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11 March 2004

**NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME  
(NICNAS)**

**FULL PUBLIC REPORT**

**Silver sodium hydrogen zirconium phosphate**

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**Director  
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**FULL PUBLIC REPORT****Silver sodium hydrogen zirconium phosphate****1. APPLICANT AND NOTIFICATION DETAILS**

## APPLICANT(S)

Walk Off Mats Asia Pacific P/L (ABN 14 002 708 830) of U7/95 O'Sullivan Beach Rd, Lonsdale, South Australia 5160

and

Ontera Modular Carpets P/L (ABN 70 083 532 129) of 171 Briene Road, Northmead, NSW, 2152

## 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:

Details of impurities

Import volume

Manufacturing process

## 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 1993 (Accession number 179238)

EU ELINCS 1998 (422-570-3)

Japan ENCS (1-723 and 1-9)

Korea ECL (2003-189)

US FIFRA (11631-2 and 11631-3)

EU BPD (Notification no. N272)

**2. IDENTITY OF CHEMICAL**

## CHEMICAL NAME

Phosphoric acid, silver (1+) sodium zirconium (4+) salt

## OTHER NAME(S)

Silver sodium hydrogen zirconium phosphate

## MARKETING NAMES

Antimicrobial AlphaSan RC 2000, Antimicrobial AlphaSan RC 5000, Antimicrobial AlphaSan RC 7000 (this is blend containing 31% RC 2000 and 69% zinc oxide).

## CAS NUMBER

265647-11-8

## MOLECULAR FORMULA

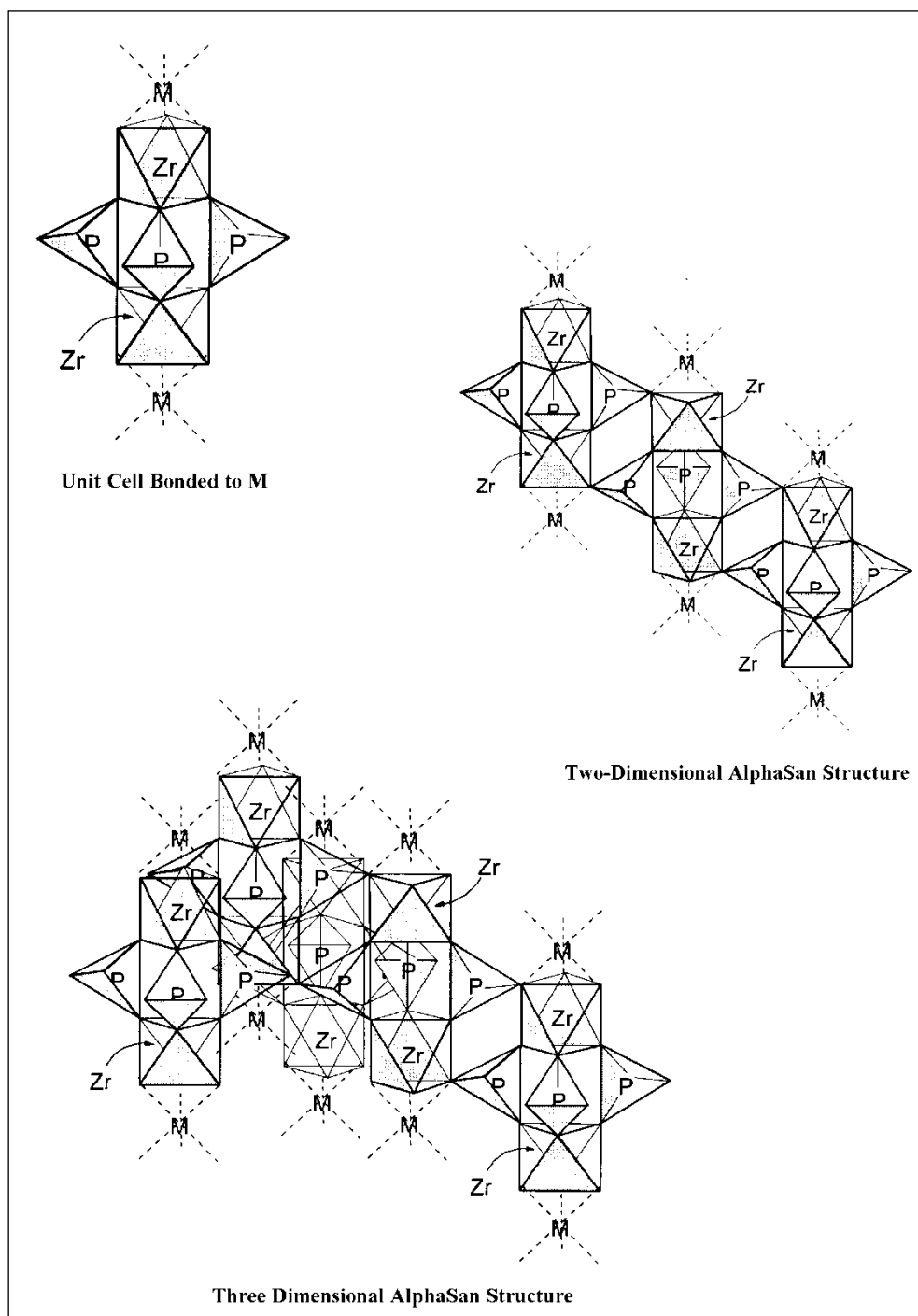
$\text{Ag}_{(0.1-0.5)} \text{Na}_{(0.1-0.8)} \text{H}_{(0.1-0.8)} \text{Zr}_2 (\text{PO}_4)_3$  (general formula)

