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July 2010

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Additive-M

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health and Ageing, 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, Water, Heritage and the Arts.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at our NICNAS office by appointment only at 334-336 Illawarra Road, Marrickville NSW 2204.

This Full 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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FULL PUBLIC REPORT

This assessment report is for an extension of original assessment certificate for Additive-M. Based on the submission of new information by the extension notifier, some sections of the original assessment report have been modified. These modifications have been made under the heading 'Extension Applicant' in the respective sections.

Additive-M

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Toyo Ink Australia Pty. Ltd. (ABN 29 006 294 837)
29 Garden Street
Kilsyth, VIC 3137

Applicant for an Extension of the Original Assessment Certificate:
Createc Pty Ltd (ABN 89 094 263 537)
25 South Street
Rydalmere, NSW 2116

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, Other Names, CAS Number, Molecular Formula, Structural Formula, Molecular weight, Spectral Data, Degree of Purity, Hazardous and Non Hazardous Impurities, Additives, Importation Volume and Use Details.

Extension Applicant:
Data items and details claimed exempt from publication: Importation Volume and Use Details.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
No variation to the schedule of data requirements is claimed.

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
Japan

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Additive-M

MOLECULAR WEIGHT
<500

ANALYTICAL DATA
Reference NMR, IR, HPLC, GC, GPC, UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY >90%

4. PHYSICAL AND CHEMICAL PROPERTIES

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

Property	Value	Data Source/Justification
Melting Point/Freezing Point	15°C ± 0.5°C	Measured
Boiling Point	258°C ± 0.5°C at 100.71 kPa	Measured
Density	1170 kg/m^3 at 20°C	Measured
Vapour Pressure	4.54 x 10^{-2} kPa at 25°C	Measured
Water Solubility	Miscible at all proportions	Measured
Hydrolysis as a Function of pH	$t_{1/2}$ >365 at pH = 4, 7 and 9	Measured
Partition Coefficient (n-octanol/water)	log Pow = -0.731at 22.5°C ± 1°C	Measured
Adsorption/Desorption	log K_{oc} <1.25 at 30°C	Measured
Dissociation Constant	pKa = -1.34 ± 0.20	Estimated
Surface Tension	72.6 mN/m at 20.5 ± 0.5°C	Measured
Flash Point	140°C ± 2°C at 102.84 kPa	Measured
Flammability	Negative	Estimated based on the structure
Autoignition Temperature	>400 °C	Measured
Explosive Properties	Not expected to be explosive	Estimated based on the structure

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

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

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The substance will not be manufactured in Australia, but will be imported as a component in liquid preparation(s) at concentrations ranging from 2.5 to 10% (w/w).

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	3-10	3-10	3-10	3-10	3-10
Extension Applicant:					
Year	*1*	*2*	*3*	*4*	*5*
Tonnes	3-10	3-10	3-10	3-10	3-10

PORT OF ENTRY
Sydney

IDENTITY OF RECIPIENTS
Toyo Ink Australia Pty Ltd.

TRANSPORTATION AND PACKAGING
The product containing the notified chemical will be packaged in sealed 500 mL or 1 L ink cartridges and imported principally by sea freight and also possibly by airfreight. It will be then transported by road for supply within the distribution network to the end users.

USE
The notified chemical is an additive in inks used for industrial applications, for example, printing outdoor advertising signs.

Extension Applicant:
The notified chemical is an additive in inks used for industrial applications.

OPERATION DESCRIPTION

The imported ink cartridge containing the notified chemical will be used directly, therefore, no reformulation or repackaging of the ink cartridges will occur in Australia. For replacement of the ink cartridges, operators will manually load the cartridge into a processor machine. The printing process will be a fully automated and enclosed system.

The printer will run approximately 8 hours per day, 5 days per week. Changes of cartridges will be performed approximately once per month, taking roughly 15 seconds. The printing heads will be cleaned daily and the cleaning process will take approximately 3 minutes. The above processes will be usually conducted by a single trained printer operator. The printer will be serviced and maintained by a trained technician on a regular basis, but it will be an infrequent event.

The printed media will be cured in an enclosed system and the notified chemical will be irreversibly bound to a polymer matrix (the PVC billboard sheets).

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

Worker exposure during transport and storage will be unlikely except when packaging is accidentally breached. Should a spill occur, it is expected to be contained and collected using absorbent materials and placed into suitable containers for recovery or disposal in accord with the MSDS and official regulations.

