File No: STD/1268

December 2007

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Benzenamine, 4,4'-methylenebis[2-methyl-6-(1-methylethyl)-

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 and Water Resources.

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:

Street Address:	334 - 336 Illawarra Road MARRICKVILLE NSW 2204, AUSTRALIA.
Postal Address:	GPO Box 58, SYDNEY NSW 2001, AUSTRALIA.
TEL:	+ 61 2 8577 8800
FAX	+ 61 2 8577 8888
Website:	www.nicnas.gov.au

Director
NICNAS

TABLE OF CONTENTS

FULL PUBLIC REPORT

Benzenamine, 4,4'-methylenebis[2-methyl-6-(1-methylethyl)-

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Hawker de Havilland Aerospace Pty Ltd (ABN: 15 103 165 466)
226 Lorimer Street
Port Melbourne VIC 3207

Hexcel Pacific Rim Corporation (ABN: 45 078 469 619)
Suite 2, 86 Grimshaw Street
Greensborough VIC 3088

The Trustee for Australian Composites Trust Trading as Australian Composites Pty Ltd (ABN: 49 188 122 103)
124-130 Cochranes Road
Moorabbin VIC 3189

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:
Molecular formula; Structural formula; Molecular weight; Other names; Spectral data; Purity, Impurities; Additive/Adjuvants; Identity of manufacturers/recipients; Import volume; Use details.

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:
Absorption/Desorption; Dissociation Constant

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
CEC/647, CEC/728, EOP/8

NOTIFICATION IN OTHER COUNTRIES
None

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Lonzacure M-MIPA
Chemical in RTM 6

CAS NUMBER
16298-38-7

CHEMICAL NAME
Benzenamine, 4,4'-methylenebis[2-methyl-6-(1-methylethyl)-

OTHER NAME(S)
4,4'-Methylenebis[2-methyl-6-isopropylaniline]

ANALYTICAL DATA
Reference ^{1}H NMR, IR, GC, UV spectra were provided.

3. COMPOSITION

DEGREE OF PURITY >80 %

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (>1% by weight) None

4. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE AT 20°C AND 101.3 kPa: Red/brown solidified melt

Property	Value	Data Source/Justification
Pour Point	29°C	Measured
Boiling Point	419.5 - 423°C at 103.3 kPa	Measured
Density	1023.7 kg/m^3 at 20°C	
Vapour Pressure	1.20 x 10^{-3} kPa at 25 °C	Measured
Water Solubility	0.00823 g/L at 20°C	Measured
Hydrolysis as a Function of pH	No significant hydrolysis of the notified chemical occurred at 50°C	Measured
Partition Coefficient (n-octanol/water)	log Pow = 3.8 at 20.3°C	Measured
Surface Tension	57.1 mN/m at 20°C	Measured
Adsorption/Desorption	Not determined	The notified chemical has the potential to adsorb to some extent in the environment as it is not very water soluble and has a relatively high log P_{ow}. It is also potentially cationic. However, under normal circumstances, the notified chemical is not likely to enter the environment except once cured onto composite parts when it is no longer biologically available.
Dissociation Constant	Not determined	The notified chemical contains two potentially cationic functional groups but it is not expected to ionise under normal conditions of use. The notified chemical has very low aqueous solubility and is therefore unlikely to ionise to any significant extent. A pKa value of 4-5 is expected.
Particle Size	Not determined	The notified chemical is imported as a solidified melt that is unlikely to exist as discrete particles.
Flash Point	232.5 °C at 111.1 kPa	Measured
Flammability	Not flammable	Measured
Pyrophoric Properties	Not pyrophoric	Measured
Autoignition Temperature	407 °C	Measured
Explosive Properties	Not explosive	Measured

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

Reactivity
The notified chemical is stable under normal conditions of use. The notified chemical is not known to react with water.

Dangerous Goods classification
The notifier has stated that the notified chemical should have the following transport classification:
UN3077
Class 9
Packing group III
Proper shipping name: Environmentally Hazardous Substance, Solid, n.o.s (chemical name)

5. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical may initially be imported as a component of an epoxy resin product (RTM 6) at concentrations of <20%. It may also be imported as a raw material.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	<15	<25	<35	<40	<40

PORT OF ENTRY:
Major seaports throughout Australia, particularly Melbourne.

IDENTITY OF MANUFACTURER/RECIPIENTS
Aerospace components manufacturers.

TRANSPORTATION AND PACKAGING
The notified chemical as a constituent of an epoxy resin formulation will be imported in 10 kg or 20 kg pails. As a raw material it will be imported in 20 kg or 25 kg cardboard or steel drum containers. The notified chemical will be transported by road or rail to the processing and reformulation sites.

USE
The notified chemical will be used in the production of composite aerospace components.

OPERATION DESCRIPTION
Reformulation
The contents of the import drums containing the notified chemical will be automatically emptied into a mixing vessel through a pneumatic rotary vane pump directly connected to the mixing vessel. Other ingredients will be added manually or via pneumatic pump to the open mixing vessel. The blending process is performed at room temperature, is expected to take 10 to 30 minutes to complete, and is likely to involve two workers. The final formulation (<20% notified chemical) is transferred to the storage packaging (likely to be pails) via a closed pump system that is connected to the bottom of the mixing vessel. The mixing vessel and transfer equipment will be cleaned with a solvent rinse. The final product is then distributed by road or rail to customer sites.

End use
The notified chemical (as a <20% component of an epoxy resin formulation) is to be used with composite fabrics. The steps involved in this process are:

1) preparing the resin for use,
2) injecting the resin into the composite fabric part,
3) curing the resin,
4) cleaning of equipment and materials,
5) disposal of resin contaminated materials.

The epoxy resin formulation is brought to room temperature and mechanically decanted into a resin vessel using fully automated processes. The resin vessel is transported to an oven chamber where it is connected via pipes to the chamber containing the composite material part. The resin material is heated in the resin vessel, which is sealed within a resin oven unit, using a computerised process. When it reaches the correct temperature and pressure the resin enters the oven through the pipes from the resin vessel and the fabric part is infused with the resin material. At certain temperatures, the resin becomes cured.

After completion of the infusion process, all vessel connection pipes are manually disconnected from the chamber and disposed of. The resin vessel is then cleaned in a designated section of the manufacturing site. Resin vessels are securely transported around the site using resin transport trolleys. Uncured resin that may remain in the resin vessel is scraped out and disposed of. The resin vessel is thoroughly washed using an industrial dishwashing machine. Individual components of the resin vessel are cleaned or disposed of. Wastewater generated from the dishwasher is fed through a separator. The separator is cleaned approximately once a week.

The resin impregnated composite materials may need to undergo sanding or trimming processes before their

final 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 (hr/day)*	*Exposure Frequency (days/year)*
Reformulation			
Waterside workers	10	4	10
Storage and transport personnel	20	4	50
Reformulation personnel	5	2	200
End use			
Waterside workers	20	4	10
Storage and transport personnel	50	4	20
Lay-up technician	50	5	90
Material and process engineers	11	1	50

Reformulation
Worker exposure to the notified chemical is expected to be low during reformulation processes. Transfer of the notified chemical into the mixing vessel utilises automated processes, and an exhaust fan is located above the open mixing vessel during blending of the product. Workers involved in all processes, including maintenance and cleaning operations, wear personal protective equipment, including safety goggles, gloves and coveralls.

