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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Nonitol, 1,2,3-trideoxy-4,6:5,7-bis-O-[(4-propylphenyl)methylene]-

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

Nonitol, 1,2,3-trideoxy-4,6:5,7-bis-O-[(4-propylphenyl)methylene]-

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Walk Off Mats Asia Pacific Pty Ltd (ABN 14 002 708 830)
Unit 4, 345 Plummer Street, Port Melbourne VIC 3207

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:
Other names, Molecular and Structural Formula, Spectral Data, Non-hazardous impurities, Additives

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
US TSCA (2006), EU ELINCS (2008), US FDA (2006 & 2008)

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Millad NX8000J (neat), Millad NX8000 (product blend)

CAS NUMBER
882073-43-0

CHEMICAL NAME
Nonitol, 1,2,3-trideoxy-4,6:5,7-bis-O-[(4-propylphenyl)methylene]-

MOLECULAR WEIGHT
< 500 Da

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

3. COMPOSITION

DEGREE OF PURITY > 99.0%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: White powder

Property	Value	Data Source/Justification
Melting Point	239°C	Measured
Boiling Point	> 400°C at 100.02 kPa	Measured
Density	1220 kg/m^3 at 21.6°C	Measured
Vapour Pressure	3.9×10^{-14} kPa at 25°C	Measured. The result indicates that the notified chemical is not volatile.
Water Solubility	1.51×10^{-6} g/L at 20°C	Measured. The low water solubility corresponds to the hydrophobic nature of the notified chemical.
Hydrolysis as a Function of pH	Not determined.	Measurement could not be performed due to the low water solubility. No hydrolysable functional group exists in the chemical and therefore, hydrolysis is not expected.
Partition Coefficient (n-octanol/water)	log Pow = 5.71	Measured. A high log P_{OW} is consistent with the hydrophobic nature of the chemical.
Adsorption/Desorption	log K_{oc} = 4.57	Measured. Based on its hydrophobic structure and high value of log P_{OW}, the notified chemical is expected likely to absorb onto organic carbon rich soil from water
Dissociation Constant	Not determined	The chemical does not contain any functional groups that are expected to dissociate in water.
Surface Tension	Not determined	Substances with water solubility < 1 mg/L need not to be tested.
Particle Size	Inhalable fraction (<100 μm): 21.1% Respirable fraction (<10 μm): 6.50%	Measured
Solid Flammability	Determined to be not highly flammable	Measured
Autoignition Temperature	> 239°C	Measured
Explosive Properties	negative	Estimated
Oxidising Properties	negative	Estimated

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

Reactivity
The notified chemical is stable at normal conditions.

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. It will be imported at 100%.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	6	15	30	45	45

PORT OF ENTRY
Sydney and Melbourne

IDENTITY OF RECIPIENTS
Walk Off Mats Asia Pacific Pty Ltd

TRANSPORTATION AND PACKAGING
The notified chemical will be imported by sea or air, transported from the port by road and/or rail to a warehouse and then to the compounding facility. It will be imported and distributed in 10 kg bags, and/or 20 and 40 kg fibre drums or superbags.

USE
The notified chemical will be used at up to 0.5% as a clarifying agent in moulded articles and films manufactured from polypropylene or high-propylene copolymers. Some specific examples of the industry/commercial/consumer application would be: plastic plates/cups, bottles, deli/grocery packaging containers, food storage containers, automotive parts, appliances, storage containers and DVD cases.

OPERATION DESCRIPTION
At the plastic processing site, the notified chemical is transferred from the import containers to the additive hopper, and is metered into an extruder with the polyolefin resin and other additives to produce plastic resin pellets containing up to 0.5% of the notified chemical or masterbatch pellets concentrates containing up to 66% of the notified chemical. Extruded, finished product pellets and masterbatch concentrates are collected and shipped to various plastic processing companies to manufacture articles for end use.

6. HUMAN HEALTH IMPLICATIONS

6.1 Exposure assessment

6.1.1 Occupational exposure

NUMBER AND CATEGORY OF WORKERS

Category of Worker	*Number*	*Exposure Duration (hours/day)*	*Exposure Frequency (days/year)*
Transport and storage			
Polymer stage	15	2	50
Article containing the notified polymer stage	15	1-2	40-50
Compounding and Manufacturing			
Extruder operation	50	8	20
Equipment maintenance	20	1-2	240
Material analysis	1-2	1	40
Manufacture of articles or film	> 100	6	40
End use	> 1000	1-8	240

EXPOSURE DETAILS
Transport and storage
The notified chemical will be transported by road to a warehouse and then to the compounding facility. Exposure of receivers and transport personnel should only occur in the event of an accidental spillage.

Compounding of plastic pellets
The notified chemical is introduced as a powder with 6.5% of particles in the respirable range (< 10 μm). Dermal, ocular and inhalation exposure to the notified chemical may occur during transfer of the notified chemical to the weighing vessel.

Dermal exposure during manual weighing and addition of the notified polymer is estimated using EASE (1997) modelling, in which it is assumed that intermittent, non-dispersive use occurs with direct handling, to be in the range 0.1-1 mg/cm^2/day. Assuming 100% dermal absorption, a surface area for hands at 820 cm^2 and forearms at 1140 cm^2 and a bodyweight of 70 kg, systemic exposure is estimated to be 2.8-28 mg/kg bw/day. The model is a conservative one and may overestimate exposure. The model does not take into account the duration of the activity and the use of PPE and ventilation. Taking these factors into consideration the lower end of the modelled exposure range is considered to be a more appropriate estimate of the dermal exposure.

According to EASE (1997) modelling of this work environment, in which it is assumed that dry manipulation of non-fibrous, non-aggregating dust occurs in the presence of exhaust ventilation, the estimated atmospheric concentration during weighing and manual transfer is 2-5 mg/m^3. Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m^3/hour, a 2 hour exposure time and 100% bioavailabilty, inhalation exposure is estimated to be 0.07 – 0.18 mg/kg bw/day. This estimate assumes that no respiratory protection is worn.

The notified chemical is then metered into a closed system and hence dermal exposure is not expected during the extrusion process, although the elevated temperatures required may result in inhalation exposure to the notified chemical.

According to EASE (1997) modelling of this work environment, in which it is assumed that the worker is segregated from the extrusion process, the estimated atmospheric concentration is 0 – 2 mg/m^3. Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m^3/hour, a 2 hour exposure time and 100% bioavailabilty, inhalation exposure is estimated to be 0– 0.07 mg/kg bw/day.