$\text{Ag}_{0.46} \text{Na}_{0.29} \text{H}_{0.25} \text{Zr}_2 (\text{PO}_4)_3$  (RC 2000, containing approximately 10% silver by weight)

$\text{Ag}_{0.18} \text{Na}_{0.57} \text{H}_{0.25} \text{Zr}_2 (\text{PO}_4)_3$  (RC 5000, containing approximately 3.8% silver by weight)

#### STRUCTURAL FORMULA

The structure of the substance consists of a rhombohedral form of sodium zirconium phosphate,  $\text{NaZr}_2(\text{PO}_4)_3$ , which has a framework structure, rather than layered structure, and contains no waters of hydration. M denotes the metal ions Na or Ag and also the hydrogen ions which fill the non-sodium and non-silver sites.



MOLECULAR WEIGHT  
481-531

SPECTRAL DATA

ANALYTICAL METHOD FTIR  
Remarks Peaks at 1202 (P=O bond stretch), 1039 (P-O bond stretch)

METHODS OF DETECTION AND DETERMINATION

ANALYTICAL METHOD Powder X-ray diffraction  
Remarks Study summary provided. Used to characterise the chemical.

METHODS OF DETECTION AND DETERMINATION

ANALYTICAL METHOD Atomic absorption spectroscopy  
Remarks Study summary provided. Used to establish the presence of silver.

### 3. COMPOSITION

DEGREE OF PURITY **Non-Confidential**  
> 99%

HAZARDOUS IMPURITIES/RESIDUAL MONOMERS  
None

ADDITIVES/ADJUVANTS  
None

### 4. INTRODUCTION AND USE INFORMATION

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

The notified chemical will be imported into Australia. Importation will be primarily by sea, but also potentially by air.

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

| Year   | 1    | 2    | 3    | 4    | 5    |
|--------|------|------|------|------|------|
| Tonnes | 3-10 | 3-10 | 3-10 | 3-10 | 3-10 |

USE **Non-Confidential**

Anti-microbial in polymers and textile fibres. The notified chemical works by releasing silver ions, which are absorbed by microbes and interfere with the formation of enzymes used in energy production, causing the microorganisms to lose the ability to grow and reproduce.

### 5. PROCESS AND RELEASE INFORMATION

#### 5.1. Distribution, Transport and Storage

PORT OF ENTRY  
Sydney

IDENTITY OF RECIPIENTS  
Use of AlphaSan in carpet manufacturing will occur at:  
Ontera Modular Carpets, Wentworth, NSW  
Walk Off Mats Asia Pacific P/L, Lonsdale, SA.

