5 satellite females) from the control group.

RESULTS

Group	*Number and Sex of Animals*	*Dose (mg/kg bw/day)*	*Mortality*
Control	19 (7 M/12 F)	0	2/19
Low dose	24 (12 M/12 F)	50	0/24
Mid dose	24 (12 M/12 F)	250	2/24
High dose	19 (7 M/12 F)	1000	7/19
Control recovery	10 (5 M/5 F)	0	0/10
High dose recovery	10 (5 M/5 F)	1000	0/10

Mortality and Time to Death
All male animals survived the test until scheduled necropsy.

One female each in the control group and the high dose group, and 2 females in the mid dose group were found non-pregnant after mating. One female in the high dose group was found non-copulated and 1 female in the control group was found non-delivering. Above animals were terminated before the study was completed.

Due to total litter loss, 5 more unscheduled sacrifices were recorded in the females of the high dose group.

Clinical Observations
Decreased motor activity was noted in females of the high dose group.

Body Weight and Food Consumption
No significant difference of body weight was noted in males and females between the vehicle control and test groups throughout the dosing and recovery period, including female gestation and lactation period.

No treatment-related changes of food consumption were noted in the study. High values of food consumption were noted in females of the high dose recovery group on Day 50; however, the changes were not considered to be treatment-related since these changes were noted only at one measurement time point and no significant difference was noted in the body weight on Day 50.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Haematology findings in the high dose group at the end of dosing included low values of platelets, white blood cells, neutrophils, basophils and large unstained cells in females and low mean corpuscular haemoglobin concentration (MCHC) in males. Changes in high dose group males at the end of recovery included a reduction in mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and MCHC, but were not considered by the study authors to be treatment related.

Some changes in clinical chemistry parameters after dosing and after recovery were noted by the study authors but not considered to be treatment related.

Qualitative urinalysis parameters tested in males only did not differ from the controls.

Effects in Organs

At the end of dosing, significant increase of liver weight was noted in high dose females and males. Compared to the vehicle control group, the absolute and relative liver weight increases for the males in the group were 29.0% ($p < 0.05$) and 23.6% ($p < 0.01$) respectively. For the females, the absolute liver weight increase was 17.9% ($p < 0.05$); however, the relative liver weight increase of 12.5% was not statistically significant. Microscopic findings revealed associated minimal to mild hypertrophy of centrilobular hepatocyte. While no hypertrophy of hepatocyte was noted in the vehicle control, low dose (50 mg/kg bw /day) and mid dose (250 mg/kg bw/day) groups for both males and females, 3 of the 5 males in the high dose group were found to have minimal hepatocyte hypertrophy and 1 male was found to have mild hepatocyte hypertrophy. For females of the high dose group, 3 of the 5 animals were found to have minimal hepatocyte hypertrophy.

Significant decrease of epididymides weight was recorded in the males of the high dose group at the end of dosing. Compared to the vehicle control group, the absolute and relative epididymides weight decreases were 21.5% and 24.2% (both $p < 0.01$) respectively. The decreases in weights of epididymides were associated with microscopic findings including degeneration/necrosis of spermatocyte/spermatid, decrease of sperm and cell debris in the duct of the epididymis. In addition, significant reduction of relative thymus weights in males of the high dose group was also noted ($p < 0.05$).

At the end of the recovery period, relative liver weight of high dose males remained 12.27% higher than the vehicle control group ($p < 0.05$). For females of the high dose group, absolute and relative liver weights were not significantly different from the vehicle control after the recovery. Hepatocyte hypertrophy was not seen in the recovery animals.

The weights of epididymides and testes were statistically significantly reduced for the males of the high dose group after the recovery. Compared to the vehicle control group, the absolute and relative epididymides weight decreases were 31.3% and 29.6% (both $p < 0.01$) respectively. The absolute and relative testes weight decreases were 26.0% ($p < 0.01$) and 23.3% ($p < 0.05$) respectively.

Other organ weight changes in the high dose recovery group, including thyroid weight increase in females and heart weight increase in males, were considered by the study authors not to be treatment-related.