End use
Dermal and ocular exposure are the main routes of worker exposure to the notified chemical during use of the epoxy resin product (<20% concentration).

Worker exposure to the notified chemical may occur during disposal of the empty pails containing residues of the notified chemical following decanting into the resin vessel. However, such exposure is expected to be minimised by workers wearing personal protective equipment, including safety shoes, shoe covers, face shields, overalls, and gloves.

During infusion of the composite material parts, worker exposure to the notified chemical is unlikely to occur. The following measures are in place to minimise worker exposure: computerised processes are used to control the resin oven unit, the resin vessel is sealed within the resin oven unit, all air exhausts are filtered through carbon filters prior to release to outdoor air, infusion processes occur in well ventilated areas, the resin oven has the capacity to contain any spills that may occur, and water and cooling stations are located adjacent to resin ovens to enable containment of any spillages.

Dermal and ocular exposure of workers to the notified chemical (<20%) may occur during manual disconnecting of pipes from the chamber. Exposure is likely to be minimised by workers wearing appropriate PPE, including glasses, gloves and coveralls.

Dermal and ocular exposure of workers to the notified chemical (<20%) may occur during cleaning operations. There are measures in place to minimise such exposure, including transport of the resin vessels to the designated cleaning area using secure resin transport trolleys, and lifting resin vessels using lifting trolleys to reduce the likelihood of spills and avoid worker contact. In addition, a local extraction hood is located above the sink used for all manual cleaning work, and the majority of the cleaning operations utilise an industrial dishwashing machine to avoid handling by workers.

EASE modelling of the pipe disconnection and cleaning operations was performed to estimate dermal exposure of workers to the notified chemical. The following assumptions were used for these estimates: direct handling, non-dispersive use (only used by workers with knowledge of the processes and use of controls), and incidental contact level (assumed to be one event per day). The predicted dermal exposure to the notified chemical is 0-

0.02 mg/cm^2/day. This is equivalent to 0-0.12 mg/kg bw/day, based on assumptions outlined by the European Commission (EC, 2003).

Dermal, ocular and inhalation exposure of workers to the notified chemical may occur during sanding and trimming of the resin impregnated composite materials. Exposure is likely to be minimised by the use of robotics controlled from outside of an enclosed area, or by undertaking such tasks in existing controlled environment facilities, where dust particles will be captured and removed, preferably at the point of generation. Operators will also wear suitable breathing protection such as air respirators and disposable overalls.

6.1.2. Public exposure

The notified chemical will not be directly available to the public. Members of the public may occasionally come into contact with an aerospace part that has been infused with the notified chemical, however, in such circumstances, the notified chemical will be cured and will not be available for exposure.

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	harmful toxicity, oral LD50 1770 - 2500 mg/kg bw
Rat, acute dermal toxicity	low toxicity, LD50 > 2000 mg/kg bw
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test (Study 1)	no evidence of sensitisation
Guinea pig, skin sensitisation – adjuvant test (Study 2)	test inadequate
Rat, repeat dose oral toxicity – 28 days.	NOAEL 15 mg/kg bw/day NOEL 1.5 mg/kg bw/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosomal aberration	positive
Genotoxicity – in vivo mouse micronucleus	non genotoxic

Acute toxicity

The acute oral toxicity study revealed harmful toxicity (LD50 1770 - 2500 mg/kg bw). Several deaths were observed, particularly at dose levels of 2500 and 5000 mg/kg bw. Clinical observations considered to be due to treatment with the notified chemical were noted in several animals at a number of dose levels. At necropsy, major pathological findings were associated with the liver and lungs.

The notified chemical was found to be of low toxicity by the dermal route (LD50 > 2000 mg/kg bw). No dermal irritation was observed and there were no deaths observed during the study period. In addition, no signs of systemic reaction to treatment with the notified chemical or abnormalities on macroscopic examination were observed.

The notified chemical was non-irritating to the skin and slightly irritating to the eyes according to the tests provided.

Sensitisation

Two guinea pig maximisation tests were performed on the notified chemical. One such test revealed no evidence of skin sensitisation, whilst the other was deemed to be inadequate to draw conclusions on the sensitisation potential of the notified chemical.

NICNAS was advised that during the initial trial period using the RTM6 resin (containing the notified chemical at <20%) under a previous commercial evaluation permit, some workers developed sensitisation reactions. According to the notifier, the incident was the result of filter pump failure, causing air contaminated with the RTM6 resin to be released into the immediate vicinity of workers. Five or six workers of the approximately 25 workers who had worked with the RTM6 resin developed allergic contact dermatitis to the resin.

External testing was conducted by ODREC (Occupational Dermatology Research and Education Centre)

(ODREC 2006) to diagnose the allergic contact dermatitis in workers. Patch testing with RTM6, diluted to 1% in petrolatum, was performed. The study concluded that another component of the RTM6 resin (a chemical containing reactive epoxide groups), was responsible for the sensitisation reactions, rather than the notified chemical. This other chemical is widely reported to be a strong skin sensitiser. This conclusion is also consistent with the two negative skin sensitisation tests performed on the notified chemical. In addition, the ODREC report states that inadvertent contact with RTM6 is the likely cause of sensitisation. It was also considered unlikely that airborne exposure to RTM6 would have caused worker sensitisation, however, it may have been sufficient to elicit an allergic reaction in those already sensitised. Procedures for handling of the resin containing the notified chemical have since been amended to reduce the potential for worker exposure.

Repeated dose toxicity
In a 28-day oral repeat dose study in rats, adverse effects in the liver, spleen, adrenal glands and blood were observed in animals treated with 150 mg/kg bw/day. The effects observed were considered to be of concern and warranted R48 classification. The NOAEL was determined to be 15 mg/kg bw/day, as only adaptive liver effects were observed at this dose level. The NOEL was 1.5 mg/kg bw/day, based on the absence of treatment-related findings in rats at this dose level.

The notified chemical fits into the US EPA category of concern for dianilines (US EPA, 2002). As such, it has the potential to be a retinotoxic agent, as well as a reproductive and systemic toxicant.

Mutagenicity
The notified chemical was found to be non-mutagenic in a bacterial reverse mutation study. This result is confirmed by published studies on dianiline chemicals. In one such study (Benigni, 1998), quantitative structure activity relationship calculations were performed to provide an indication of the mutagenicity of several chemicals. The results indicated negative mutagenicity of the notified chemical. In another report (Rao, 1982), the Ames test was performed using the TA98 and TA100 bacterial strains on a number of 4,4'-methylenedianiline derivatives, including the notified chemical. This study indicated negative mutagenic activity of the notified chemical. The paper also concluded that certain substitutions on the 4,4'-methylenedianiline structure could significantly minimise mutagenic activity of such chemicals, suggesting that the steric hindrance may be a factor in reduction of their mutagenicity.

The notified chemical was found to be non-genotoxic in the in vivo mouse micronucleus assay provided. As the 28 day repeated dose study did not examine bone marrow, it cannot be determined from the toxicity data provided whether the notified chemical is likely to have reached the bone marrow of the animals, although there were some significant haematological changes, especially in female animals of the 28 day study. Therefore, the positive in vitro chromosomal aberration test cannot be disregarded. Thus potential genotoxicity of the notified chemical cannot be ruled out.