During the printing process, worker exposure will be negligible due to the automated and enclosed process. However, workers may have dermal and occasionally ocular exposure to the notified chemical during change of cartridges and printer head cleaning, especially if these are manual processes. However, the exposure will be limited due to short exposure duration, infrequent changes of cartridges and use of personal protective equipment (PPE). Service engineers may be intermittently exposed to the notified chemical contained in the cartridge via skin and ocular contact during cleaning and maintenance tasks. The service engineers will wear PPE and receive appropriate training in servicing techniques. Dermal and possible ocular exposure could also occur when handling faulty or ruptured cartridges.

Workers exposure via inhalation is expected to be negligible based on the low vapour pressure of the notified chemical and the majority of the process will be in an enclosed/automated system.

Exposure to the notified chemical from handling of the printed media will be negligible, as the notified chemical will be irreversibly bound to a polymer matrix.

6.1.2. Public exposure

The notified chemical will not be available to the public. The advertising signs onto which the notified chemical will be printed will incorporate the notified chemical as a part of the polymer matrix. Therefore, public exposure is expected to be negligible.

6.2. Human health effects assessment

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

Endpoint	*Result and Assessment Conclusion*
Rat, acute oral	LD50 = 2500 mg/kg bw, low toxicity
Rat, acute dermal	LD50 > 2000 mg/kg bw, low toxicity
Rat, acute inhalation	LC50 >4.89mg/L/4 hours, low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	moderately irritating
Mouse – Local Lymph Node Assay	no evidence of sensitisation
Rat, oral, repeat dose toxicity – 28 days	NOAEL 1000 mg/kg bw/day
Bacterial reverse mutation assay	non mutagenic
in vitro Chromosome aberration test	non clastogenic

Toxicokinetics
No data on toxicokinetics, metabolism and distribution were provided. Based on its properties, the notified chemical will have limited absorption via the skin and inhalation due to its high water solubility with low log P_{ow} (less than zero) and low vapour pressure. Lack of evidence of dermal and inhalation absorptions was also observed in the acute dermal and inhalation toxicity study (see below). Oral absorption is expected due to its high water solubility, which is also supported by the deaths observed in the acute oral study and the systemic effects of the notified chemical in the repeated oral toxicity study (see below).

Acute toxicity
The acute animal tests indicated that the notified chemical is of low toxicity via oral, dermal and inhalation. In the acute oral study, although 2 deaths in 6 test animals (with abnormal necropsy findings of red lungs, dark liver and dark kidneys) were found at a dose level of 2000 mg/kg bw, there were no signs of systemic toxicity and no deaths were noted at a dose level of 300 mg/kg. The oral LD_{50} was estimated to be 2500 mg/kg bw. The test dose used in the acute inhalation study (4.89 mg/L/4hr) was slightly below the dose for hazard classification (≤ 5 mg/L/4hr) under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004). However, the inhalation LC_{50} is expected to be higher than 4.89 mg/L/4hr based on the absence of deaths and transient clinical signs of toxicity, which recovered 5 days after exposure.

Irritation and sensitisation
Slight skin irritation (very slight erythema and oedema that were recovered within 72 hours and 48 hours post exposure, respectively) was observed in a dermal irritation study. Although an eye irritation study indicated moderate irritation to the conjunctiva (irritation), cornea (scattered or diffuse corneal opacity) and iris (signs of inflammation), the severity of the effects, together with the reversibility, does not meet the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

A LLNA test yielded low Stimulation Index (SI, 1.02, 0.85, and 0.90 for test concentrations of 25, 50 and 100%, respectively), indicating that the notified chemical has low potential of causing skin sensitisation.

Repeated dose toxicity
A 28-day repeated oral study resulted in treatment-related effects in the liver (centrilobular or generalised hepatocyte enlargement, together with increased liver weight), and thyroid (follicular cell hypertrophy) of either sex treated with 1000 and 150 mg/kg bw/day. However, these changes were confined to adaptive microscopic changes which are not considered to represent adverse effects (ECETOC, 2002). No such changes were demonstrated in animals of either sex treated with 15 mg/kg bw/day. Therefore, 1000 mg/kg bw/day has been determined as the No Observed Adverse Effect Level (NOAEL) and 15 mg/kg bw/day as the the No observed Effect Level (NOEL).