Dermal contact with the extruded pellets containing the notified chemical will occur during transfer and packaging, however, the notified chemical is physically bound within the plastic matrix and therefore exposure to the notified chemical is expected to be low.

Dermal, ocular and inhalation exposure may occur during material analysis, if material analysis of the notified chemical is required and during any cleaning activities.

Local exhaust ventilation may be employed at all workplace areas where natural ventilation is considered inadequate. Workers, particularly for those operators involved in any open transfer operations, are expected to wear personal protective equipment (PPE) including overalls, safety glasses/goggles or face shields, protective gloves, and are assumed to operate using appropriate industrial hygiene practices.

Product manufacture
Exposure to the notified chemical may occur during the processing of plastic compound to manufacture end-use products. However, the notified chemical is physically bound within the plastic matrix and therefore exposure is expected to be low. However, during product manufacture by processes such as extrusion and injection moulding, the elevated temperatures required may result in inhalation exposure to the notified chemical. Workers are expected to wear PPE including overalls, gloves and eye protection.

6.1.2. Public exposure

The notified chemical in its imported form (100%) will only be available to industrial customers, and not to the general public. However, public exposure to the notified chemical may occur due to its migration from end use articles.

In a migration study (Milliken 2006) conducted on polypropylene plaques (thickness 1.27 mm) containing the notified chemical at a level of 0.5%, the notified chemical was not detected when 10% ethanol and 3% acetic acid were used as extraction solvents, however, migration of the notified chemical did occur with solvents 50% ethanol and olive oil.

Results of the migration study are summarised below (for full details of the test, please refer to Appendix A):

Extraction solvent	Conditions	Amount of notified chemical in extract solution (µg/L)	Migration (mg/dm^2)
10% ethanol	100ºC for 30 minutes	Not detected	-
10% ethanol	100ºC for 30 minutes followed by 40ºC for 238 hours	Not detected	-
3% acetic acid	100ºC for 30 minutes	Not detected	-
3% acetic acid	100ºC for 30 minutes followed by 40ºC for 238 hours	Not detected	-
50% ethanol	66ºC for 2 hours	Average 29.5	0.005*
50% ethanol	66ºC for 2 hours followed by 40ºC for 238 hours	Average 39.7	0.006*
Olive oil	100ºC for 30 minutes	Not reported	0.015**
Olive oil	100ºC for 240 hours	Not reported	0.007**

*volume of extraction solvent = 250 mL; plaque surface area = 25 in^2; and 1 in^2 = 0.06452 dm^2
** using conversion factor 1 in^2 = 0.06452 dm^2

Information on migration to other food simulants and representative food stuffs was not provided. Based on the notified chemicals lipophilicity, migration into olive oil is likely to represent worst case due to its high fat content compared with other food simulants.

EFSA (2009) reported that the specific migration of the notified chemical into 10% ethanol, 3% acetic acid, and olive oil from a polypropylene sample containing 0.5% w/w of the substance after a contact time of 4 hours at 100°C was 0.361, 0.014 and 2.72 mg/kg food, respectively. The concentration of one of the hydrolysis products was 0.15, 0.36 and 0.29 mg/kg food, respectively.

Members of the public are likely to make limited dermal contact with food packaging, general plastic appliances, and/or automotive parts containing the notified chemical. Significant exposure to the notified chemical in plastic products as a result of casual contact during handling is not expected, as it is expected to be sufficiently bound within the plastic matrix. However, as the notified chemical will not be chemically bound, it may be released from products in low levels over time. Therefore, the public may be exposed to the notified chemical from its applications in products such as general plastic appliances and automotive parts and through possible ingestion of the notified chemical following its migration from food packaging into food.

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 toxicity	oral LD50 > 2000 mg/kg bw low toxicity
Rat, acute dermal toxicity	LD50 > 2000 mg/kg bw low toxicity
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Mouse, skin sensitisation – local lymph node assay	no evidence of sensitisation
Rat, repeat dose oral toxicity – 90 days.	NOAEL = 424 mg/kg bw/day
Mutagenicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro <Mammalian Cell Gene Mutation Test>	non genotoxic
Genotoxicity – in vitro <Mammalian Chromosome Aberration Test>	non genotoxic

Toxicokinetics, metabolism and distribution
The molecular weight of the notified chemical indicates that absorption following oral and dermal exposure may

occur, however, the rate of penetration may be limited by its log P_{ow} of 5.7. The notified chemical is expected to hydrolyse especially under acidic conditions. Due to a rapid hydrolysis in acidic media and further biotransformation of the formed hydrolysis products to polar compounds, an accumulation of the notified chemical or its hydrolysis products is considered unlikely. No specific toxicity data on the hydrolysis products were available. However, the hydrolysis products are expected to be formed in the S9-mix used for genotoxicity testing and their genotoxicity is then covered by the data on the notified chemical. Moreover they are also expected to be formed in the rat stomach in the 90-day study.

Acute toxicity
The notified chemical is of low acute toxicity *via* the oral and dermal routes. No acute inhalation toxicity data are provided although the notified chemical is available in powder form. Effects in the lung/respiratory system following acute exposure has not been investigated.

Irritation
Based on the studies provided, the notified chemical is considered to be slightly irritating to eyes and skin.

Sensitisation
There was no evidence of skin sensitisation to the notified chemical in a local lymph node assay using mouse under the conditions of the test. As the notified chemical was tested at relatively low concentrations, the potential for sensitisation cannot be ruled out.

Repeated dose oral toxicity
In a 90-day oral toxicity (dietary) study in rats, the notified chemical induced only minor histopathological changes at a concentration of 1682 mg/kg bw/day. The changes were not accompanied by treatment related changes in other parameters. A statistically significant increase in absolute and relative thyroid weights at the highest dose level in both sexes and in females at 424 mg/kg bw/day was not associated with any macroscopic or microscopic changes. Therefore it was considered there was insufficient evidence that the weight increase was an adverse effect. A NOAEL of 424 mg/kg bw/day can be derived.

Effects in the lungs following repeat exposure have not been investigated.

Genotoxicity
The notified chemical tested was not mutagenic in a bacterial reverse mutation study and not genotoxic in an *in vitro* mammalian cell gene mutation test or an *in vitro* mammalian chromosome aberration test.

Health hazard 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

The notified chemical is a slight irritant to eyes and skin and the notifier's MSDS states that it may cause irritation to the respiratory tract. Acute and long term effects in the lungs/respiratory system have not been investigated.

Transport and storage

Transport and storage workers should only be exposed to the notified chemical in the event of an accidental spillage, and so are unlikely to experience any risk from the notified chemical.