It should also be noted that the notified chemical fits into the US EPA category of concern for dianilines (US EPA, 2002) for potential mutagenicity and carcinogenicity, thus again the potential for mutagenicity of the notified chemical cannot be ruled out. However, the weight of evidence does not meet the criteria for classification. Carcinogenicity needs to be determined by further testing.

Based on the acute oral toxicity, the oral repeat dose toxicity, and the other available data, the notified chemical is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2004).

The following risk phrase should be applied:
R48/22: Harmful – danger of serious damage to health by prolonged exposure if swallowed.

6.3. Human health risk characterisation

6.3.1. Occupational health and safety

Dermal and accidental ocular exposure are the main routes of worker exposure to the notified chemical at concentrations of <20% during end use processes, particularly when disconnecting pipes, and during cleaning operations. Given the relatively low molecular weight of the notified chemical (<500), as well as its partition coefficient (1<Log Pow<4), dermal absorption upon skin contact is likely to occur.

Acute effects from dermal exposure to the notified chemical are unlikely to occur, given its low acute toxicity.

Skin or eye irritation is unlikely to occur during such exposure, given that the notified chemical is non-irritating to the skin, only slightly irritating to the eyes, and is present at concentrations below the irritation cut off (ie. <20%).

The notified chemical is not expected to present a risk of sensitisation upon repeated or prolonged exposure, given that the notified chemical is not likely to be a sensitiser based on two separate guinea pig maximisation tests.

Whilst the acute dermal toxicity of the notified chemical was found to be low, health effects resulting from repeated dermal exposure to the notified chemical cannot be ruled out, particularly given the systemic toxicity observed following repeated oral exposure. During pipe disconnection and cleaning processes, dermal exposure of worker is estimated to be 0-0.12 mg/kg bw/day. A dermal NOEL/NOAEL was not determined, however, a NOEL of 1.5 mg/kg bw/day and NOAEL of 15 mg/kg bw/day was established in a 28 day oral study in the rat. Use of the NOEL results in a margin of exposure (MOE) of 12.5, whilst use of the NOAEL results in a margin of exposure (MOE) of 125. The MOE based on the NOEL suggests that the risk is not acceptable if workers are exposed to the notified chemical repeatedly on the skin. The notified chemical has the risk of causing serious damage to health by prolonged exposure. Workers should be trained and informed of the hazards associated with the notified chemical. As the notifier has described the operations to be highly controlled, and good worker practices are in place during limited activities where worker handling is required, the risk of adverse effects is significantly reduced and is considered acceptable.

Based on the available data, the potential for the notified chemical to present a mutagenicity and carcinogenicity hazard cannot be conclusively ruled out. However, the notified chemical will be handled under controlled conditions. Effective control measures and safe workplace practices should be exercised to minimise the exposure.

Overall, the risk to occupational health and safety from the notified chemical is considered acceptable provided that the notified chemical is only used under controlled conditions by trained workers.

6.3.2. Public health

Members of the public will only occasionally come into contact with finished aerospace parts in which the notified chemical has been infused and cured. As such, the risk to public health is considered to be low.

7. ENVIRONMENTAL IMPLICATIONS

7.1. Environmental Exposure & Fate Assessment

7.1.1 Environmental Exposure

RELEASE OF CHEMICAL AT SITE

The notified chemical is used in the aerospace industry for incorporation into composite fibres. The notified chemical is imported as a component of an epoxy resin formulation and remains as part of that formulation throughout. All formulation processes are tightly controlled and safely contained on site. The notified chemical is cured to the aerospace structure before it is exported.

Any spillage of the formulation at the manufacturer's site will be removed by authorised and licensed waste management companies.

RELEASE OF CHEMICAL FROM USE

The notified chemical is used as part of a resin formulation that is infused into fabric materials. Once the resin is cured, the notified chemical is inert and no longer biologically available.

The release of the notified chemical is likely to occur via the following routes:

1) Residual material in containers after decanting	2% (annual introduction volume) - uncured resin.
2) Accidental spillage from containers	<1% - uncured resin.
3) Residue in formulation equipment	5 - 10% - cured resin.
4) Waste resin produced	10 – 40% - cured and uncured resin (maximum during evaluation period, typically less)

Note: All resin materials are sent to a licensed treater for disposal by recycling and incineration (energy recovery)

The notified chemical can be released from the customer site as part of waste resin material. Waste resin or resin contaminated materials are usually contained in steel pails or locally accumulated into hazardous waste bins for subsequent disposal as Prescribed Industrial Waste.

The notified chemical can also be released on site in incidents where a spill has occurred. However, spill kits are located throughout resin handling and manufacturing areas to immediately contain any local spills that may occur. Workers are trained in the proper use of spill kits and the procedures that are necessary in the case of a spill.

RELEASE OF CHEMICAL FROM DISPOSAL

At the manufacturer's site, the notified chemical and formulations containing the notified chemical will be disposed of during manufacturing through removal by authorised and licensed contract companies in the waste management industrial sector.

At the customer site, the notified chemical and contaminated products will be disposed off-site as Prescribed Industrial Waste and is to be immobilised by competent professionals before being disposed to a controlled Prescribed Waste landfill. Aerospace materials that are infused with the notified chemical can end up in landfill at the end of their useful life, or when the composite material does not pass quality tests. The notified chemical is expected to degrade over time and not to pose any significant exposure risks.

7.1.2 Environmental fate

For the details of the environmental fate and ready biodegradability studies please refer to Appendix C.

The notified chemical, as a component of a resin formulation, is expected to remain infused with the fabric materials. Once the resin is cured, the notified chemical becomes inert and no longer biologically available. Assuming that 2% of the chemical will remain in empty containers, 98% (up to 38000 kg per annum) will be used for its intended purpose as resin. Approximately 50% of cured and uncured resin is recycled and incinerated. Residual chemical in the empty containers will be recycled, with any recycled product likely to also be landfilled at the end of its useful life.

The notified chemical may have the potential to bioaccumulate in the environment. It is not readily biodegradable, has a low aqueous solubility and has a log Pow of 3.8. However, the notified chemical is unlikely to reach the environment as all wastes generated from manufacturing processes are collected and isolated for disposal as prescribed industrial wastes and treated prior to environmental release.

7.1.3 Predicted Environmental Concentration (PEC)

Based on the reported use pattern a predicted environmental concentration (PEC) cannot be calculated.

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 2.0 mg/L	Toxic to Rainbow trout.
Daphnia Toxicity	EC50 2.4 mg/L	Toxic to *Daphnia magna*.

Algal Toxicity	EC50 > 5.9 mg/L	At worst, toxic to Green algae under the conditions of this test.
Inhibition of Bacterial Respiration	EC50 >10 mg/L	

7.2.1 Predicted No-Effect Concentration

A predicted no effect concentration (PNEC – aquatic ecosystems) of 20 µg/L has been derived by dividing the end point value of 2.0 mg/L by a worst-case scenario uncertainty (safety) factor of 100 (as usable toxicity data are available for three trophic levels).

7.3. Environmental risk assessment

The notified chemical is used in a controlled manner within Australia and only a small release of spilled notified chemical to authorised landfill is expected. Residual chemical from equipment washing will be retained and reused, being maintained in a closed system with no sewer entry points.
Based on the reported use pattern a predicted environmental concentration (PEC) cannot be calculated for Australia. However, the chemical is used in a highly controlled manner within Australia and little if any release to the aquatic environment is expected. Consequently the PEC is expected to be extremely low.