#### TRANSPORTATION AND PACKAGING

AlphaSan products (RC 2000 and RC 5000 consisting of the notified chemical or RC 7000 consisting of the notified chemical within a mixture) will be imported in palletised boxes each containing 48 x10 kg aluminised bags of powder. These will be transported from the port of entry and stored at the temperature-controlled warehouse(s) of the importer and/or formulators before use. Once the notified chemical has been incorporated into articles, these articles will be sold for both commercial and residential use. Packaging and transport at this stage will depend on the nature of the articles and their intended use.

### 5.2. Operation Description

The notified chemical will be imported in 10 kg aluminised bags, with boxes as secondary packaging. It will be transported to formulation sites where it will be incorporated at a level of 0.1 – 2.0% in polymers or textile fibres. At present, the intended use is in the latex backing for carpets. At, at least 2 sites in Australia the chemical will be weighed and added to the latex formulation during the mixing stage. The latex mixture will be pumped to the carpet production area and applied to the back of the carpet. When cured, the carpets will be dispatched for sale through normal distribution channels. The end use of the carpets will be in commercial or residential buildings.

Possible future applications for the notified chemical are many, as polymers and textiles are used widely throughout society. Product categories quoted in overseas technical literature for uses of the chemical are:

- Plastics, coatings, films and laminates, including shower curtains
- Fibres
- Adhesives and sealants
- Miscellaneous manufactured products, including water pipes.
- Heating, Ventilation and Air Conditioning
- Food contact materials

A detailed list of possible uses can be found in at the end of this report.

### 5.3. Occupational exposure

#### *Exposure Details*

#### *Transport and Storage*

Exposure to the notified chemical should only occur in the event of an accident.

#### *Formulation*

Workers will be exposed to 100% notified chemical (in powder form) during the weighing process and transfer to the blending vessel. Dermal and inhalation exposure are the most likely routes. Other powdered additives are used in coating formulations and plastic compoundings, therefore, it is expected that facilities will be equipped with local exhaust ventilation and that the workers would use gloves. The notifier's MSDS recommends the use of chemical goggles and states that the notified chemical should only be used with adequate ventilation. The final article or finished coating may contain from 0.1% to 2.0% by weight of the notified chemical. Therefore following blending, workers will only be exposed to the notified chemical at this concentration. In addition, studies indicate the notified chemical has a very low level of extraction from polymer matrices thus reducing exposure even further.

#### *End-Use*

Due to the extensive number of articles in which the notified chemical could be incorporated, it is likely that a number of workers will have frequent contact with articles containing the notified chemical. The current intended use is in latex backing for carpets. Carpet fitters have the potential for dermal exposure from the fitting of carpet. In the final article, the notified chemical is bound in the polymer matrix and therefore release is expected to be negligible, however, there is potential for the migration of silver ions.

## 5.4. Release

### RELEASE OF CHEMICAL AT PRODUCT MANUFACTURING SITE

The notified chemical will be manufactured overseas and imported into Australia in concentrations of 3.8% and 10% silver (w/w). Environmental release is unlikely during importation, storage and transportation, and spillage during a transport accident is the most likely reason for environmental release. Individual container capacity (10 kg aluminised bags), powdered form and established spill response procedures would limit the extent of release.

Release of the notified chemical during application to the backing of carpets is unlikely. A batch process is used at at least two textile-manufacturing facilities, where the notified chemical is added by hand into a mixing vessel, mixed with other products, applied to carpet and then cured. Any spills would be contained and reused.

### RELEASE OF CHEMICAL FROM USE OF PRODUCTS CONTAINING THE NOTIFIED CHEMICAL

Use of carpet containing the notified chemical will be widespread and diffuse. As the carpets containing the notified chemical will have internal domestic and commercial applications, the potential for environmental release is very low. In addition, the notified chemical will be contained within a polymer matrix with a very low leachability based on leachability studies undertaken on various materials containing the notified chemical (see below). Cleaning of carpet containing the notified chemical is likely to result in only a fraction of the notified chemical entering the wastewater stream due to its very low leaching potential from these materials.