Compounding of plastic pellets

Exposure to the notified chemical is most likely during the weighing and transfer of the powdered notified chemical. These activities are expected to take place in the presence of adequate ventilation and use of worker PPE such as overalls and safety glasses. Workers should also have access to dust masks or respirators in the event that excessive dust is created or relevant exposure standards are not met. These control measures should reduce the potential for respiratory irritation and lung effects.

Total dermal and inhalation exposure to the notified chemical was estimated to be 3 mg/kg bw/day. The margin of exposure (MOE) based on a NOEL of 424 mg/kg bw/day is calculated as 139. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Therefore, the risk of adverse systemic effects are not expected.

Article/film manufacture

Workers involved in the manufacture of plastic articles or film are expected to have lower exposure to the notified chemical than workers handling the neat notified chemical. Therefore the risk to these workers is considered to be acceptable.

6.3.2. Public health

The notified chemical is not chemically bound and therefore has the potential to migrate from the articles which it is incorporated. Therefore the public may be exposed to the notified chemical from its applications in products such as general plastic appliances and automotive parts and through possible ingestion of the notified chemical following its migration from food packaging into food.

Although some histopathological changes were observed in a 90 day study in rats, these were only observed at the highest dose of 1682 mg/kg bw/day, which is expected to be significantly higher than levels to which the public will be exposed. The available toxicity data for the notified chemical indicates a low potential to cause adverse local effects following dermal or oral exposure.

Although a quantitative risk assessment for use in food contact materials has not been undertaken, the notified chemical is approved for use in the USA in polypropylene and high propylene olefin copolymer food contact materials at a level of 0.5% by weight of the finished polymer. The notified chemical has also recently been reviewed by the European Food Safety Authority (EFSA). Based on the available toxicological data, it was classified by the EFSA panel as List 3 (substances for which an ADI (Acceptable Daily Intake) or a TDI (Tolerable Daily Intake) could not be established, but where the present use could be accepted), and restricted to 5 mg/kg in food including the sum of hydrolysis products.

A copy of the NICNAS assessment report will be referred to Food Standards Australia New Zealand (FSANZ).

Overall, the notified chemical is not considered to pose an unacceptable risk to public health.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE
The notified chemical will be imported for use as the clarifying agent in plastics processing industry in Australia.

No significant release of the notified chemical is expected from the processing site. Potential release into the environment would be from the residues in the import containers, which will be sent to landfill together with the containers. Manufacturing scrap from the processing will be recycled due to the high cost of the material.

RELEASE OF CHEMICAL FROM USE
The notified chemical will be incorporated in the finished plastic articles, and therefore, no significant release of the notified chemical is expected from use.

RELEASE OF CHEMICAL FROM DISPOSAL
Finished articles containing the notified chemical will be sent to landfill at the end of the use life.

7.1.2 Environmental fate

The notified chemical is not readily biodegradable according to the study provided. Based on the log P_{OW} (5.71) there is potential for bioaccumulation. However, the aquatic exposure will be very low based on its reported use pattern and low water solubility. For the details of the environmental fate studies please refer to Appendix C.

Limited release from residues in containers will be sent to landfill. Most of the notified chemical will be incorporated into the finished plastic articles via processing and end up in landfill, which is the environmental fate of the associated plastic goods at the end of their use life.

In landfill, the notified chemical will not leach due to the low water solubility and will undergo slow degradation processes via biotic and abiotic pathways, forming small molecules of water and oxides of carbon.

7.1.3 Predicted Environmental Concentration (PEC)

The calculation of PEC is not possible since no significant release of the notified chemical to the aquatic environment is expected based on the reported use pattern.

7.2. Environmental effects assessment

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

Endpoint	*Result*	*Assessment Conclusion*
Fish Toxicity	LC50 > 0.00056 mg/L	Not toxic to fish up to the limit of solubility
Daphnia Toxicity	EC50 > 0.00087 mg/L	Not toxic to daphnia up to the limit of solubility
Algal Toxicity	EC50 > 0.00076 mg/L	Not toxic to algae up to the limit of solubility
Inhibition of Bacterial Respiration	IC50 = 1900 mg/L	Not harmful to sludge micro-organisms

The notified chemical is not toxic to the aquatic life up to the limit of the solubility.

7.2.1 Predicted No-Effect Concentration

The PNEC has not been calculated since no significant release of the notified chemical to the environment is expected based on the reported use pattern.

7.3. Environmental risk assessment

The Risk Quotient (PEC/PNEC) has not been calculated since no significant release of the notified chemical to the environment is expected based on the reported use pattern.

The notified chemical is not considered to pose an unacceptable risk to the aquatic ecosystem based on its reported use pattern and hydrophobic nature.

8. 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)].

In addition, the notified chemical is not classified using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) (United Nations 2003). This system is not mandated in Australia and carries no legal status but is presented for information purposes.

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.

Overall, the notified chemical is not considered to pose an unacceptable risk to public health. Although a risk assessment for dietary exposure has not been carried out, the notified chemical has been approved for similar food contact use in the USA and EU. A copy of this assessment report will be referred to Food Standards Australia New Zealand (FSANZ).

Environmental risk assessment

On the basis of the reported use pattern, the notified chemical is not considered to pose a risk to the environment.

Recommendations

REGULATORY CONTROLS
CONTROL MEASURES
Occupational Health and Safety

- Employers should implement the following engineering controls to minimise occupational exposure to the notified chemical as introduced:
  - Use of local exhaust ventilation during transfer and weighing activities
  - Use of adequate general ventilation during other industrial processes

- Employers should implement the following safe work practices to minimise occupational exposure during the handling of the notified chemical as introduced:
  - Avoid direct skin and eye contact
  - Avoid breathing dust

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - where engineering controls and work practices do not reduce vapour and particulate exposure to safe levels below the NOHSC exposure standard for nuisance dust (10mg/m^3) (NOHSC 1995), respiratory protection should be used.

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

- 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.

Disposal

- The notified chemical should be disposed of to landfill.

Emergency procedures

- 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 a clarifying agent at up to 0.5% in moulded articles or films manufactured from polypropylene or high-propylene olefin copolymers, or is likely to change significantly;
- the amount of chemical being introduced has increased from 45 tonne per annum, 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.

No additional secondary notification conditions are stipulated.

Material Safety Data Sheet
The MSDS of the notified chemical and product 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.