The risk to the aquatic environment is expected to be low as virtually no release to the aquatic system of the notified chemical within Australia is expected.

8. CONCLUSIONS AND REGULATORY OBLIGATIONS

Hazard classification
Based on the available data the notified chemical is classified as hazardous under the *Approved Criteria for Classifying Hazardous Substances* [NOHSC:1008(2004)]. The classification and labelling details are:

R48/22: Harmful – danger of serious damage to health by prolonged exposure if swallowed.

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

	Hazard category	***Hazard statement***
Acute toxicity (oral)	4	Harmful if swallowed
Target organ systemic toxicity following repeat exposure	2	May cause damage to organs through prolonged or repeated exposure
Acute hazards to the aquatic environment	2	Toxic to aquatic life
Chronic hazards to the aquatic environment	2	Toxic to aquatic life with long lasting effects

Human health risk assessment
The risk to occupational health and safety from the notified chemical is considered acceptable provided that the notified chemical is only used under controlled conditions by trained workers.

When used in the proposed manner the risk to the public is considered to be acceptable.

Environmental risk assessment
The notified chemical is not considered to pose a risk to the environment based on its reported use pattern (controlled).

Recommendations

REGULATORY CONTROLS
Hazard Classification and Labelling

- The Office of the ASCC, Department of Employment and Workplace Relations (DEWR), should consider the following health hazard classification for the notified chemical:
  - R48/22: Harmful – danger of serious damage to health by prolonged exposure if swallowed.

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - Concentration ≥ 10%: R48/22: Harmful – danger of serious damage to health by prolonged exposure if swallowed.

Health Surveillance

- As the notified chemical is a health hazard (poses danger of serious damage to health by prolonged exposure if swallowed), employers should carry out health surveillance of any workers involved in its handling.

CONTROL MEASURES

Occupational Health and Safety

- Employers should ensure that the facility is equipped such that operations involving the notified chemical are performed in a highly controlled manner. The following isolation and engineering controls should be in place to minimise occupational exposure to the notified chemical:
  - Automated processes
  - Local exhaust ventilation
  - Sealed equipment

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical:
  - If swallowed, seek medical advice immediately
  - Avoid skin contact
  - Workers must have adequate education and training before handling the notified chemical.

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical when worker handling is required for limited activities such as pipe disconnection and cleaning:
  - Safety glasses
  - Gloves
  - Coveralls

  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. The MSDS must have adequate information to inform workers of the hazards of the notified chemical.

- 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

Disposal

- Do not discharge into drains, ground water or soil.
- Dispose of by high temperature incinerator in an approved plant or to landfill.
- Do not re-use any container contaminated with the notified chemical.

Storage

- Containers should be securely closed and stored according to container label instructions.

Emergency procedures

- Any spills of the notified chemical, or products containing the notified chemical, should be contained immediately using a nearby spill kit or absorbent materials like sawdust, sand or soil. Any contaminated material should be appropriately swept up, collected and sealed in a suitable container for disposal as Prescribed Industrial Waste.

Regulatory Obligations

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

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

(1) Under Section 64(1) of the Act; if
- adverse incidents involving the notified chemical occur;
- regulatory action on the notified chemical is undertaken by other jurisdictions;
- details of the operation description are altered such that exposure to workers or the environment may be increased;
- additional data becomes available on the genotoxicity or carcinogenicity of the notified chemical;

or

(2) Under Section 64(2) of the Act; if
- the function or use of the chemical has changed from production of composite aerospace components, or is likely to change significantly;
- the amount of chemical being introduced has increased from 40 tonnes per annum, 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.

AICS Annotation

- When the notified chemical is listed on the Australian Inventory of Chemical Substances (AICS) the entry should be annotated with the following statement:
  - The notified chemical should only be used for industrial purposes under highly controlled conditions.

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

APPENDIX A: PHYSICAL AND CHEMICAL PROPERTIES

Pour Point 29 ºC

Method	EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks	Due to lack of a distinct freezing temperature, the pour point test was conducted.
Test Facility	Huntingdon (1994b).

Boiling Point 419.5 - 423 ºC at 103.3 kPa

Method	EC Directive 92/69/EEC A.2 Boiling Temperature.
Remarks	Determined using a reduced scale distillation method due to the high boiling point of the notified chemical.
Test Facility	Huntingdon (1994b).

Density 1023.7 kg/m^3 at 20 ± 0.5 ºC

Method	EC Directive 92/69/EEC A.3 Relative Density.
Remarks	Determined using the pycnometer method.
Test Facility	Huntingdon (1994b).

Vapour Pressure 1.20 x 10^{-3} kPa at 25 °C

Method	OECD TG 104 Vapour Pressure. EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks	Determined using static technique.
Test Facility	RCC (1990a)

Water Solubility 0.00823 g/L at 20ºC

Method	EC Directive 92/69/EEC A.6 Water Solubility.
Remarks	Flask Method After the standard test the solutions were filtered and then analysed by HPLC.
Test Facility	Huntingdon (1994a).

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)*	*$t_{½}$ (years)*
4	25 °C	>1
7	25 °C	>1
9	25 °C	>1

Remarks	HPLC analysis confirmed no significant hydrolysis of the notified chemical occurred at 50°C under the conditions of this test.
Test Facility	Huntingdon (1994b).

Partition Coefficient (n-octanol/water) log P_{ow} at 20.3ºC = 3.8

Method	OECD TG 117 Partition Coefficient (n-octanol/water). EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks	Analytical Method: Gas chromatography
Test Facility	RCC (1990b).

Surface Tension 57.1 mN/m at 20ºC

Method EC Directive 92/69/EEC A.5 Surface Tension using a torsion balance.

Remarks	Concentration: 90% saturated aqueous solution. The notified chemical is surface active.
Test Facility	Huntingdon (1994b).

Flash Point 232.5 °C at 111.1 kPa

Method	EC Directive 92/69/EEC A.9 Flash Point.
Remarks	Determined using Pensky-Martens closed cup method.
Test Facility	Huntingdon (1994b).

Flammability Not highly flammable

Method	EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks	The notified chemical did not burn.
Test Facility	RCC (1990c)

Flammability Not flammable

Method	EC Directive 92/69/EEC A.12 Flammability (Contact with Water).
Test Facility	Huntingdon (1994b).

Pyrophoric Properties Not pyrophoric

Method	EC Directive 92/69/EEC A.13 Pyrophoric Properties of Solids and Liquids.
Test Facility	Huntingdon (1994a).

Autoignition Temperature 407 °C

Method	EC Directive 92/69/EEC A.15 Auto-Ignition Temperature (Liquids and Gases).
Remarks	Due to its high viscosity the test sample was preheated up to 65 °C prior to injection into the heated test flask.
Test Facility	TNO (1994c).

Autoignition Temperature Not self igniting up to temperatures of 450 °C.

Method	EC Directive 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Test Facility	Huntingdon (1994b).

Explosive Properties Not explosive

Method	EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks	During each of the thermal sensitivity tests, the notified chemical ignited and burnt, although no explosions or deformation of the tubes were recorded.
Test Facility	Huntingdon (1994b).

APPENDIX B: TOXICOLOGICAL INVESTIGATIONS

B.1. Acute toxicity – oral

TEST SUBSTANCE: Notified chemical

METHOD: Similar to OECD TG 401 Acute Oral Toxicity.
- Species/Strain: Rat/Wistar-derived Crl:(WI)BR strain
- Vehicle: Corn oil
- Remarks - Method: No significant protocol deviations. A screening study was performed to determine suitable dose levels for the main study.