The notified chemical did not induce mutations in bacterial test and failed to induce significant chromosomal aberrations in mammalian cells in vitro. These results suggest that the notified chemical is not likely to be mutagenic to humans.

Classification
Based on the available data the notified chemical is not classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Based on the available data, the notified chemical may present a potential risk of eye irritation and slight skin irritation to workers, especially during manual changes of cartridges, printer head cleaning, service and maintenance, and when handling faulty or ruptured cartridges. However, this risk is expected to be limited due to short exposure duration, relatively low concentration of the notified chemical in the printing inks (up to 10%), low frequencies of these processes, and use of PPE at workplaces. In addition, the printer operators and service technicians will be trained workers. The enclosed nature of other processes will restrict any risk presented by the notified chemical. However, employers should implement appropriate control measures to minimise ocular and dermal exposure.

6.3.2. Public health

As there will be negligible exposure of the public to the notified chemical, the risk of eye and skin irritation from the notified chemical is considered to be negligible.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The chemical is not manufactured in Australia; the notified chemical is used in the same printer cartridge in which it is imported. Cartridges are loaded manually into printers but the remainder of the printing process is automated preventing exposure to the environment.

Due to the nature of the process, spills of the inks containing the notified chemical are not anticipated. However, in the case of such accident the waste notified chemical would be cleaned up appropriately and sent to landfill and, where available, for incineration for licensed waste handling facilities.

Finished printer cartridges are anticipated to contain up to approximately 1 mL of the ink containing notified chemical.

All wastes will be sent to landfill, and where available, for incineration to a licensed facility.

RELEASE OF CHEMICAL FROM USE

Due to the automated nature of the printing machinery containing the notified chemical, direct release of the notified chemical is not anticipated. The inks will be printed onto PVC sheeting and will be irreversibly bound to the polymer matrix of the sheets.

There maybe accidental release of the notified chemical through accidental spillage or malfunction of the printer, but any spills would be cleaned up appropriately and waste sent to landfill or, where possible, for incineration to a licensed waste handling facility.

Wastes resulting from cleaning of printing heads would also be sent to landfill or incineration.

RELEASE OF CHEMICAL FROM DISPOSAL

The cartridges, at disposal, are anticipated to contain approximately 1 mL of ink (containing the notified chemical at concentration of up to 10%).

All wastes will be sent to landfill and, where available, for incineration.

7.1.2 Environmental fate

All wastes of the notified chemical are expected to go to landfill (or incinerated). In addition, according to the reported test results the chemical is readily biodegradable and has no ecotoxicological effects. For the details of the environmental fate studies please refer to Appendix C.

7.1.3 Predicted Environmental Concentration (PEC)

There would be no aquatic release of the notified chemical. As such release into the environment is expected to be negligible and no PEC can be derived.

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	LC50 >100 mg/L	Not harmful
Daphnia Toxicity	LC50 >100 mg/L	Not Harmful
Algal Toxicity	EC50 >100 mg/L	Not Harmful
Inhibition of Bacterial Respiration	IC50 = 3700 mg/L	Not Harmful

7.2.1 Predicted No-Effect Concentration

Aquatic ecotoxicity data were provided for three trophic levels. The following Predicted No-Effect Concentration has been calculated using an assessment factor of 100.

Predicted No-Effect Concentration (PNEC) for the Aquatic Compartment	
E_rC50 (algal)	>100 mg/L
Assessment Factor	100
Mitigation Factor	1.00
PNEC:	>1000 µg/L

7.3. Environmental risk assessment

The wastes of the notified chemical from the cartridges and accidental spills from printers will be sent to land fill or for incineration to a licensed operator**.** In these circumstances, a PEC cannot be estimated and hence the calculation of the risk quotient is not possible.

Based on the limited exposure to the aquatic compartment and its low ecotoxicity, the risk to the environment is considered to be acceptable.

8. RISK ASSESSMENT RELATING TO EXTENSION APPLICANT

Extension Applicant:
The proposed use, introduction volume and fate of the notified chemical will not change significantly under the proposed extension. The circumstances in the extension application are not expected to impact on the original human health and environmental risk assessment.

9. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified chemical is not classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)].

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

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

Environmental risk assessment
On the basis of the PNEC ratio, the reported use pattern and disposal, the notified chemical is not considered to pose a risk to the environment.

Recommendations

CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  - *Prevent leaks and spills.*

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced:
  - *Avoid contact with eyes and skin;*
  - *Avoid spills and splashing during use.*

- A copy of the MSDS should be easily accessible to employees.

- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)] workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Environment

- The notified chemical should be disposed of by landfill or where possible to a licensed incineration facility.

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

Regulatory Obligations

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

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

(1) Under Section 64(2) of the Act; if
  - the function or use of the chemical has changed from additive in inks for industrial applications, or is likely to change significantly;
  - the amount of chemical being introduced has increased from 10 tonnes, or is likely to increase, significantly;
  - if the chemical has begun to be manufactured in Australia;
  - additional information has become available to the person as to an adverse effect of the chemical on occupational health and safety, public health, or the environment.

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

No additional secondary notification conditions are stipulated.

Material Safety Data Sheet
The MSDS of the notified chemical and products containing the notified chemical provided by the notifier were reviewed by NICNAS. The accuracy of the information on the MSDS remains the responsibility of the applicant.

Extension Application:
The extension applicant has provided an MSDS for a product containing the notified chemical. The accuracy of the information on the MSDS remains the responsibility of the extension applicant.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Clear colourless viscous liquid

Melting Point/Freezing Point 15ºC ± 0.5°C

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Boiling Point 258ºC ± 0.5°C at 100.71 kPa

METHOD EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks Determined by differential scanning calorimetry
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Density 1170 kg/m^3 at 20ºC

METHOD EC Directive 92/69/EEC A.3 Relative Density.
Remarks Determined by pycnometer method
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Vapour Pressure 4.54 x 10^{-2} kPa at 25ºC

METHOD EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Determined using an isoteniscope system with measurements being taken at several temperatures and linear regression analysis used to calculate the vapour pressure at 25°C.
TEST FACILITY Safepharm Laboratories Ltd (2006bb)

Water Solubility The test material was miscible at all proportions with water at ambient temperature.

METHOD EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Flask Method
Analytical Method: Visual inspection
Based on a preliminary test, the notified chemical was considered miscible in all proportions with water at ambient temperature.
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Hydrolysis as a Function of pH

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

pH	*T (°C)*	$t_{½}$
4	25	>365 days
7	25	>365 days
9	25	>365 days

Remarks The notified chemical obtained less than 10% hydrolysis (by GC) after 5 days at 50°C at pH 4, 7 and 9. This is considered equivalent to a half life greater than 1 year at 25°C.
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Partition Coefficient (n-octanol/water) log Pow at 22.5ºC ± 1°C = -0.731

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient. (flask method)
Remarks Analytical Method: Gas Chromatography
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Adsorption/Desorption log K_{oc} < 1.25 at 30°C.

– screening test

METHOD EC Directive 2001/59/EC C.19 Estimation of the Adsorption Coefficient (Koc) on Soil and
Sludge using High Performance Liquid Chromatography
Remarks The test substance was eluted before acetanilide, the first of 12 reference substances.
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Dissociation Constant pKa = -1.34 ± 0.20

METHOD OECD TG 112 Dissociation Constants in Water.
Remarks No determination of dissociation constant was possible by method 112 of the OECD guidelines as the test material contained no modes of dissociation within the range and scope of the method. The dissociation constant was predicted using ACD/I-Lab Web Service 8.03
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Surface Tension 72.6 mN/m at 20.5 ± 0.5°C

METHOD EC Directive 92/69/EEC A.5 Surface Tension.
Remarks Determined using a White Electrical Institute interfacial tension balance. There was one minor deviation but had no impact on the integrity of the study. The notified chemical is not surface active.
TEST FACILITY Safepharm Laboratories Ltd (2006aa)

Flash Point 140°C ± 2°C at 102.84 kPa

METHOD EC Directive 92/69/EEC A.9 Flash Point.
Remarks Close cup method
TEST FACILITY Safepharm Laboratories Ltd (2006bb)

Autoignition Temperature >400°C

METHOD 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks Flask method
TEST FACILITY Safepharm Laboratories Ltd (2006bb)

Explosive Properties Not determined

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks Based on the chemical structure of the test material the result for the explosive properties has been predicted negative.
TEST FACILITY Safepharm Laboratories Ltd (2006bb)