## 5.5. Disposal

Toxic Characteristic Leaching Procedure (TCLP, assumed to be US EPA Method 1311; pH 4.5 acidified elutriate) testing of the notified chemical powder produced a leachate containing 17 mg Ag/L. Due to the potential for leaching, disposal of neat powdered product may not meet Australian State/Territory waste management regulations for inert/solid waste disposal, and such wastes will require special waste management arrangements prior to landfill disposal.

Manufacturing scrap waste will either be recycled or, along with residues in emptied imported bags (<1%), removed by a waste contractor for landfill disposal or incineration.

During application activities, the notified chemical (neat) and articles containing the notified chemical will not be sent to sewer for disposal.

Practically all products containing the notified chemical will eventually be sent to landfill for disposal as solid waste. TCLP testing of latex polymer backing and carpet each containing 0.2% notified polymer, produced no detectable silver in the leachate. On review of State/Territory guidance, these TCLP results for carpet are likely to meet Solid waste classification (i.e.  $\leq 5$  mg Ag/L).

## 5.6. Public exposure

Except in the unlikely event of a transport accident, the public should only be exposed to the notified chemical in the final articles. In the case of the latex carpet backing, potential exposure could only occur whilst fitting the carpet. In the final article, the notified chemical is bound in the polymer matrix and therefore release is expected to be negligible, however, there is potential for the migration of silver ions.

Future uses of the notified chemical such as in food contact materials may result in a different pattern of public exposure.

## 6. PHYSICAL AND CHEMICAL PROPERTIES

**Appearance at 20°C and 101.3 kPa**                      White powder

**Melting Point/Freezing Point**                      > 1000°C

**Remarks**                      Study not conducted. Estimate based on complex inorganic nature of chemical.

**Density** 2914 kg/m<sup>3</sup> at 20°C

METHOD EC Directive 92/69/EEC A.3 Relative Density.  
 Remarks Test performed on RC 5000.  
 TEST FACILITY Huntington Research Centre Ltd (1995a).

**Vapour Pressure** Estimated as very low.

Remarks Study not conducted, on basis of estimate of high melting point and inorganic ionic form.

**Water Solubility** <2.6 x 10<sup>-4</sup> g/L at 20°C

METHOD EC Directive 92/69/EEC A.6 Water Solubility.  
 Remarks Flask stirring method. Test substance (0.05 g) and distilled water (240 mL) were combined in each of six 250 mL stoppered and foil-covered conical flasks. After stirring (30 ±0.5°C for 1-3 d) and settling (20°C for 1 d), supernatant was analysed spectrophotometrically after filtration and extraction.  
 TEST FACILITY Huntington Research Centre Ltd (1995a).

**Hydrolysis as a Function of pH** Not determined. Not relevant to minerals which may exchange ions but will not hydrolyse.

**Partition Coefficient (n-octanol/water)** Not determined. Due to the complex nature of the substance, the solubility in octanol is predicted by the notifier to be negligible, and the water solubility has been determined to be < 1 mg/L. Therefore, the partition coefficient cannot be measured by the shake-flask method or the HPLC method. Furthermore, computer modelling is not valid for inorganic substances.

**Adsorption/Desorption** Not determined. Insoluble – likely to associate with soils and sediments. Adsorption/desorption test methods for determination of K<sub>oc</sub> (HPLC and QSAR prediction) are not applicable to inorganic substances.

**Dissociation Constant** Not determined. Unlikely to dissociate but may exchange ions.

#### Particle Size

METHOD OECD TG 110 Method A. Particle Size Distribution .

| <i>Range (µm)</i> | <i>Volume (%)</i> |
|-------------------|-------------------|
| ≤ 1.98            | 39.39             |
| ≤ 10.22           | 94.26             |
| < 200.2           | 99.63             |
| ≥ 200.2           | 0.37              |

Remarks Test conducted on RC 5000. Coulter counter method used. When viewed under a microscope at X1000 magnification, most particles were too small to make an assessment of their shape. The remainder of the particles were of irregular shape.

TEST FACILITY Huntington Research Centre Ltd (1995a).

#### Particle Size

METHOD AND RESULTS Laser diffraction particle size analysis. The distribution of particle sizes over the range 0.5 µm to 10.1 µm was examined. It is not clear whether there were particles outside this size range in the sample tested. The mean particle size was

Remarks found to be around 1 µm with 99.9% by volume of all particles falling below 2 to 2.6 µm.  
Study not provided.