RESULTS

Dose mg/kg bw	*Number and Sex of Animals*	*Mortality*
1250	5 per sex	1/10
1770	5 per sex	1/10
2500	5 per sex	9/10
5000	5 per sex	10/10

- LD50: 1770 - 2500 mg/kg bw
- Signs of Toxicity: Animals treated with 5000 mg/kg showed lethargy or prostration and piloerection. Also noted were hunched posture, chromodacryorrhoea, laboured breathing, high stepping gait and red staining around the mouth and nose. Three animals died on day 4, six animals on day 5, and one animal on day 6.

  Animals treated with 2500 mg/kg showed lethargy and occasional prostration, piloerection, hunched posture, chromodacryorrhoea, red staining around the nose and mouth, emaciation, ataxia and shallow slow breathing. Four of the animals died on day 6, and five died on day 7.

  Animals treated with 1770 mg/kg were lethargic with piloerection, and this continued until day 7. One of the animals died on day 6.

  Animals treated with 1250 mg/kg appeared lethargic up to 48 hours after treatment and occasionally showed signs of piloerection, hunched posture, and swollen abdomen up to day 8 of treatment. One animal died on day 7.
- Effects in Organs: The lungs of many animals, particularly those treated with 2500 mg/kg, were dark or bright red in colour. In addition, the livers were often abnormal in appearance and the stomach and gastrointestinal tract were occasionally gas or fluid-filled.
- Remarks - Results: All surviving animals showed body weight gains at the end of the study period.

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

TEST FACILITY: Hazleton (1983a)

B.2. Acute toxicity – dermal

TEST SUBSTANCE: Notified chemical

METHOD: EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal).
- Species/Strain: Rat/Hsd/Ola:Sprague-Dawley(CD)
- Vehicle: Corn oil

Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

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

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

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

TEST FACILITY Huntingdon (1993b)

B.3. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 females
Vehicle	None
Observation Period	72 hours
Type of Dressing	Occlusive
Remarks - Method	No significant protocol deviations.

RESULTS

Remarks - Results	No irritation or corrosive effects were observed.

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

TEST FACILITY Hazleton (1983b)

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	1 female, 2 males
Observation Period	72 hr
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	1	0.3	1.3	2	<72 hr	0
Conjunctiva: chemosis	0.3	0	1	2	<72 hr	0
Conjunctiva: discharge	0	0	0	1	<24 hr	0

Corneal opacity	0	0	0	0	0	0
Iridial inflammation	0	0	0	0	0	0

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

Remarks - Results	Slight to moderate conjunctival redness was noted in all treated eyes up to 48 hours after treatment. A small amount of discharge was observed in all treated eyes at the 1 hour observation. Moderate chemosis was observed in one animal at 24 hr but reduced to slight by 48 hr, and fully reversed by 72 hr.
CONCLUSION	The notified chemical is slightly irritating to the eye.
TEST FACILITY	SafePharm (1989a)

B.5. Skin sensitisation (Study 1)

TEST SUBSTANCE	Notified chemical
METHOD	EC Directive 96/54/EC B.6 Skin Sensitisation – guinea pig maximisation test
Species/Strain	Guinea pig/Albino Dunkin-Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: None (lowest dose tested (0.1% v/v in 5% acetone in Alembicol D) and the vehicle control were slightly irritating) topical: 90% v/v in acetone
MAIN STUDY	
Number of Animals	Test Group: 10 Control Group: 5
INDUCTION PHASE	Induction Concentration: intradermal: 7.5% v/v in 5% acetone in Alembicol D topical: 90% v/v in acetone (24 hours prior to topical induction, the site was pre-treated with 10% sodium lauryl sulphate, due to the non-irritancy of the test substance at the maximum practical concentration that could be prepared in acetone)
Signs of Irritation	Slight irritation was observed in test animals treated intradermally with 7.5% v/v in 5% acetone in Alembicol D and in control animals receiving only 5% acetone in Alembicol D. Slight erythema was observed in both control and treated animals receiving 90% v/v of the test substance in acetone topically.
CHALLENGE PHASE	
1st challenge	topical: 90% and 45% v/v in acetone
Remarks - Method	No significant protocol deviations.

RESULTS

Remarks - Results	During the challenge phase there was no evidence of dermal reactions seen in any of the test or control animals.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Huntingdon (1994d)

B.6. Skin sensitisation (Study 2)

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 406 Skin Sensitisation – guinea pig maximisation test EC Directive 96/54/EC B.6 Skin Sensitisation – guinea pig maximisation

test

Species/Strain	Guinea pig/Albino Dunkin-Hartley
PRELIMINARY STUDY	Maximum Non-irritating Concentration: intradermal: 25% w/v in arachis oil B.P. topical: 100%
MAIN STUDY	
Number of Animals	Test Group: 20 Control Group: 20
INDUCTION PHASE	Induction Concentration: intradermal: 25% w/v in arachis oil B.P. topical: Undiluted
Signs of Irritation	In most animals, following topical induction, the test substance solidified at the site of application. This was considered to have precluded an accurate evaluation of the skin reactions in some of the animals. Occasionally some physical damage was noted at the treated skin sites following removal of the test material. Scattered mild redness was also observed.
CHALLENGE PHASE	
1st challenge	topical: undiluted
Remarks - Method	No significant protocol deviations.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after challenge:*	
		24 h	*48 h*
Test Group	100%	5	2
Control Group	100%	2	2

Remarks - Results

Scattered mild redness was noted at the test material sites of five test animals at the 24 hour observation time and persisted in two animals at the 48 hour observation time. Similar dermal reactions were also noted at test material sites of two control group animals at the 24 and 48-hour observations. Thus the reactions were considered to be indicative of skin irritation rather than sensitisation.

Some hair loss at the test material sites for both treated and control group animals were noted following removal of the patches. At the test material sites of two test group animals, slight physical damage (dermal haemorrhage and fur loss) precluded accurate assessment of erythema, however, it was considered that no contact sensitisation responses were present.

CONCLUSION No conclusion was made as the test is considered to be inadequate.

TEST FACILITY SafePharm (1989b)

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 BR VAF PLUS)
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: 14 days

Vehicle	Corn oil
Remarks - Method	No significant protocol deviations. Dosage levels were chosen based on a 14 day preliminary oral toxicity study.

RESULTS

Dose mg/kg bw/day	*Number and Sex of Animals*	*Mortality*
0	5M, 5F	0
1.5	5M, 5F	0
15	5M, 5F	0
150	5M, 5F	0
0 (recovery)	5M, 5F	0
150 (recovery)	5M, 5F	0

Clinical Observations

CLINICAL SIGNS

Abnormal gait (waddling and walking on toes), hunched posture, and lethargy were seen in rats treated with 150 mg/kg bw/day, generally from week 2 onwards. Increased salivation following dosing was frequently seen in animals from around the first or second week of dosing and onwards. This was often associated with wet and/or greasy fur. On some occasions, this was also associated with brown staining around the mouth, though this was mostly in female animals. There were also isolated incidences of yellow/brown staining around the urogenital region in animals of this dose group.

Some of these signs were also seen occasionally in animals treated with 15 mg/kg bw/day.

Abnormal gait observed in animals dosed with 150 mg/kg bw/day persisted for two days into the recovery period.