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Melting Point 239 ± 0.5°C

Method	OECD TG 102 Melting Point/Melting Range. ASTM E537-86
Remarks	The differential scanning calorimetry was used.
Test Facility	SafePharm Laboratories (2006a)

Boiling Point > 400 ± 0.5°C at 100.02 kPa

Method	OECD TG 103 Boiling Point. ASTM E537-86
Remarks	The differential scanning calorimetry was used. No sign of boiling or decomposition was noted up to the maximum temperature of 400°C. The boiling point was calculated to be 598°C.
Test Facility	SafePharm Laboratories (2006a)

Density 1220 kg/m^3 at 21.6 ± 0.5°C

Method	OECD TG 109 Density of Liquids and Solids.
Remarks	A gas comparison pycnometer was used.
Test Facility	SafePharm Laboratories (2006a)

Vapour Pressure 3.9×10^{-14} kPa at 25°C

Method	OECD TG 104 Vapour Pressure.
Remarks	The vapour pressure was determined using a vapour pressure balance. A sequence of runs was started after a sample of the notified chemical had been under vacuum for approximately 28½ hours, with measurements being made at several temperatures between 180 and 190°C, and the vapour pressure being calculated using linear regression analysis.
Test Facility	SafePharm Laboratories (2006b)

Water Solubility 1.51×10^{-6} g/L at 20.0 ± 0.5°C

Method	OECD TG 105 Water Solubility.
Remarks	Flask Method was used. Following a preliminary test, triplicate solutions of the notified chemical were prepared and analysed using HPLC in duplicate for each sample solution. Duplicate standard solutions with a nominal concentration of 0.1 mg/L were prepared and analysed.
Test Facility	SafePharm Laboratories (2006a)

Partition Coefficient (n-octanol/water) log Pow = 5.71

Method	OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks	The test was conducted using HPLC method with a column temperature of 30˚C and a pH (mobile phase) of 8.3. A preliminary test was carried out by visual assessment. Based on the preliminary test, a definitive test was conducted with a solution of 0.023 g/L in acetonitrile. The dead time was determined by measuring the retention time of thiourea. The retention time of the notified chemical was detected as 17.85 minutes, corresponding to a P_{OW} value of 5.16×10^5 (log P_{OW} = 5.71). A high log P_{OW} is consistent with the hydrophobic nature of the chemical.
Test Facility	SafePharm Laboratories (2006a)

Adsorption/Desorption log K_{oc} = 4.57

Method	OECD TG 121 Estimation of the Adsorption Coefficient (K_{OC}) on soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC).
Remarks	The test was conducted using HPLC method with a column temperature of 30˚C and a pH (mobile phase) of 7.5. The test solution was prepared by diluting 0.0025 g of the notified chemical with 100 mL acetonitrile. The dead time was determined by measuring the retention time of formamide. The retention time of the notified chemical was detected as 5.54 minutes, corresponding to a K_{OC} value of 3.68×10^4 (log K_{OC} = 4.57). A high log K_{OC} is consistent with the hydrophobic nature and the high log P_{OW} of the chemical.
Test Facility	SafePharm Laboratories (2006a)

Solid Flammability Determined to be not highly flammable

Method	EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks	The test substance did not propagate combustion over the 200 mm of the preliminary screening test.
Test Facility	SafePharm Laboratories (2006c) and Chilworth Technology (2006)

Autoignition Temperature > 239 ± 0.5°C

Method	EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Test Facility	SafePharm Laboratories (2006b)

Explosive Properties Not explosive

Method	EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks	Based on the chemical structure and oxygen balance of the test substance (-237.7) the result for the explosive properties has been predicted to be negative.
Test Facility	SafePharm Laboratories (2006b)

Oxidising Properties Predicted negative

Method	EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks	Based on the chemical structure
Test Facility	SafePharm Laboratories (2006b)

Migration Testing

TEST SUBSTANCE	Notified chemical
METHOD	
Test Samples	The migration testing was conducted on plaques prepared from polypropylene random copolymer with ethylene. The grade of polypropylene used for this study was SA849, manufactured by Basell Inc. The resin was melt compounded when adding the clarifier with standard additives, including Irganox 1010, Irgafos 168, and calcium stearate. For these extraction tests, a sample of the notified chemical was used that contained 0.056% specified impurity to simulate worst case migration conditions for this low molecular weight impurity. The actual specification limit for this impurity is 0.040%. The notified chemical as an additive was added gravimetrically to polypropylene pellets (5.0 grams per 1000 grams of additive/polymer mixture), mixed in a Welex high intensity mixer, and extruded on 1 24:1 Killion Extruder at 220°C. Plaques were prepared using a 25 ton Arburg injection moulder with a barrel temperature of 230°C. The concentrations of the notified chemical in polypropylene plaques were determined by GC/MS.
Migration testing solvents	Migration testing was conducted using 3% acetic acid, 10% ethanol, 50%

	ethanol and olive oil.
Extraction vessels	Extractions were conducted in 400 mL stainless steel vessels with Teflon-lined, stainless steel lids. Glass slides were used to ensure separation of polymer samples during migration testing.
Migration testing conditions	Triplicate migration tests in each solvent were performed using two plaques (25 in^2 in total surface area) immersed in 250 mL of solvent. The solvents were placed in the stainless steel vessels and preheated in the 100°C oven for 1 hour prior to addition of the plaques. Polypropylene samples were extracted for 30 minutes at 100°C followed by 238 hours at 40°C. Control plaques were also prepared without the notified chemical and extracted using the same conditions. The control solutions generated from the 240 hour migration test were used for method validation (i.e. recovery) analyses. For the 50% ethanol extraction test, the solvent was placed in the stainless steel vessels and preheated to 66°C oven for 1 hour prior to addition of the plaques. The vessels were then placed in a 66°C oven for 2 hours followed by 238 hours at 40°C.
Analytical methods	In order to determine levels of the notified chemical in the solvent extracts, the extracted solution samples (250 mL) were concentrated individually on a rotary evaporator. Each sample vessel was rinsed with 10-15 mL of deionised water to ensure all the extracted solution was removed from the stainless steel vessel. After evaporation of the extraction solvent, the concentrated extract was then reconstituted in 10.0 mL of HPLC grade acetonitrile. The samples were then filtered through 20 micron filters and analysed on the HPLC at 215 nm. The control solution generated from the 240 hour migration test on polypropylene specimens containing no notified chemical were used as the matrix for method validation (i.e. recovery) analysis for the notified chemical extraction experiments.
Analytical method calibration and validation	Recovery experiments for the notified chemical in the various extraction solvents were prepared using control extract solutions obtained via 240 hour extraction of plaques prepared without the notified chemical. The control solutions were spiked in triplicate at several levels. The % recovery levels were obtained using calibration data obtained by spiking known levels of the notified chemical in acetonitrile.
Sample preparation and analysis using olive oil	1. Plaques were removed from olive oil immediately after heating. 2. 5.0 mL aliquots of olive oil extraction solutions were then transferred to 22 mL vials, and 5.0 mL of acetonitrile was added. 3. Samples were shaken for 1 minute, then centrifuged at 2000 rpm for 20 minutes to separate the olive oil and acetonitrile phases. 4. After centrifugation, an aliquot of the top (acetonitrile) phase was transferred to an HPLC vial for analysis.