Oxidising Properties Not determined

METHOD EC Directive 2004/73/EC A.21 Oxidizing Properties (Liquids).
Remarks Based on the chemical structure the result for the oxidising properties has been predicted negative.
TEST FACILITY Safepharm Laboratories Ltd (2006bb)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 423 Acute Oral Toxicity – Acute Toxic Class Method. EC Directive 2004/73/EC B.1tris Acute Oral Toxicity – Acute Toxic Class Method.
Species/Strain	Rat/Sprague Dawley CD
Vehicle	None
Remarks – Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	3 females	300	0
2	3 females	2000	1
3	3 females	2000	1

LD50	2500 mg/kg bw
Signs of Toxicity	Two out of 6 animals treated at a dose level of 2000 mg/kg were found dead one day after dosing. There were no deaths noted at a dose level of 300 mg/kg. There were no signs of systemic toxicity. The surviving animals showed expected gains in bodyweight over the study period.
Effects in Organs	Abnormalities noted at necropsy of the animals that died during the study were abnormally red lungs, dark liver and dark kidneys. No abnormalities were noted at necropsy of animals that were killed at the end of the study.
Remarks – Results	The LD_{50} was estimated to be 2500 mg/kg bw according to the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations, 2003).
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Safepharm Laboratories Ltd (2006a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 402 Acute Dermal Toxicity. EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal).
Species/Strain	Rat/Sprague Dawley CD
Vehicle	None
Type of dressing	Semi-occlusive
Remarks – Method	No significant protocol deviations

RESULTS

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

LD50	>2000 mg/kg bw
Signs of Toxicity - Local	None
Signs of Toxicity - Systemic	None
Effects in Organs	None

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

TEST FACILITY Safepharm Laboratories Ltd (2008)

B.3. Acute toxicity – inhalation

TEST SUBSTANCE Notified Chemical

METHOD OECD TG 403 Acute Inhalation Toxicity – Limit Test.
EC Directive 92/69/EEC B.2 Acute Toxicity – Inhalation.

Species/Strain	Rat/Sprague-Dawley Crl:CD
Vehicle	None
Method of Exposure	Oro-nasal exposure
Exposure Period	4 hours
Observation duration	14 days
Physical Form	liquid aerosol
Particle Size	3.57 µm
Remarks – Method	The Mean Achieved Atmosphere Concentration was 4.89 mg/L. The Mean Mass Median Aerodynamic Diameter was 3.57µm The Inhalable Fraction (% <4 µm) was 55.0

RESULTS

Group	*Number and Sex of Animals*	*Concentration mg/L*		*Mortality*
		Nominal	*Actual*	
1	5 male		4.89	0
2	5 female		4.89	0

LC50	>4.89 mg/L/4 hours
Signs of Toxicity	Wet fur and increased respiratory rate (RR) were noted in all animals during the 4-hour exposure period. These observations were considered to be due to restraint procedures. Wet fur was also seen on Day 1, which might be due to air conditioning failure on that day. Following removal from the exposure chamber, all test animals displayed increased RR, hunched posture, and pilo erection. These findings were fully recovered by Day 5. Normal bodyweight development was noted for all animals during the study.
Effects in Organs	No macroscopic abnormalities were detected amongst animals at necropsy.

CONCLUSION The notified chemical is of low toxicity via inhalation.

TEST FACILITY Safepharm Laboratories Ltd (2006b)

B.4. Irritation – skin

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 404 Acute Dermal Irritation/Corrosion. EC Directive 2004/73//EC B.4 Acute Toxicity (Skin Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Vehicle	None
Exposure duration	3 minutes (in 1 animal), 1 hour (in 1 animal), 4 hours (in 3 animals)
Observation Period	72 hours
Type of Dressing	Semi-occlusive
Remarks – Method	No significant protocol deviations

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0.33	0.67	0.67	1	<3d	0
Oedema	0	0.33	0.33	1	<2d	0

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

Remarks – Results	Vert slight erythema was noted at all treated skin sites one hour and 24 hours after patch removal and at two treated skin sites at the 48-hour observation. All treated sites appeared normal at the end of the observation period. Very slight oedema was noted at all treated skin sites one hour after patch removal and at two treated skin sites at the 24-hour observation. All treated sites appeared normal at the 48-hour observation.
CONCLUSION	The notified chemical is slightly irritating to skin.
TEST FACILITY	Safepharm Laboratories Ltd (2006c)

B.5. Irritation – eye

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 405 Acute Eye Irritation/Corrosion. EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	14 days
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	2	2	1.67	2	<14d	
Conjunctiva: chemosis	1.33	1.67	1.33	2	<14d	
Conjunctiva: discharge	1.67	2.67	1.33	3	<14d	
Corneal opacity	0	0.67	0	1	<14d	
Iridial inflammation	0.33	0.67	0.33	1	<3d	

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

Remarks – Results

Scattered or diffuse corneal opacity was noted in one treated eye at the 48 hour, 72 hour and 7 day observations.