BODYWEIGHT

Animals treated with 150 mg/kg bw/day were observed to have statistically significantly lower bodyweight gains than control values during Weeks 2 to 4. In females, this difference was minimal, and not dose related. By the end of the recovery period, the bodyweights of the treated animals were similar to controls.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

HAEMATOLOGY

Female rats treated with 150 mg/kg bw/day exhibited packed cell volume, haemoglobin concentration, mean corpuscular haemoglobin concentration and mean corpuscular volume values that were statistically significantly lower than control values. After the recovery period, lower packed cell volume and haemoglobin concentration values were also recorded, however the values were within the expected range.

In males treated with 150 mg/kg bw/day some statistically significant changes in haematological values were observed. However, these were not considered to be of toxicological significance, either due to the absence of the expected corresponding parameters, the wide variation in individual values for these parameters, or individual values within the expected ranges for the animals used.

BIOCHEMISTRY

Glutamic-pyruvic transaminase, glutamic-oxaloacetic transaminase, γ-GT, cholesterol, triglyceride and bilirubin levels were higher in males rats treated with 150 mg/kg bw/day when compared with control group rats. Female rats in this treatment group showed higher than control levels of γ-GT, cholesterol, triglyceride and globulin (together with higher total protein and lower A/G ratio). Other statistically significant changes were observed in animals treated at this dose level, however, they were not considered to be of toxicological significance. The reasons for such determinations include: the absence of a dose-response relationship, considerable variation of individual values, and values within expected ranges. Glucose levels were statistically significantly higher than controls in male rats treated with 1.5, 15, and 150 mg/kg bw/day, however, there were significant variations in the individual values and no dose-response relationship, and as such, this was not considered to be of toxicological significance.

After the recovery period, higher than control levels of total proteins in female rats and cholesterol in male rats treated with 150 mg/kg bw/day were also recorded.

URINALYSIS
There were no changes of toxicological significance observed in urinalytical parameters.

Effects in Organs
LIVER
Liver weights (bodyweights adjusted) were statistically significantly higher than control for male and female rats receiving 150 mg/kg/day and female rats receiving 15 mg/kg/day. In animals dosed at 150 mg/kg/day the absolute liver weights were higher than expected for the rats of this age and strain.

Macroscopically, all animals treated with 150 mg/kg/day had enlarged livers at the end of the study. In some of the animals, the livers were also pitted. Pitted livers were also noted in some rats in this dosage group after the two week recovery period.

Microscopical changes were seen in centrilobular areas in male and female animals treated with 150 mg/kg bw/day. The changes mainly consisted of hepatocellular necrosis, mainly single cell necrosis, resulting in centrilobular collapse with sinusoidal dilation/congestion and prominent pigmented sinusoidal lining cells. Centrilobular or generalised hepatocellular hypertrophy was found in four males and five females.

In animals of both sexes receiving 150 mg/kg/day, pigmentation of the sinusoidal lining cells was observed after the recovery period.

Centrilobular hypertrophy was seen in 3 of 5 female animals receiving 15 mg/kg bw/day, which is associated with increased liver weight in females at this dose.

SPLEEN
Statistically significantly higher spleen weights (bodyweights adjusted) were observed in males at all doses compared to controls. However, this change was not dose related.

Extramedullary haemopoiesis was seen in 3 of 5 male rats treated with 150 mg/kg bw/day, which may be associated with spleen weight changes at this dose level.

No significant changes were observed in the spleen of female animals.

ADRENALS
Statistically significantly lower than control adrenal weights were recorded for female rats treated with 150 mg/kg bw/day. Associated microscopical change (adrenal cortical atrophy) was seen in 3 of 5 females at this dose level.

LUNGS
In some animals treated with 150 mg/kg bw/day, pale foci were observed macroscopically in the lungs. This is associated with mainly inflammatory microscopic changes.

Remarks – Results
Toxic effects of the test substance were seen in the liver, spleen, adrenal glands and blood. Abnormal findings were confined to the 150 mg/kg bw/day dose group, and recovery was evident following the two week post treatment period. The only change at 15 mg/kg bw/day was the increase in liver weight and the associated centrilobular hypertrophy observed in females, which is considered to be an adaptive effect.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 15 mg/kg bw/day in this study, based on the adverse effects in the liver, spleen and adrenals observed at 150 mg/kg bw/day. The No Observed Effect Level (NOEL) was established as 1.5 mg/kg bw/day in this study, based on the absence of treatment-related findings in rats at this dose level.

TEST FACILITY Huntingdon (1994e)

B.8. Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100
Metabolic Activation System	S-9 mix derived from Aroclor 1254 induced Wistar rat liver.
Concentration Range in Main Test	a) With metabolic activation: 100-5000 µg/plate b) Without metabolic activation: 100-5000 µg/plate
Vehicle	Dimethyl sulfoxide
Remarks - Method	The test did not include an *E.coli* strain. The positive controls used in the TA100 and TA1537 strains (without metabolic activation) were not those recommended by the test guideline. In addition, 2-Aminoanthracene was used as the only positive control for assays with metabolic activation. The test guideline advises against this.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	>5000*	>5000	≥1000	Negative
Test 2	-	>5000	≥1000	Negative
Present				
Test 1	-	>5000	≥1000	Negative
Test 2	-	>5000	≥1000	Negative

*Using TA100 only.

Remarks - Results	During Test 1, both in the presence and absence of metabolic activation, some reductions in background bacterial lawn were observed.
CONCLUSION	The notified chemical was not mutagenic to bacteria under the conditions of the test.
TEST FACILITY	NOTOX(1986).

B.9. 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.
Species/Strain	Human
Cell Type/Cell Line	Blood lymphocytes
Metabolic Activation System	S-9 mix derived from Aroclor 1254 induced rat liver.
Vehicle	Dimethyl sulfoxide
Remarks - Method	No significant protocol deviations. The highest concentration used in this study (200 µg/mL) was chosen on the basis of higher concentrations resulting in significant precipitation.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	3.1, 6.3*, 12.5, 18, 25*, 32, 42*, 50, 75, 100	18 hr	18 hr
Test 2	6.3*, 12.5, 18, 25*, 32, 42*, 50, 75, 100	18 hr	18 hr
Test 3	0.4, 0.8, 1.6*, 3.1, 6.3*, 12.5*, 25, 50, 100, 200	32 hr	32 hr
Present			
Test 1	0.4, 0.8, 1.6, 3.1, 6.3, 12.5, 25*, 50, 100*, 200*	3 hr	18 hr

Test 2	12.5, 25*, 50, 100*, 150*, 200	3 hr	18 hr
Test 3	12.5, 25*, 50, 100*, 150, 200*	3 hr	32 hr

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	>32	>100	Negative
Test 2	-	>42	>100	Negative
Test 3	-	>6.3	>200	Negative
Present				
Test 1	-	>100	>200	Positive
Test 2	-	>100	>200	Positive
Test 3	-	>200	>200	Equivocal

Remarks - Results

In the absence of S9 mix, negative results were observed.

In the presence of S9 mix, the results for the three tests are as follows:

In Test 1, statistically significant and dose-dependent increases in the proportion of aberrant cells were observed at 200 μg/mL and 100 μg/mL. The observed values fall outside the historical control range of the test laboratory and were considered indicative of clastogenic activity.