RESULTS

Levels of the notified chemical in polypropylene extraction solutions

Extraction solvent	Test conditions	Area @ 215 nm	The notified chemical in extract solution (µg/L)
10% ethanol	100°C for 30 minutes	Not detected	< 56
		Not detected	< 56
		Not detected	< 56
10% ethanol	100°C for 30 minutes followed by 40°C for 238 hours	Not detected	< 56
		Not detected	< 56
		Not detected	< 56
3% acetic acid	100°C for 30 minutes	Not detected	< 31
		Not detected	< 31
		Not detected	< 31
3% acetic acid	100°C for 30 minutes followed by 40°C for 238	Not detected	< 31

Levels of the notified chemical in polypropylene extraction solutions

Extraction solvent	Test conditions	Area @ 215 nm	The notified chemical in extract solution (µg/L)
	hours		
		Not detected	< 31
		Not detected	< 31
50% ethanol	66ºC for 2 hours	154716	30.6
		159204	31.6
		136131	26.3
50% ethanol	66ºC for 2 hours followed by 40ºC for 238 hours	181586	36.8
		201596	41.5
		199227	40.9

Levels of the notified chemical in olive oil extraction solutions

Solvent	Extraction time	Peak Area	mg/in^2
Olive oil	100ºC for 30 minutes	33817	0.00024
		78247	0.00150
		65264	0.00113
Olive oil	100ºC for 240 hours	48242	0.00065
		40531	0.00043
		36131	0.00030

CONCLUSION

The migration testing procedures and conditions, analytical methods and migration testing results for the notified chemical from polypropylene to 3% acetic acid, 10% ethanol, 50% ethanol and olive oil were provided. Migration was not detected for 3% acetic acid and 10% ethanol while migration was detected for 50% ethanol and olive oil.

TEST FACILITY

Milliken (2006)

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD
- Species/Strain: Rat/Sprague-Dawley CD strain
- Vehicle: Arachis oil BP
- Remarks - Method: No deviations from the protocol. A total of five animals were dosed individually in sequence with sufficient time (at least 48 hours) between each animal.

RESULTS

Number and Sex of Animals	*Dose (mg/kg bw)*	*Mortality*
1 F	175	0
1 F	550	0
1 F	2000	0
1 F	2000	0
1 F	2000	0

- LD50: > 2000 mg/kg bw
- Signs of Toxicity: There were no sign of systemic toxicity.
- Effects in Organs: No abnormalities were noted at necropsy.
- Remarks - Results: All animals showed expected gains in bodyweight over the study period.

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

TEST FACILITY: SafePharm Laboratories (2006d)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 402 Acute Dermal Toxicity – Limit Test.
EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test.
- Species/Strain: Rat/Sprague-Dawley CD strain
- Vehicle: Moistened with arachis oil BP
- Type of dressing: Semi-occlusive.
- Remarks - Method: No deviations from the protocol.

RESULTS

Number and Sex of Animals	*Dose (mg/kg bw)*	*Mortality*
5 per sex	2000	0

- LD50: > 2000 mg/kg bw
- Signs of Toxicity - Local: There were no signs of dermal irritation.
- Signs of Toxicity - Systemic: There were no sign of systemic toxicity.
- Effects in Organs: No abnormalities were noted at necropsy.
- Remarks - Results: All animals showed expected gains in bodyweight over the study period.

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

TEST FACILITY: SafePharm Laboratories (2008a)

B.3. Irritation – skin

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 M
Vehicle	Moistened with distilled water
Observation Period	7 days
Type of Dressing	Semi-occlusive.
Remarks - Method	No deviations from the protocol.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	1	1	1	1	72 hours	0
Oedema	0.3	0.3	0.3	1	24 hours	0

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

Remarks - Results: Very slight erythema was noted at two treated skin sites one hour after patch removal and at all treated skin sites at the 24, 48 and 72-hour observations.
Very slight oedema was noted at all treated skin sites at the 24-hour observation.
All treated skin sites appeared normal at the 7-day observation.

CONCLUSION: The notified chemical is slightly irritating to the skin.

TEST FACILITY: SafePharm Laboratories (2007b)

B.4. 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 M
Observation Period	72 hours
Remarks - Method	No deviations from the protocol.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.3	0.3	1	2	48 hours	0
Conjunctiva: chemosis	0	0	0.3	1	24 hours	0
Conjunctiva: discharge	0	0	0	1	1 hour	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: No corneal or iridial effects were noted during the study.
Moderate conjunctival irritation was noted in all treated eyes one hour

after treatment with minimal conjunctival irritation in all treated eyes at the 24-hour observation and in one treated eye at the 48-hour observation. Two treated eyes appeared normal at the 48-hour observation and the remaining treated eye appeared normal at the 72-hour observation.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY SafePharm Laboratories (2007c)

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

TEST SUBSTANCE Notified chemical

METHOD OECD TG 429 Skin Sensitisation: Local Lymph Node Assay.
EC Directive 2004/73/EEC B.42 Skin Sensitisation (Local Lymph Node Assay).

Species/Strain Mouse/CBA/Ca (CBA/CaBkl)

Vehicle Acetone/olive oil 4:1 (this vehicle was chosen as it produced the highest concentration that was suitable for dosing)

Remarks - Method No deviations from the protocol. The preliminary screening test at 5% suggested that the test substance would not produce systemic toxicity or excessive local irritation at the highest suitable concentration. Experiments with vehicles established at Acetone/olive oil 4:1 at 10% would be suitable for dosing. It is not known why a higher concentration than 5% was not tested.

RESULTS

Concentration (% w/w)	*Proliferative response (DPM/lymph node)*	*Stimulation Index (Test/Control Ratio)*
Test Substance		
0 (vehicle control)	1988.22 ± 530.51	
1	1862.99 ± 594.55	0.94
2.5	1366.01 ± 847.83	0.69
5	2183.85 ± 740.63	1.10
Positive Control (α-hexylcinnamaldehyde)		
5		2.50
10		4.03
25		9.13

Remarks - Results A stimulation index of less than 3 was recorded for three concentrations of the test substance.
There were no deaths. No signs of systemic toxicity were noted in the test or control animals during the test.
Bodyweight changes of the test animals between Day 1 and Day 6 were comparable to those observed in the corresponding control group animals over the same period.
The chemical was tested at relatively low concentrations, and the potential for sensitisation cannot be ruled out.