**Flammability** Not highly flammable

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).

Remarks Test carried out on RC 5000. The test substance pile did not ignite.  
TEST FACILITY Huntington Research Centre Ltd (1995a).

**Autoignition Temperature** > 450°C

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.  
Remarks Test carried out on RC 5000. Did not ignite under the conditions of the test.  
TEST FACILITY Huntington Research Centre Ltd (1995a).

**Explosive Properties**

Remarks Based on the chemical composition, and since the notified chemical is an inorganic material, it is not expected to pose a fire or explosion hazard.

**Reactivity** No oxidising properties. Not water reactive

Remarks No study provided

## ADDITIONAL TESTS

**Dust Explosivity**

Not explosible

|               |                                                                                                                                                           |
|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| METHOD        | Vertical Tube Apparatus. In this method all reasonable measures are taken to ignite the dispersed dust sample in air at ambient temperature and pressure. |
| Remarks       | Test carried out on RC 2000.                                                                                                                              |
| TEST FACILITY | Chilworth (1999)                                                                                                                                          |

## 7. TOXICOLOGICAL INVESTIGATIONS

| <i>Endpoint and Result</i>                                     | <i>Assessment Conclusion</i>                      |
|----------------------------------------------------------------|---------------------------------------------------|
| Rat, acute oral                                                | LD50 >5000 mg/kg bw, low toxicity                 |
| Rat, acute dermal                                              | LD50 >2000 mg/kg bw, low toxicity                 |
| Rat, acute inhalation                                          | LC50 >5.18 mg/L/4 hour, low toxicity              |
| Rabbit, skin irritation                                        | non-irritating                                    |
| Rabbit, eye irritation                                         | slightly irritating                               |
| Guinea pig, skin sensitisation - adjuvant test.                | no evidence of sensitisation.                     |
| Rat, oral (diet) repeat dose toxicity - 90 days.               | NOAEL 389 mg/kg bw/day, no NOEL                   |
| Dog, oral (diet) repeat dose toxicity - 90 days.               | NOAEL 400 mg/kg bw/day,<br>NOEL 200 mg/kg bw/day  |
| Genotoxicity - bacterial reverse mutation                      | non mutagenic                                     |
| Genotoxicity – in vitro mammalian cell gene mutation test      | clastogenic (weak)                                |
| Genotoxicity – in vitro mammalian chromosomal aberration test  | non-clastogenic                                   |
| Genotoxicity – in vivo mammalian erythrocyte micronucleus test | non genotoxic                                     |
| Genotoxicity – in vivo UDS test                                | non genotoxic                                     |
| Developmental effects                                          | developmental and maternal NOAEL 1000mg/kg bw/day |
| Two Generation Reproduction Study in Rat                       | NOEL 1000 ppm, NOAEL 5000 ppm                     |

### 7.1. Acute toxicity – oral

|                  |                                               |
|------------------|-----------------------------------------------|
| TEST SUBSTANCE   | Alphasan RC 2000                              |
| METHOD           | OECD TG 401 Acute Oral Toxicity – Limit Test. |
| Species/Strain   | Rat/Hsd/Ola:Sprague-Dawley (CD)               |
| Vehicle          | 1% w/v aqueous methylcellulose                |
| Remarks - Method | No significant protocol deviations            |

#### RESULTS

| <i>Group</i> | <i>Number and Sex of Animals</i> | <i>Dose mg/kg bw</i> | <i>Mortality</i> |
|--------------|----------------------------------|----------------------|------------------|
| 1            | 5/male                           | 5000                 | 0                |
| 2            | 5/female                         | 5000                 | 0                |

LD50 >5000 mg/kg bw

Signs of Toxicity Clinical signs of reaction to treatment were confined to piloerection and hunched posture (seen in all rats). Recovery was complete in all rats by day 4.