Iridial inflammation was noted in all treated eyes 1 and 24 hours after treatment and in one treated eye at the 48-hour observation.

Moderate conjunctival irritation was noted in all treated eyes one hour after treatment and at the 24 and 48-hour observations. Moderate conjunctival irritation was noted in two treated eyes with minimal conjunctival irritation in one treated eye at the 72-hour observation. Moderate conjunctival irritation persisted in one treated eye at the 7-day observation.

A pale area on the nictating membrane approximately 2mm x 2mm in size was noted in one treated eye at the 48 hour and 72 hour observations.

Two treated eyes appeared normal at the 7-day observation and one treated eye appeared normal at the 14-day observation.

CONCLUSION

The notified chemical is moderately irritating to the eye.

TEST FACILITY

Safepharm Laboratories Ltd (2006d)

B.6. Skin sensitisation – mouse local lymph node assay (LLNA)

TEST SUBSTANCE

Notified chemical

METHOD

OECD 429 Skin Sensitisation: Local Lymph Node Assay
Method B42 Skin sensitization (Local Lymph Node Assay) of Commission Directive 2004/73/EC

Species/Strain

Mouse/CBA/Ca (Female)

Vehicle

Dimethyl formamide

Remarks – Method

No significant protocol deviations. A preliminary screening test was conducted and the dose for the main study was determined to be 25%, 50% and 100%.

RESULTS

Concentration	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
25% v/v in Dimethyl formamide	810.30	1.02
50% v/v in Dimethyl formamide	670.16	0.85
100%	711.41	0.90
Positive Control		
α-Hexylcinnamaldehyde 5%	NA	2.50
α-Hexylcinnamaldehyde 10%	NA	4.03
α-Hexylcinnamaldehyde 25%	NA	9.13

NA, not available.

Remarks – Results

Evidence of T-cell proliferation was not observed during the study as indicated by the SI of less than 3 at each of the concentrations tested.

There were no unscheduled deaths and no signs of systemic toxicity were noted in the test or the control animals. Bodyweight changes in the test animals were comparable to those in the control animals.

The positive control substance α-Hexylcinnamaldehyde , Tech 85% was considered to be a sensitiser under the conditions of the control experiments.

CONCLUSION

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

TEST FACILITY

Safepharm Laboratories Ltd (2006e)

B.7. Repeat dose toxicity

TEST SUBSTANCE

Notified Chemical

METHOD

OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
EC Directive 96/54/EC B.7 Repeated Dose (28 Days) Toxicity (Oral).

Species/Strain: Rat/Sprague-Dawley Crl:CD (SD) IGS BR
Route of Administration: Oral – gavage
Exposure Information: Total exposure days: 28 days;
Dose regimen: 7 days per week;
Post-exposure observation period: none
Vehicle: Polyethylene glycol 400
Remarks – Method: No significant protocol deviations

RESULTS

Dose mg/kg bw/day	*Number and Sex of Animals*	*Mortality*
0	5/sex	0
15	5/sex	0
150	5/sex	0
1000	5/sex	0

Mortality and Time to Death

There were no unscheduled deaths.

Clinical Observations

No clinical signs of toxicity were observed in test or control animals throughout the study period.

There were no treatment-related changes in sensory reactivity and in the behavioural and functional parameters measured.

Laboratory Findings
No toxicologically significant changes were detected in blood chemistry analysis or haematological investigations.

Effects in Organs
Animals of either sex treated with 1000 and 150 mg/kg bw/day showed a statistically significant increase in liver weight, both absolute and relative to bodyweight. No such effects were detected in animals of either sex treated with 15 mg/kg bw/day.

No toxicologically significant macroscopic abnormalities were detected upon necropsy.

During histopathological analysis the following treatment-related microscopic changes were detected:

Liver
Hepatocyte enlargement, centrilobular or generalised, was observed in animals of either sex treated with 1000 and 150 mg/kg bw/day, but not at 15 mg/kg bw/day. Such changes are commonly observed in the rodent liver following the administration of xenobiotics and are generally regarded as adaptive in nature.