Reproductive/Developmental Effects

In male animals, the significant decreases in weights of epididymides and testes in the high dose group were associated with histopathological changes, both at the end of dosing and end of the recovery period. (Testes weight changes were statistically significant only after the recovery period). Microscopic findings included minimal to mild degeneration/necrosis of spermatocyte/spermatid, decrease of sperm and cell debris in the duct of the epididymis. The study authors noted that the degree and incidence of these changes were greater at the end of the recovery period than at the end of dosing. At the end of dosing, minimal spermatocyte/spermatid degeneration/necrosis was found in 2 of 5 males in the high dose group while mild spermatocyte/spermatid degeneration/necrosis was found in 1 of the 5 animals. After the recovery period, minimal spermatocyte/spermatid degeneration/necrosis was found in 3 of the 5 males in the high dose group while mild spermatocyte/spermatid degeneration/necrosis was found in 1 of the 5 animals. Similar situations were seen in

the examinations of the epididymis of the high dose group with decrease of sperm and appearance of cell debris in the duct. The study authors considered that the changes in the testes were suggestive of effects on the spermatocytes/spermatids and the changes in the epididymis suggested degeneration of the seminiferous epithelium.

In female animals, prolongation of gestation period and decrease of delivery index were noted in the high dose group, with delivery index of 79.5% comparing to 91.9% in the vehicle control. Decrease of litter number and birth index and increase of number of stillborn were observed in the offspring of high dose females, with birth index of 70.5% comparing to 90.0% and stillborn rate of 11.2% comparing to 1.8% in the vehicle control. Total litter loss in 5 females of the high dose group was recorded, mostly due to cannibalism and loss of suckling. At postnatal Day 4, the offspring in the high dose had a lower viability index and body weight. The total viability index in this group was 48.2%, significantly lower than 98.7% in the vehicle control ($p < 0.01$). The study authors noted that there were no changes indicating implantation failure, however there was a decrease in delivery index and an effect on the maintenance of pregnancy.

The study authors suggested that although the causes of the changes in offspring remain unclear, it is possible that the test substance may have affected the offspring via milk.

No effect of the test substance was noted on mating or conception, despite the abnormalities seen in the testis and epididymis in males of the high dose group. The study authors suggested that this may be related to the maturation time of the sperm, and it is likely that the test substance may affect reproductive function if administered for a longer period before mating to cover a full spermatogenesis cycle.

Remarks – Results

The study authors considered the main treatment related observations for repeated dose toxicity were changes in organ weights and histological changes, in liver, testes and epididymis. For reproductive toxicity, they considered the effects on dams and offspring to be the main treatment related observations.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was established as 250 mg/kg bw/day in this study for both the repeated dose toxicity and the reproductive toxicity, based on the adverse effects observed at the dose level of 1,000 mg/kg bw/day.

TEST FACILITY Mitsubishi (2014a)

B.9. Genotoxicity – bacterial reverse mutation test (1)

TEST SUBSTANCE	Notified chemical (99.98% in purity)
METHOD	OECD TG 471 Bacterial Reverse Mutation Test Pre-incubation method
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2*uvr*A
Metabolic Activation System	S9 mix (commercial phenobarbital and 5,6-benzoflavone induced rat liver homogenate)
Concentration Range in Main Test	a) With metabolic activation: 313 – 5,000 µg/plate b) Without metabolic activation: 313 – 5,000 µg/plate
Vehicle	Water
Remarks - Method	No significant deviations of the protocol were noted. Dosages for the main test were chosen on the basis of the preliminary test. Preliminary Test: 1 plate/dose Main Tests: 3 plates/dose

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Preliminary Test	> 5,000	-	> 5,000	Negative

Main Test I	-	> 5,000	> 5,000	Negative
Main Test II	-	> 5,000	> 5,000	Negative
Present				
Preliminary Test	> 5,000	-	> 5,000	Negative
Main Test I	-	> 5,000	> 5,000	Negative
Main Test II	-	> 5,000	> 5,000	Negative

Remarks - Results: Cytotoxicity and precipitation of the test substance were not observed with or without metabolic activation during the study.

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

TEST FACILITY: Japan Oilstuff Inspectors' Corporation (2013a)

B.10. Genotoxicity – bacterial reverse mutation test (2)

TEST SUBSTANCE: Notified chemical

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

Species/Strain: *S. typhimurium*: TA1535, TA1537, TA98, TA100
E. coli: WP2*uvr*A-

Metabolic Activation System: S9 mix (microsomal enzyme fraction of Aroclor 1254 induced rat liver homogenate)

Concentration Range in Main Test: a) With metabolic activation: 50 – 5,000 µg/plate
b) Without metabolic activation: 50 – 5,000 µg/plate

Vehicle: Water

Remarks - Method: The purity of the test substance was not specified. Preliminary toxicity study was conducted on TA100 and WP2*uvr*A- without metabolic activation with test substance in the range of 50 to 5,000 µg/plate.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Preliminary Test	> 5,000	-	> 5,000	Negative
Main Test I	-	> 5,000	> 5,000	Negative
Main Test II	-	> 5,000	> 5,000	Negative
Present				
Main Test I	-	> 5,000	> 5,000	Negative
Main Test II	-	> 5,000	> 5,000	Negative

Remarks - Results: Cytotoxicity and precipitation of the test substance were not observed with or without metabolic activation during the study.