In Test 2, statistically significant and dose-dependent increases in the proportion of aberrant cells were observed at 150 μg/mL and 100 μg/mL. The observed values were just within the historical control range but substantially higher than the concurrent solvent control values. This was considered to be a positive clastogenic response.

In Test 3, a statistically significant increase in the proportion of aberrant cells were observed at 200 μg/mL and the observed value of 6.5% falls outside the historical control range of the test laboratory. However, there is a lack of a dose response relationship in this test. In fact, the number of aberrant cells at 25 and 100 μg/mL were lower than the concurrent controls.

The notified chemical is considered to have clastogenicity to human lymphocytes treated in vitro under the conditions of the test, based on the weight of evidence of: (i) an increase in the number of aberrant cells were found in all the tests in the presence of S9 mix, indicating a non-scattered effect, (ii) two out of three studies with metabolic activation showed statistically significant increases in the number of aberrant cells at doses of 100 μg/mL and above, together with clear dose relationships from dose levels of 25 μg/mL, and (iii) the equivocal test (Test 3) confirmed the clastogenicity at the highest dose level tested (200 μg/mL), in spite of the lack of a dose relationship in this test.

CONCLUSION

The notified chemical was clastogenic to human lymphocytes treated in vitro under the conditions of the test.

TEST FACILITY

Huntingdon (1994f)

B.10. Genotoxicity – in vivo

TEST SUBSTANCE

Notified chemical

METHOD: EC Directive 2000/32/EC B.12 Mutagenicity - Mammalian Erythrocyte Micronucleus Test.

Species/Strain: Mouse/CD-1

Route of Administration: Intraperitoneal injection

Vehicle: Corn oil

Remarks - Method: No significant protocol deviations. A preliminary test determined the maximum tolerated dose was 750 mg/kg bw.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time hours*
I (vehicle control)	5 per sex	0	24
II (vehicle control)	5 per sex	0	48
III (low dose)	5 per sex	187.5	24
IV (mid dose)	5 per sex	375	24
V (high dose)	5 per sex	750	24
VI (high dose)	5 per sex	750	48
VII (positive control*)	5 per sex	12	24

*Mitomycin C

RESULTS

Doses Producing Toxicity: No treatment related mortalities occurred during the test period. Animals in the low dose group showed no adverse clinical signs. Animals in the mid dose group showed slight piloerection, hunched posture and swollen abdomen. Animals in the high dose group showed severe convulsions, lethargy and some became comatosed. No adverse clinical signs were obtained for the vehicle control or positive control treated animals over the duration of the test.

Genotoxic Effects: The test substance did not cause any statistically significant increases in the number of micronucleated polychromatic erythrocytes or the incidence of micronucleated normochromatic erythrocytes.

CONCLUSION: The notified chemical was not clastogenic under the conditions of this in vivo mouse micronucleus test.

TEST FACILITY: Huntingdon (1994g)

APPENDIX C: ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL INVESTIGATIONS

C.1. Environmental Fate

C.1.1. Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 D Ready Biodegradability: Closed Bottle Test. EC Directive 92/69/EEC C.4-E Biodegradation: Determination of the "Ready" Biodegradability: Closed Bottle Test Test.
Inoculum	Activated sewage (obtained locally from the HRC sewage treatment plant).
Exposure Period	28 days
Auxiliary Solvent	Diethyl ether
Analytical Monitoring	Electrochemical analysis of dissolved oxygen
Remarks - Method	No significant protocol deviations.

RESULTS

Test substance		*Sodium benzoate*	
Day	*% degradation*	*Day*	*% degradation*
4	4	4	59
7	7	7	76
11	2	11	78
14	1	14	73
18	0	18	79
21	0	21	76
25	2	25	80
28	1	28	83

Remarks - Results	The notified chemical was not found to be inhibitory to activated sewage sludge bacteria under the conditions of this test. Cultures containing both notified chemical and standard substances combined showed an oxygen depletion value 2% higher than that anticipated on the basis of results from separate cultures by day 14. Consequently the notified chemical is not considered to have an inhibitory effect on sewage bacteria under the condition of this test.
CONCLUSION	The notified chemical cannot be classed as ready biodegradable.
TEST FACILITY	Huntingdon (1993c)

C.1.2. Bioaccumulation

No data was provided for this endpoint. The notified chemical may have the potential to bioaccumulate in the environment. It is not readily biodegradable, has a low aqueous solubility and has a log Pow of 3.8. However, the notified chemical is unlikely to reach the environment as all wastes generated from manufacturing processes are collected and isolated for disposal as prescribed industrial wastes and treated prior to environmental release.

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. EC Directive 92/69/EEC C.1 Acute Toxicity for Fish - semi static
Species	Rainbow trout (*Oncorhynchus mykiss*).
Exposure Period	96 hours.
Auxiliary Solvent	10% Tween 80 - acetone
Water Hardness	161 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	No significant protocol deviations.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual*		*3 h*	*24 h*	*48 h*	*72 h*	*96 h*
Control	Control	7	0	0	0	0	0
Solvent control	Solvent control	7	0	0	0	0	0
0.22	0.18	7	0	0	0	0	0
0.46	0.39	7	0	0	0	0	0
1.0	0.85	7	0	0	0	0	0
2.2	1.9	7	0	0	0	0	3
4.6	4.2	7	0	5	7	7	7

LC50	3.3 mg/L at 24 hours 2.8 mg/L at 48 hours 2.8 mg/L at 72 hours 2.0 mg/L at 96 hours (95% confidence limit = 1.4-2.8 mg/L)
NOEC	0.39 mg/L at 96 hours
Remarks – Results	Environmental parameters (pH, temperature and dissolved oxygen) remained within acceptable limits throughout the duration of the test. Although measured concentrations were slightly lower than expected, the notified chemical was reasonably stable under the semi-static conditions employed in the test. The sub-lethal effects observed at ≥ 1 mg/L were loss of equilibrium, lethargy, swimming at the surface and morbidity. LC 50 values and 95% confidence limits were calculated according to the method of Thompson and Weil (1952).
CONCLUSION	The notified chemical is toxic to Rainbow trout.
TEST FACILITY	Huntingdon (1993d)

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 EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia-Static
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	10% Tween 80 - acetone
Water Hardness	Not reported
Analytical Monitoring	HPLC
Remarks - Method	No significant protocol deviations.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
Control	Control	20	0	0
Solvent control	Solvent control	20	0	0
0.1	0.084	20	0	0
0.22	0.20	20	0	0
0.46	0.43	20	0	0
1.0	1.0	20	0	0
2.2	2.2	20	0	6
4.6	4.6	20	18	20
10	9.9	20	20	20

LC50	3.5 mg/L at 24 hours 2.4 mg/L at 48 hours (95% confidence limit = 2.1-2.8 mg/L)
NOEC (or LOEC)	1.0 mg/L at 48 hours
Remarks - Results	Environmental parameters (pH, temperature and dissolved oxygen) remained within acceptable limits throughout the duration of the test. *Daphnia* were considered to be immobilised if they were unable to swim for approximately 15 seconds after gentle agitation. No sub lethal effects were noted. EC_{50} values and 95% confidence limits were calculated according to the method of Thompson and Weil (1952). The "no-effect level" is the highest concentration at and below which the incidence of immobilisation is equal to or less than 10%.