Effects in Organs No abnormalities detected

Remarks - Results

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

TEST FACILITY Huntingdon Life Sciences Ltd (1997a)

### 7.2. Acute toxicity - dermal

|                |                                                                                                                     |
|----------------|---------------------------------------------------------------------------------------------------------------------|
| TEST SUBSTANCE | Alphasan RC 2000                                                                                                    |
| METHOD         | OECD TG 402 Acute Dermal Toxicity – Limit Test.<br>EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal) – Limit Test. |
| Species/Strain | Rat/Sprague-Dawley CD                                                                                               |

Vehicle  
Type of dressing  
Remarks - Method

Test substance moistened with distilled water  
Semi-occlusive.  
No significant protocol deviations

## RESULTS

| <i>Group</i> | <i>Number and Sex<br/>of Animals</i> | <i>Dose<br/>mg/kg bw</i> | <i>Mortality</i> |
|--------------|--------------------------------------|--------------------------|------------------|
| 1            | 5/male                               | 2000                     | 0                |
| 2            | 5/female                             | 2000                     | 0                |

LD50  
Signs of Toxicity - Local  
Signs of Toxicity - Systemic  
Effects in Organs  
Remarks - Results

>2000 mg/kg bw  
No signs of skin irritation observed.  
None  
No abnormalities detected

CONCLUSION

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

TEST FACILITY

Safepharm Laboratories (2000a)

**7.3. Acute toxicity - inhalation**

TEST SUBSTANCE

Alphasan RC 2000

METHOD

OECD TG 403 Acute Inhalation Toxicity – Limit Test.  
EC Directive 92/69/EEC, 93/21/EEC B.2 Acute Toxicity (Inhalation) – Limit Test.

Species/Strain  
Method of Exposure  
Exposure Period  
Physical Form  
Particle Size  
Remarks - Method

Rat/Sprague-Dawley Crl:CD<sup>®</sup>BR  
Nasal exposure only.  
4 hours  
solid aerosol (particulate).  
MMAD: 1.7 µm. Inhalable fraction %<4 µm: 91  
A dust atmosphere was produced from the test material using a ‘Wright’s Dust Feed’ mechanism.

## RESULTS

| <i>Group</i> | <i>Number and Sex<br/>of Animals</i> | <i>Concentration<br/>mg/L</i> |               | <i>Mortality</i> |
|--------------|--------------------------------------|-------------------------------|---------------|------------------|
|              |                                      | <i>Nominal</i>                | <i>Actual</i> |                  |
| 1            | 5/male                               | 25.8                          | 5.18          | 1                |
| 2            | 5/female                             | 25.8                          | 5.18          | 0                |

LC50  
Signs of Toxicity

>5.18 mg/L/4 hours

During exposure: wet fur and increased and decreased respiratory rate were commonly observed. Upon removal from the test chamber, wet fur, hunched posture, pilo-erection and increased or decreased respiratory rate were commonly noted and there were signs of laboured respiration and ptosis.

One hour post exposure: Similar signs of toxicity were observed although incidents of wet fur had diminished. Frequent sneezing was apparent in two females.

One day following exposure: Signs of toxicity included increased incidents of laboured respiration together with additional isolated signs of lethargy, noisy respiration, tiptoe gait and red/brown staining around the snout.

Two days following exposure: One male was found dead. Abnormalities in surviving animals were confined to hunched posture, piloerection and increased respiratory rate.

Three days following exposure: One female showed hunched posture, lethargy, pilo-erection, increased respiratory rate, laboured and noisy respiration, pallor of the extremities and tiptoe gait.

Signs of toxicity in all of the surviving animals gradually diminished and all recovered to appear normal four to six days after exposure.

#### Effects in Organs

The animal that died during the study showed enlarged lungs which were abnormally red with dark patches, patchy pallor of the liver and congestion of the small intestine.

At the end of the study several animals showed lung changes which included general grey mottling or dark foci. No abnormalities were detected in four animals.

#### Remarks - Results

#### CONCLUSION

The notified chemical is of low toxicity via inhalation.