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

TEST FACILITY: Safepharm (1997b)

B.11. Genotoxicity – simplified *in vitro* mammalian chromosome aberration test

TEST SUBSTANCE: Notified chemical (≥ 99% in purity)

METHOD: Mutagenicity Test: Chromosome Aberration Test Using Cultured Mammalian Cells, Japan (simplified chromosome aberration test)

	The test substance was examined at 1 sample per dose level.
Species/Strain	Chinese hamster
Cell Type/Cell Line	Lung fibroblasts (CHL/IU)
Metabolic Activation System	S9 mix (commercially prepared from rat liver, induction system not specified)
Vehicle	Water
Remarks - Method	The study was not conducted in compliance with GLP.

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	23.1, 46.3, 92.5, 185, 370*, 740*, 1480*	6 hours	24 hours
Test 2	23.1, 46.3, 92.5, 185, 370*, 740*, 1480*	24 hours	24 hours
Present			
Test 1	23.1, 46.3, 92.5, 185, 370*, 740*, 1480*	6 hours	24 hours

*Cultures selected for metaphase analysis

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	> 1,480	> 1,480	Negative
Test 2	-	> 1,480	> 1,480	Negative
Present				
Test 1	-	> 1,480	> 1,480	Negative

Remarks - Results	Positive controls produced high numbers of aberrations, indicative of sensitivity of the test system.
CONCLUSION	The notified chemical was not clastogenic to Chinese hamster lung cells treated *in vitro* under the conditions of the test.
TEST FACILITY	CERI (2013)

B.12. Genotoxicity – *in vitro* mammalian chromosome aberration test

TEST SUBSTANCE	Notified chemical (99.98% in purity)
METHOD	OECD TG 473 *In vitro* Mammalian Chromosome Aberration Test
Species/Strain	Chinese hamster
Cell Type/Cell Line	Lung cell line (CHL)
Metabolic Activation System	S9 mix (commercial Aroclor-1254 induced rat liver homogenate)
Vehicle	Distilled water
Remarks - Method	No significant deviations of the protocol were noted. Concentrations of the test substance for the main tests were determined using a range-finding test. Cytotoxicity was < 50% at all concentrations tested (up to 1,500 μg/mL).

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	375*, 750*, 1500*	6 hours	24 hours
Test 2	375*, 750*, 1500*	24 hours	24 hours
Present			
Test 1	375*, 750*, 1500*	6 hours	24 hours
Test 2	375*, 750*, 1500*	6 hours	24 hours

*Cultures selected for metaphase analysis

RESULTS

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

Remarks - Results The positive controls produced a high number of aberrations, indicative of sensitivity of the test system.

CONCLUSION The notified chemical was not clastogenic to Chinese hamster lung cells treated *in vitro* under the conditions of the test.

TEST FACILITY KTR (2014d)

B.13. Genotoxicity – *in vivo* mammalian erythrocyte micronucleus test

TEST SUBSTANCE Notified chemical (99.98% in purity)

METHOD OECD TG 474 Mammalian Erythrocyte Micronucleus Test
Species/Strain Mouse/CrljOri:CD1 (ICR)
Route of Administration Oral – gavage
Vehicle Water
Remarks - Method No significant deviation of the protocol were noted.

The test substance was orally administered twice at a 24-hour interval to the test animals and 5 animals per dose group were used in the study.

Positive control (CP) was administered intraperitoneally once to the test animals.

Group	*Number and Sex of Animals*	*Dose (mg/kg bw)*	*Sacrifice Time (hours)*
I (vehicle control)	5 M	0	24
II (low dose)	5 M	500	24
III (mid dose)	5 M	1,000	24
IV (high dose)	5 M	2,000	24
V (positive control, CP)	5 M	70	24

CP = cyclophosphamide

RESULTS
Doses Producing Toxicity No bone marrow toxicity was observed at any dose level for the notified chemical. No animals died and body weights of test animals were consistent with the negative control. A reduction in PCE/NCE ratio was seen in the positive control, indicating that it has bone marrow toxicity.
Genotoxic Effects No significant increases in micronucleated polychromatic erythrocytes (MPCEs) were observed at any dose level for the test or negative control groups, indicating that there were no genotoxic effects.
Remarks - Results There were statistically significant increases in MPCEs in the positive control group, confirming the sensitivity of the test system.