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

TEST FACILITY Huntingdon (1993e)

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	Green algae (*Selenastrum capricornutum*)
Exposure Period	72 hours
Concentration Range	Nominal: 0.625 - 10 mg/L Actual: 0.45 - 5.9 mg/L
Auxiliary Solvent	10% Tween 80 - acetone
Water Hardness	Not reported
Analytical Monitoring	HPLC: Absorbance at 665 nm
Remarks - Method	No significant protocol deviations.

RESULTS

Biomass		*Growth*	
E_bC_{50} mg/L at 72 h	*NOEC mg/L*	*E_bC_{50} mg/L at 72 h*	*NOEC mg/L*
>5.9	5.9	>5.9	5.9

Remarks - Results	5.9 mg/L was the highest concentration that could be prepared due to the limited solubility of the notified chemical in water (solubility 8.23 mg/L).

CONCLUSION The notified chemical is at worst toxic to Green algae under the

	conditions of this test.
TEST FACILITY	Huntingdon (1993f)

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	Mixed population of activated sewage sludge micro-organisms (obtained from local sewage treatment plant HRC Ltd).
Exposure Period	3 hours
Concentration Range	Nominal: 0-10 mg/L
Remarks – Method	No significant protocol deviations.
RESULTS	
EC_{50}	> 10 mg/L (30 minutes) > 10 mg/L (3 hours)
NOEC	< 3.2 mg/L
Remarks – Results	10 mg/L was the highest test concentration that could be prepared due to limited solubility of the notified chemical in water.
CONCLUSION	The EC_{50} values for the notified chemical with activated sewage sludge have been determined as > 10 mg/L for the 30-minute contact time and > 10 mg/L for the 3-hour contact time.
TEST FACILITY	Huntingdon (1993g)

BIBLIOGRAPHY

Benigni R, Passerini L, Gallo G, Giorgi F, Cotta-Ramusino M (1998) QSAR models for discriminating between mutagenic and nonmutagenic aromatic and heteroaromatic amines, Environmental and Molecular Mutagenesis 32, 75-83.

European Commission (2003) Technical Guidance Document on Risk Assessment in Support of Commission Directive 93/67/EEC on Risk Assessment for New Notified Substances and Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances and Directive 98/8/EC of the European Parliament and of the Council Concerning the Placing of Biocidal Products on the Market – Part I. Institute for Health and Consumer protection, European Chemicals Bureau, European Communities.

Hazleton Laboratories Europe (1983a). Acute oral toxicity study (LD_{50}) in the rat. Report Number 933. Hazleton Laboratories Europe Ltd., North Yorkshire, England. (Unpublished report provided by notifier).

Hazleton Laboratories Europe (1983b). A primary skin irritation and corrosivity study in the rabbit. Report Number 934. Hazleton Laboratories Europe Ltd., North Yorkshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1993a). Infra-red spectrum. Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1993b). Acute dermal toxicity to the rat. Report Number 2142, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1993c). Ready biodegradability (closed bottle test). Report Number 2170, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1993d). Acute toxicity for Rainbow Trout (*Oncorhynchus mykiss)*. Report Number 2144, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1993e). Acute toxicity to *Daphnia magna*. Report Number 2143, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1993f). Algal growth inhibition. Report Number 2145, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1993g). Inhibitory effect on the respiration of activated sewage sludge. Report Number 2169, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1994a). Ultraviolet spectra. Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1994b). Physico-chemical properties. Report Number 71/932317, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1994c). Abiotic degradation: hydrolysis as a function of pH. Report Number 2167, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1994d). Skin sensitisation in the guinea pig. Report Number 1101, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1994e). Four-week oral toxicity study in the rat with two-week recovery period. Report Number 2284, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1994f). Metaphase chromosome analysis of human lymphocytes cultured in vitro. Report Number 2198, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Huntingdon Research Centre (1994g). Mouse micronucleus test. Report Number 1105, Huntingdon Research Centre Ltd., Cambridgeshire, England. (Unpublished report provided by notifier).

Lonza (1991). Purity control with GLC. Report Number 2164, Lonza Group. (Unpublished report provided by notifier).

NOHSC (1994) National Code of Practice for the Labelling of Workplace Substances [NOHSC:2012(1994)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOHSC (2004) Approved Criteria for Classifying Hazardous Substances, 3rd edition [NOHSC:1008(2004)]. National Occupational Health and Safety Commission, Canberra, AusInfo.

NOHSC (2003) National Code of Practice for the Preparation of Material Safety Data Sheets, 2nd edition [NOHSC:2011(2003)]. National Occupational Health and Safety Commission, Canberra, Australian Government Publishing Service.

NOTOX Toxicological Research and Consultancy (1986). Evaluation of the mutagenic activity in the Ames Salmonella/microsome test. Report Number 931, Notox Toxicological Research and Consultancy 5231 DD 's-Hertogenbosch, The Netherlands. (Unpublished report provided by notifier).

Occupational Dermatology Research and Education Centre (ODREC) (2006) Rashes in workers at Boeing, Hawker de Havilland: A report to Boeing, Hawker de Havilland

Rao T K, Dorsey G F, Allen B E, Epler J L (1982) Mutagenicity of 4,4'-methylenedianiline derivatives in the salmonella histidine reversion assay, Arch Toxicol 49, 185-190.

RCC Notox Research and Consultancy Company B.V. (1990a). Determination of the vapour pressure. Report Number 1498, Notox Toxicological Research and Consultancy 5231 DD 's-Hertogenbosch, The Netherlands. (Unpublished report provided by notifier).

RCC Notox Research and Consultancy Company B.V. (1990b). Determination of the partition coefficient (n-octanol/water). Report Number 1497, Notox Toxicological Research and Consultancy 5231 DD 's-Hertogenbosch, The Netherlands. (Unpublished report provided by notifier).

RCC Notox Research and Consultancy Company B.V. (1990c). Determination of the flammability. Report Number 1330, Notox Toxicological Research and Consultancy 5231 DD 's-Hertogenbosch, The Netherlands. (Unpublished report provided by notifier).

Safepharm Laboratories (1989a). Acute eye irritation test in the rabbit. Report Number 932. Safepharm Laboratories Limited, Derby, U.K. (Unpublished report provided by notifier).

Safepharm Laboratories (1989b). Magnusson & Kligman maximisation study in the guinea pig. Report Number 102/47. Safepharm Laboratories Limited, Derby, U.K. (Unpublished report provided by notifier).

Thompson, W.R & Weil, C.S (1952) Biometrics 8; 51-54.

TNO (1994). Auto-ignition temperature. Report Number 2277. TNO Prins Maurits Laboratory, Rijswijk, The Netherlands. (Unpublished report provided by notifier).

Tweats D J, Blakey D, Heflich R H, Jacobs A, Jacobsen S D, Morita T, Nohmi T, O'Donovan M R, Sasaki Y F, Sofuni T, Tice R (2007), Report of the IWGT working group on strategies and interpretation of regulatory in vivo tests I. Increases in micronucleated bone marrow cells in rodents that do not indicate genotoxic hazard, Mutation Res., 627, 78-91.

United Nations (2003) Globally Harmonised System of Classification and Labelling of Chemicals (GHS). United Nations Economic Commission for Europe (UN/ECE), New York and Geneva.

University of North London (1993). 1H NMR spectrum. School of Applied Chemistry, University of North London. (Unpublished report provided by notifier).

US EPA (2002). TSCA New Chemicals Program (NCP) Chemical Categories. http://www.epa.gov/opptintr/newchems/pubs/cat02.htm.