Thyroid
A marginally higher incidence of follicular cell hypertrophy was seen in males treated with 1000 mg/kg bw/day but not at any other treatment level. Such change is also considered to be adaptive in nature and often associated with hepatocyte hypertrophy.

Remarks – Results
This study resulted in treatment-related effects in the animal liver and thyroid of either sex treated with 1000 and 150 mg/kg bw/day. No such changes were demonstrated in animals of either sex treated with 15 mg/kg bw/day. The No observed Effect Level (NOEL) was, therefore, considered to be 15 mg/kg bw/day.

However, the changes in the liver and thyroid detected at 1000 and 150 g/kg/day were confined to adaptive microscopic changes. These were not considered to represent adverse effects (ECETOC, 2002). For this reason 1000 mg/kg bw/day has been determined as the No Observed Adverse Effect Level (NOAEL).

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

TEST FACILITY Safepharm Laboratories Ltd (2006f)

B.8. Bacterial reverse mutation assay

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2 uvrA$^-$
Metabolic Activation System	Phenobarbitone/ß-naphthoflavone activated rat liver S9
Concentration Range in Main Test	a) With metabolic activation: 50-5000µg/plate. b) Without metabolic activation: 50-5000 µg/plate.
Vehicle	Distilled water
Remarks – Method	No significant protocol deviations

RESULTS	The test material caused no visible reduction in the growth of the bacterial background lawn at any dose level. The test material was, therefore, tested up to the maximum recommended dose level of 5000µg/plate. No test material precipitate was observed on the plates at any of the doses tested in either the presence or absence of S9-mix. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, with any dose of the test material, either with or without metabolic activation. The vehicle control plates gave counts of revertant colonies within the normal range. All of the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies, both with or without metabolic activation. Thus the sensitivity of the assay and the efficacy of the S9-mix were validated.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	Safepharm Laboratories Ltd (2006g)

B.9. Mammalian chromosomal aberration test – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosomal Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - *In vitro* Mammalian Chromosome Aberration Test
Species/Strain	Human (*Homo sapiens*)
Cell Type/Cell Line	Lymphocytes
Metabolic Activation System	Phenobarbitone/ß-naphthoflavone activated rat liver S9
Vehicle	Minimal Essential Media
Remarks – Method	No significant protocol deviations

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Present			
Test 1	0*, 31.6, 63.2, 126.4, 252.8*, 505.5*, 1011*	4h	24h
Test 2	0*, 31.6, 63.2, 126.4, 252.8*, 505.5*, 1011*	4h	24h
Absent			
Test 1	0*, 31.6, 63.2, 126.4, 252.8*, 505.5*, 1011*	4h	24h
Test 2	0*, 31.6, 63.2, 126.4, 252.8*, 505.5*, 1011*	24h	24h

*Cultures selected for metaphase analysis.

RESULTS

Remarks – Results	The maximum dose was 1011 µg/ml corresponding to the 10 mM maximum recommended dose level. The test material was non-toxic and did not induce significant increases in the frequency of cells with aberrations in either experiment. There was no precipitate of the test material at any dose level tested in the parallel blood free cultures at the end of the exposure period in either the pulse exposure or the continuous exposure period. The test material induced no evidence of dose-related toxicity. All vehicle (solvent) controls had frequencies of cells with aberrations within the range expected for normal human lymphocytes.

	All the positive control materials induced statistically significant increases in the frequency of cells with aberrations indicating the satisfactory performance of the test and of the activity of the metabolising system.
CONCLUSION	The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Safepharm Laboroatories Ltd. (2006h)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 301 B Ready Biodegradability: CO_2 Evolution Test.

Inoculum	Active sewage sludge from local STP, incubated at 21°C
Exposure Period	29 days
Auxiliary Solvent	None
Analytical Monitoring	DOC
Remarks – Method	The test material, at a concentration of 10 mg C/l, was exposed to activated sewage sludge microorganisms with culture vessels in the dark. The degradation of the test material was assessed by determination of CO_2 produced. Control solutions with inoculum and standard material, sodium benzoate, together with toxicity control were used.

RESULTS

Test substance (notified chemical)		*Sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	10	1	12
14	84	14	73
28	107	28	94

Remarks – Results: The test results attained 107% degradation after 28 days and satisfied the 10-day window validation criterion, whereby 60% degradation must be attained within 10 days of the degradation exceeding 10%. The test material can thus be considered biodegradable under the terms and conditions of the OECD guideline No 301B. The results of 107% are due to analytical variation.