#### TEST FACILITY

Safepharm Laboratories (1998a)

### 7.4. Irritation – skin

#### TEST SUBSTANCE

Alphasan RC 2000

#### METHOD

Species/Strain  
Number of Animals  
Vehicle  
Observation Period  
Type of Dressing  
Remarks - Method

Code of Federal Regulations (US) Title 16, Section 1500.41  
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).  
Rabbit/New Zealand White  
6  
Test substance moistened with distilled water  
48 hours  
Occlusive.  
Deviations from OECD TG 404 Acute Dermal Irritation/Corrosion are as follows:  
The test substance was applied to both intact and abraded skin.  
Exposure period 24 hours  
Observations were made only at 1 hour and 48 hours after patch removal.

#### RESULTS

| <i>Site</i>    | <i>Lesion</i>          | <i>Mean Score*</i> | <i>Maximum Value</i> | <i>Maximum Duration of Any Effect</i> | <i>Maximum Value at End of Observation Period</i> |
|----------------|------------------------|--------------------|----------------------|---------------------------------------|---------------------------------------------------|
| <i>Intact</i>  | <i>Erythema/Eschar</i> | 0                  | 0                    | N/A                                   | 0                                                 |
| <i>Intact</i>  | <i>Oedema</i>          | 0                  | 0                    | N/A                                   | 0                                                 |
| <i>Abraded</i> | <i>Erythema/Eschar</i> | 0.25               | 1                    | 1 hour                                | 0                                                 |
| <i>Abraded</i> | <i>Oedema</i>          | 0                  | 0                    | N/A                                   | 0                                                 |

\*Calculated on the basis of the scores at 1, and 48 hours for ALL animals.

#### Remarks - Results

Very slight erythema was seen at the abraded sites of three animals at the 1 hour reading. No dermal reactions were observed in three animals or at the intact sites of any animal at this time. Treated skin sites of all animals appeared normal at the 48-hour observation.

CONCLUSION The notified chemical is non irritating to skin.

TEST FACILITY Huntingdon Life Sciences Ltd (1997b)

### 7.5. Irritation - eye

TEST SUBSTANCE Alphasan RC 2000

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.  
EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).  
Species/Strain Rabbit/New Zealand White  
Number of Animals 3  
Observation Period 72 hours  
Remarks - Method No significant protocol deviations

#### RESULTS

| Lesion                 | Mean Score*<br>Animal No. |      |      | Maximum<br>Value | Maximum<br>Duration of Any<br>Effect | Maximum Value at<br>End of Observation<br>Period |
|------------------------|---------------------------|------|------|------------------|--------------------------------------|--------------------------------------------------|
|                        | 1                         | 2    | 3    |                  |                                      |                                                  |
| Conjunctiva: redness   | 1                         | 0.33 | 0.33 | 2                | 48 hours                             | 0                                                |
| Conjunctiva: chemosis  | 1                         | 0    | 0.33 | 2                | 48 hours                             | 0                                                |
| Conjunctiva: discharge | 0.66                      | 0    | 0.33 | 3                | 48 hours                             | 0                                                |
| Corneal opacity        | 0                         | 0    | 0    | 0                | N/A                                  | 0                                                |
| Iridial inflammation   | 0                         | 0    | 0    | 0                | N/A                                  | 0                                                |

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

Remarks - Results Moderate conjunctival irritation was noted at the 1-hour observation. Minimal to moderate conjunctival irritation was noted in all treated eyes at the 24 hour observation with minimal conjunctival irritation apparent in one treated eye at the 48 hour observation. Treated eyes appeared normal 48 or 72 hours after treatment. Residual test material was noted in all eyes at the 1 hour observation.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY Safepharm Laboratories (2000b)

### 7.6. Skin sensitisation

TEST SUBSTANCE Alphasan RC 2000

METHOD OECD TG 406 Skin Sensitisation – Magnusson & Kligman.  
EC Directive 96/54/EC B.6 Skin Sensitisation - Magnusson & Kligman.  
Species/Strain Guinea pig/Dunkin Hartley  
PRELIMINARY STUDY intradermal: 0.1% w/w (Maximum concentration that caused only mild to moderate skin irritation)  
topical induction: 50% w/w (Maximum concentration that caused only mild to moderate skin irritation)  
topical challenge: 50% w/w (Maximum non-irritant concentration)  
MAIN STUDY  
Number of Animals Test Group: 10 Control Group: 5  
INDUCTION PHASE Induction Concentration:  
intradermal: 0.1% w/w in distilled water  
topical: 50% w/w in distilled water

## Signs of Irritation

## Interdermal induction:

Discrete or patchy to moderate and confluent erythema was noted at the interdermal induction sites of nine test group animals at the 24 hour observation. Discrete or patchy erythema was noted at the interdermal induction sites of five test group animals at the 48 hour observation.