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

TEST FACILITY SafePharm Laboratories (2007d)

B.6. Repeat dose toxicity (screening)

TEST SUBSTANCE	Notified chemical
METHOD	Fourteen Day Repeated Dose Oral (Dietary) Toxicity Screening/Palatability Investigation in the Rat
Species/Strain	Rat/Sprage-Dawley Crl:CD® (SD) IGS BR
Route of Administration	Oral –diet
Exposure Information	Total exposure days: 14 days Dose regimen: 7 days per week Post-exposure observation period: not applicable
Vehicle	None
Remarks - Method	No deviations from the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration <mg/kg bw/day>*	*Mortality*
control	3 per sex	0	0
low dose	3 per sex	625	0
mid dose	3 per sex	1188	0
high dose	3 per sex	2544	0

Mortality and Time to Death
There were no unscheduled deaths.

Clinical Observations
No clinically observable signs of toxicity were detected.
No adverse effect on bodyweight gain was detected.
No adverse effect on dietary intake was detected.

Effects in Organs
No macroscopic abnormalities were detected.

Remarks – Results
Dietary administration of the test substance to rats for a period of fourteen consecutive days at dietary concentrations of up to 2544 mg/kg/day produced no toxicologically significant changes in the parameters measured.

CONCLUSION
The "No Observed Effect Level" (NOEL) was therefore considered to be 2544 mg/kg bw/day.

TEST FACILITY	SafePharm Laboratories (2006e)

B.7. Repeat dose toxicity (main study)

TEST SUBSTANCE	Notified chemical
METHOD	The study was designed to comply with the recommendations of the US Food and Drug Administration, Redbook 2000, "Toxicological Principles for the Safety Assessment of Food Ingredients' (November 2003).
Species/Strain	Rat/Sprage-Dawley Crl:CD® (SD) IGS BR
Route of Administration	Oral –diet
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week Post-exposure observation period: none.
Vehicle	None
Remarks - Method	No deviations from the protocol.

RESULTS

Group	*Number and Sex of Animals*	*Dose/Concentration <mg/kg bw/day>*	*Mortality*
control	20 per sex	0	0
low dose	20 per sex	21	0
mid dose	20 per sex	424	0
high dose	20 per sex	1682	0

Mortality and Time to Death

There were no unscheduled deaths during the treatment period.

Clinical Observations

No clinically observable signs of toxicity were detected during the treatment period.
No treatment-related effects were detected during behaviour assessments or in the functional performance test.
No adverse effect on bodyweight change, dietary intake, water consumption or food efficiency was evident for treated animals when compared to controls.
No treatment-related ocular effects were detected.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

No treatment-related changes were detected during the Week 3, Week 7 or pre-terminal haematological assessments. Slight elevation of mean cell haemoglobin concentration (MCHC) levels in mid and high dose males in Week 13 was not considered by the study authors to be related to treatment, as similar changes were not seen in females, there were no associated changes in other parameters, and a clear dose response was not established.
No treatment-related changes were detected during the Week 3, Week 7 or Week 13 blood chemical assessments. Reductions in male rats only of the levels of aspartate aminotransferase at week 7 and γ-glutamyltranspeptidase at week 13 were considered incidental. Although calcium levels were reduced in female rats at Week 13, there was no sign of electrolyte imbalance or of the increased inorganic phosphorus that would be expected if the changes were treatment related.
No treatment-related changes in the urine were detected.

Effects in Organs

A statistically significant increase in absolute and relative thyroid weights at the highest dose level in both sexes and in females at 424 mg/kg bw/day was not associated with any macroscopic or microscopic changes. Therefore it was considered there was insufficient evidence that the weight increase was an adverse effect. No other treatment-related organ weight changes were detected.
No treatment-related macroscopic abnormalities were detected at necropsy.
For histopathology, treatment-related microscopic changes were detected as follows:
In the kidney, a lower incidence of globular accumulations of eosinophilic material in the proximal tubular epithelium occurred in males at 1682 mg/kg bw/day. In the bone marrow, generally lower grades of severity of adipose infiltration of the marrow were seen among females treated with 1682 mg/kg bw/day. In the spleen, a greater incidence of higher grades of extramedullary haematopoiesis was observed in females treated with 1682 mg/kg bw/day.

Remarks – Results

Other changes noted during the study were typical of those arising spontaneously in laboratory rats or were not dose related and were considered to have arisen incidentally.

CONCLUSION

The No Observed Adverse Effect Level (NOAEL) was considered to be 424 mg/kg bw/day based on the absolute and relative thyroid weights in females at this dose level and treatment-related histopathological changes and higher thyroid weights at 1682 mg/kg bw/day.

TEST FACILITY SafePharm Laboratories (2006f)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA$^-$
Metabolic Activation System	A rat liver homogenate metabolising system (10% liver S9 in standard co-factors)
Concentration Range in Main Test	a) With metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate b) Without metabolic activation: 0, 50, 150, 500, 1500, 5000 µg/plate
Vehicle	Dimethyl formamide
Remarks - Method	No deviations from the protocol.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 5000			
Test		> 5000	> 1500	negative
Present	> 5000			
Test		> 5000	> 1500	negative

Remarks - Results	The test substance 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 5000 µg/plate. A white, globular precipitate was observed at and above 1500 µg/plate, this did not prevent the scoring of revertant colonies. No significant increases in the frequency of revertant colonies were recorded for any of the bacterial strains, at any dose level either with or without metabolic activation. All the positive control chemicals used in the test induced marked increases in the frequency of revertant colonies thus confirming the activity of the S9-mix and the sensitivity of the bacterial strains.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	SafePharm Laboratories (2006g)

B.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 476 In vitro Mammalian Cell Gene Mutation Test. EC Directive 2000/32/EC B.17 Mutagenicity - In vitro Mammalian Cell Gene Mutation Test.
Cell Type/Cell Line	L5178Y TK +/- 3.7.2c mouse lymphoma cells (heterozygous at the thymidine kinase locus)
Metabolic Activation System	PB/βNF S9 was prepared from the livers of male Sprague-Dawley rats that had each received orally three consecutive daily doses of phenobarbital/β-naphthoflavone (80/100 mg per kg per day) prior to S9 preparation on the fourth day. 20% S9-mix was prepared by mixing S9, NADP (5 mM), G6P (5mM), KCl (33mM) and $MgCl_2$ (8mM) in R0.