CONCLUSION: The test material can be considered readily biodegradable.

TEST FACILITY: Safepharm Laboratories Ltd (2006i)

C.1.2. Bioaccumulation

The notified chemical is readily biodegradable and is considered miscible in water in all concentrations. The notified chemical has a relatively low Pow and as such is considered extremely unlikely to bioaccumulate.

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 203 Fish, Acute Toxicity Test - 96 h/semi-static.
EC Directive 92/69/EEC C.1 Acute Toxicity for Fish - 96 h/semi-static.

Species	Rainbow trout (*Oncorhynchus mykiss)*
Exposure Period	96 h
Auxiliary Solvent	None
Water Hardness	100 mg $CaCO_3$/L
Analytical Monitoring	GC analysis with FID
Remarks – Method	No significant protocol deviation

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
100		20	0	0	0	0	0

LC50	>100 mg/L at 96 hours
NOEC	100 mg/L at 96 hours
Remarks – Results	The 96 h LC_{50} based on the nominal test concentration was greater than 100 mg/L and correspondingly the No Observed Effect Concentration was 100 mg/L. Analysis of test preparations at 0, 24 and 96 h showed measured test concentrations to range from 96% to 106% of nominal and so the results are based on the nominal test concentrations only. There were no sub-lethal effects.

CONCLUSION The notified chemical is practically non-toxic to rainbow trout.

TEST FACILITY Safepharm Laboratories Ltd (2006j)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - 48 h /static.
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - 48 h /static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	GC analysis with FID
Remarks – Method	No significant protocol deviation

RESULTS

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

LC50	>100 mg/L at 48 hours
NOEC	100 mg/L at 48 hours
Remarks - Results	The 48 h EC_{50} for the test material to *Daphnia magna* based on nominal test concentrations was greater than 100 mg/L and correspondingly the No Observed Concentrations was 100 mg/L. Analysis of the test preparations at 0 and 48 h showed measured test concentrations were 115-120% of nominal, so EC_{50} values are as nominal concentrations. The test preparations were observed to be clear solutions throughout the test.

CONCLUSION Notified chemical is practically non-toxic to daphnia.

TEST FACILITY Safepharm Laboratories Ltd (2006k)

C.2.3. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD	OECD TG 201 Alga, Growth Inhibition Test. EC Directive 92/69/EEC C.3 Algal Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 100 mg/L Actual: 93-99 mg/L
.Auxiliary Solvent	None
Water Hardness	Not recorded
Remarks - Method	No significant protocol deviation

RESULTS

Biomass		*Growth*	
EbC_{50} mg/L at 72 h	*NOEC mg/L*	*ErC_{50} mg/L at 0-72 h*	*NOEC mg/L*
>100	100	>100	100

Remarks - Results	Analysis of the test preparation at 0 and 72 h showed measured test concentrations to range from 93% to 99% of the nominal and so the results are based on nominal test concentrations.
CONCLUSION	The notified chemical is practically non-toxic to *Scenedesmus subspicatus.*
TEST FACILITY	Safepharm Laboratories Ltd (2006l)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Sewage sludge from local domestic sewage treatment plant.
Exposure Period	3 hours
Concentration Range	32-3200mg/l
Remarks – Method	No significant protocol deviation
RESULTS	
IC50	3700 mg/L
NOEC	100 mg/L
Remarks – Results	The validation criteria for the control respiration rates and reference material EC_{50} values have been satisfied. The IC50 values obtained by calculation using Xlfit3 software package of the 'best fit' line of the concentration response curve. In some instances the initial and final dissolved oxygen concentrations were below those recommended in the test guidelines (6.5 mg O_2/L and 2.5 mg O_2/L respectively). This was considered to have had no adverse effect on the results of the study given that in all cases the oxygen consumption rate was determined over the linear portion of the oxygen consumption trace. Relatively low initial oxygen readings were observed in 3.2 and 10 mg/L of the reference material, test material and control vessels. This was thought to be due to response of the activated sewage sludge on the day and was not considered to have had an effect on the results because the oxygen consumption rate was determined over the linear portion of the oxygen consumption trace.

CONCLUSION	The notified chemical is particularly non-toxic to sewage treatment bacteria.
TEST FACILITY	Safepharm Laboratories Ltd (2006m)

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