As no toxic effects of the test substance in the bone marrow were observed in the study, there was no clear evidence to demonstrate that the test substance was able to reach bone marrow.

CONCLUSION The notified chemical was not clastogenic under the conditions of this *in*

vivo chromosome aberration test.

TEST FACILITY	KTR (2014e)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I)
Inoculum	Activated sludge
Exposure Period	28 days
Auxiliary Solvent	Not reported
Analytical Monitoring	Measured biochemical oxygen demand (BOD). The test substance was analysed by GC.
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	Not reported	7	77.5
14	Not reported	14	84.7
28	-2.0	28	Not reported

Remarks - Results	All validity criteria for the test were satisfied. The reference compound, sodium benzoate, reached the 60% pass level by day 7 indicating the suitability of the inoculum. It was not mentioned in the study that a toxicity control was included. The degree of degradation of the notified chemical after the cultivation period was a negative value. Therefore, the test substance cannot be classified as readily biodegradable according to the OECD (301 C) guideline.
CONCLUSION	The notified chemical is not readily biodegradable
TEST FACILITY	KIT(2014)

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 Test
Species	Medaka (*Oryzias laptipes*)
Exposure Period	96 hours
Auxiliary Solvent	Not reported
Water Hardness	61 mg $CaCO_3$/L
Analytical Monitoring	GC Analysis
Remarks – Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Nominal Concentration (mg/L)	*Number of Fish*	*Cumulative mortality (%)*				
		3 h	*24 h*	*48 h*	*72 h*	*96 h*
Control	10	0	0	0	0	0
100	10	0	0	0	0	0

LC50	> 90.8 mg/L at 96 h (Time-weighted mean of measured concentrations)
NOEC	Not Applicable
Remarks – Results	All validity criteria for the test were satisfied. The treatment concentration was renewed at 48 hours during the 96-hour test period. The actual concentrations of the treatment were measured at 0 and 48 hours. The toxicity test was conducted as a limit test. The 96-hour LC50 was determined, based on the time-weighted mean of measured concentrations, by visual observations.
CONCLUSION	The notified chemical is not harmful to fish at the tested concentration.
TEST FACILITY	Mitsubishi (2014b)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 *Daphnia* sp. Acute Immobilisation Test – Static Test
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	Not reported
Water Hardness	242 mg $CaCo_3$/L
Analytical Monitoring	GC Analysis
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test guidelines were reported.

RESULTS

Nominal Concentration (mg/L)	*Number of D. magna*	*Cumulative % Immobilised*	
		24 h	*48 h*
Control	20	0	0
100	20	0	0

EC50	> 93.6 mg/L at 48 h (Time-weighted mean of measured concentrations)
NOEC	Not Applicable
Remarks - Results	All validity criteria for the test were satisfied. The treatments concentrations were measured at the beginning and end of the test. The toxicity test was conducted as a limit test. The 48-hour LC50 was determined, based on the time-weighted mean of measured concentrations, by visual observations.
CONCLUSION	The notified chemical is not harmful to aquatic invertebrates at the tested concentration.
TEST FACILITY	Mitsubishi (2014c)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test
Species	*Pseudokirchneriella subcapitata*
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L
Auxiliary Solvent	GC Analysis
Water Hardness	Not reported
Analytical Monitoring	Analysis of the test substance was not performed
Remarks - Method	The test was conducted according to the guidelines above and good laboratory practice (GLP) principles. No significant deviations from the test

guidelines were reported.

RESULTS

Biomass (72 h)		*Growth (72 h) (Time-weighted mean of measured concentrations)*	
E_yC50 (mg/L)	*NOE_yC(mg/L)*	*E_rC50 (mg/L)*	*NOE_rC(mg/L)*
Not reported	Not reported	> 89.5	89.5

Remarks - Results

All validity criteria for the test were satisfied. The end points were determined based on the time-weighted mean measured test concentrations. The treatments concentrations were measured at the beginning and end of the test. The E_rC50 value was calculated by plotting the growth inhibition rates at 0, 24, 48 and 72 hour exposure periods. The NOE_rC value was calculated by Student's t-test, subsequent to F test for homogeneity of variances. Statistical analyses were performed using Yukms Statlight #3 software.

CONCLUSION

The notified chemical is not harmful to algae at the tested concentration.

TEST FACILITY

Mitsubishi (2014d)

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