	The final concentration of S9 was 2% throughout the study.
Vehicle	Dimethyl sulfoxide
Remarks - Method	No deviations from the protocol.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*
Absent		
Test 1	0, 31.25, 62.5, 125, 250, 375, 500	4 hours
Test 2	0, 31.25, 62.5, 125, 250, 375, 500	24 hours
Present		
Test 1	0, 31.25, 62.5, 125, 250, 375, 500	4 hours
Test 2	0, 31.25, 62.5, 125, 250, 375, 500	4 hours

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 500			
Test 1		> 500	≥ 62.5	negative
Test 2		> 500	≥ 62.5	negative
Present	> 500			
Test 1		> 500	≥ 62.5	negative
Test 2		> 500	≥ 62.5	negative

Remarks - Results	The maximum dose level used was limited to 500 µg/mL by test substance formulation difficulties. A precipitate of test substance was observed at and above 62.5 µg/mL. The vehicle (solvent) controls had acceptable mutant frequency values that were within the normal range for the L5178Y cell line at the TK +/- locus. The positive control materials induced marked increases in the mutant frequency indicating the satisfactory performance of the test and of the activity of the metabolising system. The test substance did not induce any statistically significant or dose-related increases in the mutant frequency at any dose level, either with or without metabolic activation, in either the first or the second test.
CONCLUSION	The notified chemical did not induce any toxicologically significant increases in the mutant frequency at the TK +/- locus in L5178Y cells and is therefore considered to be non-mutagenic under the conditions of the test.
TEST FACILITY	SafePharm Laboratories (2006h)

B.10. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test. EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.
Cell Type/Cell Line	Human lymphocytes
Metabolic Activation System	PB/βNF S9 was prepared from the livers of male Sprague-Dawley rats that had each received orally three consecutive daily doses of phenobarbital (80 mg/kg) and β-naphthoflavone (100 mg/kg) prior to S9 preparation on the fourth day.
Vehicle	Dimethyl sulfoxide
Remarks - Method	No deviations from the protocol. The maximum dose level investigated was 500 µg/mL; which was limited by formulation difficulties, and was considered to be the maximum dose level at which accurate dosing could

be achieved.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	0*, 15.63, 31.25*, 62.5*, 125*, MMC 0.4*	4 hours	24 hours
Test 2	0*, 15.63, 31.25*, 62.5*, 125*, MMC 0.2*	24 hours	24 hours
Present			
Test 1	0*, 15.63, 31.25*, 62.5*, 125*, CP 5*	4 hours	24 hours
Test 2	0*, 15.63, 31.25*, 62.5*, 125*, CP 5*	4 hours	24 hours

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

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	> 500			
Test 1		> 125	> 125	negative
Test 2		> 125	> 125	negative
Present	> 500			
Test 1		> 125	> 125	negative
Test 2		> 125	> 125	negative

Remarks - Results

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.
The test substance was non-toxic and did not induce any statistically significant increases in the frequency of cells with aberrations, in either of two separate experiments, using a dose range that used the lowest dose level where precipitate persisted onto the slides in the 4(20)-hour pulse treatments in the preliminary toxicity test.

CONCLUSION

The notified chemical was considered to be non-clastogenic to human lymphocytes in vitro under the conditions of the test.

TEST FACILITY

SafePharm Laboratories (2006i)

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	Activated Sewage Sludge Micro-organisms
Exposure Period	28 Days
Auxiliary Solvent	None
Analytical Monitoring	DOC was analysed using a Shimadzu TOC-5050 TOC analyser. CO_2 evolution was analysed using a Tekmar-Dohrmann Apollo 9000 TOC analyser and a Shimadzu TOC-V_{CSH} TOC analyser.
Remarks - Method	Test was conducted at a nominal concentration of 13.9 mg/L, equivalent to 10 mg/L carbon/L. To achieve this, 41.7 mg of the notified chemical was dispersed by high shear mixing (7500 rpm, 15 minutes) in inoculated culture medium to form a final dispersion of 3 litres. A control (consisting of inoculated culture medium only) and a reference control (containing reference material sodium benzoate and the inoculated medium giving a concentration of 10 mg carbon/L) were conducted. All the above tests were conducted in duplicate. In addition, a toxicity control test containing both the notified chemical and sodium benzoate was conducted.

RESULTS

Test substance		*sodium benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
1	0	1	14
28	6	14	86

Remarks - Results	All criteria for test validity were met. The notified chemical attained 6% degradation after 28 days and therefore can not be considered to be readily degradable under OECD Guideline No 301B.
CONCLUSION	The notified chemical is not readily biodegradable.
TEST FACILITY	SafePharm Laboratories (2006j)

C.1.2. Ready biodegradability

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I).
Inoculum	Mixed activated sludge from 10 locations of sewage plants, surface water and surface oil in Japan.
Exposure Period	28 Days
Auxiliary Solvent	None
Analytical Monitoring	Measurement of biochemical oxygen demand (BOD) with a closed system oxygen consumption measuring apparatus. Determination of test item by HPLC.
Remarks - Method	Test was conducted at a nominal concentration of 100 mg/L in triplicates. The activity of the sludge was assessed using aniline as the reference material. In addition, a blank control (containing the sludge only) and a control test (containing the notified chemical and water without the sludge) were conducted.

RESULTS

Test substance		*aniline*	
Day	*% Degradation (BOD)*	*Day*	*% Degradation (BOD)*
1	0	7	54
28	8	28	67

Remarks - Results

All criteria for test validity were met.

Recovery tests were conducted for water/test item and sludge/test item solutions, yielding a respective recovery rate of 95.3% and 99.9%.

The notified chemical attained an average degradation of 8% by BOD and 1% by HPLC after 28 days and therefore can not be considered to be readily degradable by micro-organisms under the conditions of test.

CONCLUSION

The notified chemical is not readily biodegradable.

TEST FACILITY

CERÌ (2007)

C.2. Ecotoxicological Investigations

C.2.1. Acute toxicity to fish

TEST SUBSTANCE

Notified Chemical

METHOD

OECD TG 203 Fish, Acute Toxicity Test – semi-static.

Species: *Oncorhynchus mykiss*

Exposure Period: 96 hours

Auxiliary Solvent: Dimethylformamide

Water Hardness: 140 mg $CaCO_3$/L

Analytical Monitoring: HPLC for determination of test contents.

Remarks – Method

After a range-finding test (at a concentration of 0.0015 mg/L), a definitive (limit) test was conducted at the same concentration in duplicates at 14˚C with 10 fish used for each test vessel. This is deemed acceptable considering the low water solubility of 0.00151 mg/L, despite a loading rate of 100 mg/L is recommended in the Guideline for a limit test. Dechlorinated laboratory tap water was used in the preparation of the test solutions. Stability of the notified chemical was also tested.

The actual concentrations of the test solution were analysed at 0, 24, 48, 72 and 96 hours, for cases of untreated and treated by centrifugation at 40,000 g for 30 minutes. The centrifuged samples showed measured test concentrations of 24% to 52% of the nominal values, indicating a lower solubility than 0.00151 mg/L, which was considered to be due to the existence of electrolytes in the tap water compared to the distilled water.

A control and a solvent control (100 µL solvent /L) test were conducted under identical conditions except the absence of the notified chemical.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	0	10	0	0	0	0	0
Solvent control	0	10	0	0	0	0	0
0.0015	0.00056	20	0	0	0	0	0

LC50

> 0.00056 mg/L at 96 hours (geometric mean value of centrifuged samples).

NOEC

0.00056 mg/L at 96 hours (geometric mean value of centrifuged samples).

Remarks – Results	The notified chemical was considered stable under the test conditions. The time-weighed mean measured test concentration of the notified chemical was determined to be 0.00056 mg/L. Neither mortality nor sub-lethal effect was reported. The 96-hour LC50 was determined to be > 0.00056 mg/L, which is considered to be up to the limit of the solubility.
CONCLUSION	The notified chemical is not toxic to fish up to the limit of the solubility.
TEST FACILITY	SafePharm Laboratories (2007e)

C.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	dimethylforamide
Water Hardness	250 mg $CaCO_3$/L
Analytical Monitoring	HPLC used for test concentration determination
Remarks - Method	Following a preliminary range-finding test, 4 replicates of 5 daphnids were exposed to an aqueous solution of the notified chemical at 0.0015 mg/L for 48 hours at 20˚C. Reconstituted water with a hardness of about 250 mg $CaCO_3$/L was used in the sample preparation. A positive control test using potassium dichromate was conducted at concentrations of 0.32, 0.56, 1.0, 1.8 and 3.2 mg/L for 48 hours at 20 – 21.1˚C under static conditions. A solvent control (at 100 µL solvent /L) was also conducted under identical conditions except the absence of the notified chemical. Analysis of the test preparations throughout the test showed measured concentrations of 101% to 126% of the nominal value, while analysis of the centrifuged samples showed lower measured concentrations (69 – 70% at 0 hour and 46 – 51% at 48 hour of the nominal value). Given the decline in the concentrations for the centrifuged samples, it was considered that the notified chemical in the diluent was below 0.0015 mg/L.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0.0015	0.00087	20	0	0

LC50	> 0.00087 mg/L at 48 hours (geometric mean value of centrifuged samples)
NOEC	0.00087 mg/L at 48 hours (geometric mean value of centrifuged samples)
Remarks - Results	The 48-hour EC50 for the reference material to daphnia based on nominal concentrations was determined to be 0.85 mg/L with 95% confidence limits of 0.76 – 0.96 mg/L. No immobilisation or adverse reaction of the tested daphnids to the notified chemical was observed at the loading rate of 0.0015 mg/L. The 48-hour EC50 based on the geometric mean measured test concentrations of the centrifuged test media was determined to be > 0.00087 mg/L.

CONCLUSION	The notified chemical is not toxic to daphnia up to the limit of the solubility.
TEST FACILITY	SafePharm Laboratories (2007f)

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	*Desmodesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 0.0015 mg/L 0.00076 mg/L (geometric mean value for centrifuged solutions)
Auxiliary Solvent	Dimethylformamide
Water Hardness	Not reported
Analytical Monitoring	HPLC used for the concentration determination of test solutions
Remarks - Method	Following a preliminary range-finding test, *Desmodesmus subspicatus* was exposed to an aqueous solution of the notified chemical in 6 replicates at a concentration of 0.0015 mg/L and a temperature of 24±1˚C. Analysis of both untreated and centrifuged test preparations at 0 hour showed measured concentrations of 100% – 119% and 63% – 74% of the nominal concentration, respectively. The analysis at 72 hour showed a decline in concentrations for both untreated and centrifuged cases, with a respective measured concentration of 67% – 76% and 37% – 39% of the nominal concentration. Geometric mean value of the centrifuged sample concentrations was calculated to be 0.00076 mg/L. A positive control was conducted using potassium dichromate as the reference material at concentrations of 0.0625, 0.125, 0.25, 0.5 and 1.0 mg/L in three replicates.

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 72 h	*NOEC mg/L*	*E_rC50 mg/L at 72 h*	*NOEC mg/L*
> 0.00076	0.00076	> 0.00076	0.00076

* Based on geometric mean concentration of the measured centrifuged samples.

Remarks - Results	The 0 – 72 hour E_rC50 and E_bC50 for the positive control was determined to be 0.58 mg/L (95% confidence limits 0.47 – 0.71 mg/L) and 0.20 mg/L (95% confidence limits 0.17 – 0.24 mg/L), respectively. The decline of concentration in the untreated samples is considered to be due to the absorption to algal cells. Therefore, the notified chemical is considered not to be toxic to algae up to the solubility of the notified chemical in the test medium.
CONCLUSION	The notified chemical is not toxic to algae up to the limit of the solubility.
TEST FACILITY	SafePharm Laboratories (2007g)

C.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified Chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test.

Inoculum	Activated Sludge
Exposure Period	3 hours
Concentration Range	Nominal: 180, 320, 560, 1000, 1800and 3200 mg/L
Remarks – Method	Biological Oxygen Demand (BOD) was measured for determination of the rate of respiration. Based on two preliminary range-finding tests, the definitive test was conducted in duplicate at concentrations ranging 180 – 3200 mg/L and a temperature of 21˚C. Dechlorinated laboratory tap water (hardness of about 140 mg/L) was used in the test material preparation. A blank control test was carried out under identical conditions but without the test material. A reference control test was also conducted in duplicate using 3,5-dichlorophenol at concentrations of 3.2, 10 and 32 mg/L.

RESULTS

IC50	1900 mg/L (95% confidence limits 1700 – 2100 mg/L)
NOEC	1000 mg/L
Remarks – Results	All criteria for test validity are considered met. The 3-hour EC50 for the reference test was determined to be 7.0 mg/L with 95% confidence limits of 5.2 – 9.5 mg/L.

CONCLUSION The notified chemical is not harmful to sludge micro-organisms.

TEST FACILITY SafePharm Laboratories (2007h)

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