Discrete or patchy erythema was noted at the interdermal induction sites of three control group animals at the 24 hour observation. No skin reactions were noted at the interdermal induction sites of the control group animals at the 48 hour observation.

## Topical Induction:

Discrete or patchy erythema and incidents of very slight oedema were noted at the induction sites of nine test group animals at the 1-hour observation and in four test group animals at the 24 hour observation. Bleeding from the intradermal induction sites was noted in four test group animals at the 1 hour observation and in one test group at the 24 hour observation. Dried blood was noted at the induction sites of four test group animals at the 24 hour observation. Residual test material was noted at the induction sites of six test group animals at the 1 hour observation.

Discrete or patchy erythema and incidents of very slight oedema were noted at the treatment site of one control group animal at the 1-hour observation. Bleeding from the intradermal induction sites was noted in four control group animals at the 1 hour observation. Dried blood was noted at the treatment sites of two control group animals at the 24 hour observation. No signs of erythema or oedema were noted at the treatment sites of control group animals at the 24 hour observation.

## CHALLENGE PHASE

1<sup>st</sup> challenge

topical: 50% w/w in distilled water

topical: 25% w/w in distilled water

## Remarks - Method

No significant protocol deviations

## RESULTS

| <i>Animal</i>        | <i>Challenge Concentration</i> | <i>Number of Animals Showing Skin Reactions after:</i> |             |                                 |             |
|----------------------|--------------------------------|--------------------------------------------------------|-------------|---------------------------------|-------------|
|                      |                                | <i>1<sup>st</sup> challenge</i>                        |             | <i>2<sup>nd</sup> challenge</i> |             |
|                      |                                | <i>24 h</i>                                            | <i>48 h</i> | <i>24 h</i>                     | <i>48 h</i> |
| <i>Test Group</i>    | 50 % w/w                       | 0                                                      | 0           | N/A                             | N/A         |
|                      | 25 % w/w                       | 0                                                      | 0           | N/A                             | N/A         |
| <i>Control Group</i> | 50% w/w                        | 0                                                      | 0           | N/A                             | N/A         |
|                      | 25% w/w                        | 0                                                      | 0           | N/A                             | NA          |

## Remarks - Results

There were no deaths or remarkable body weight changes during the main study.

## CONCLUSION

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

## TEST FACILITY

Safepharm (2000c)

**7.7.1. 90-day Repeat dose oral toxicity in rats.**

## TEST SUBSTANCE

Alphasan RC 2000

## METHOD

OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.

## Species/Strain

Rat/Sprague-Dawley Crl:CD®BR

## Route of Administration

Oral –diet.

|                      |                                                                                                           |
|----------------------|-----------------------------------------------------------------------------------------------------------|
| Exposure Information | Total exposure days: 90 days;<br>Dose regimen: 7 days per week;<br>Post-exposure observation period: None |
| Vehicle              | Basal laboratory diet                                                                                     |
| Remarks - Method     | No significant protocol deviations                                                                        |

## RESULTS

| Group          | Number and Sex<br>of Animals | Concentration/ Dose |                                     | Mortality |
|----------------|------------------------------|---------------------|-------------------------------------|-----------|
|                |                              | Nominal<br>(ppm)    | Mean<br>Actual<br>(mg/kg<br>bw/day) |           |
| I (control)    | 10/male, 10/female           | 0                   | 0                                   | 0         |
| II (low dose)  | 10/male, 10/female           | 1000                | 78                                  | 0         |
| III (mid dose) | 10/male, 10/female           | 5000                | 389                                 | 0         |
| IV (high dose) | 10/male, 10/female           | 20000               | 1423                                | 0         |

*Mortality and Time to Death*

No mortality was observed during the study.

*Clinical Observations*

No clinically observable signs of toxicity were detected in the test or control animals throughout the study period.

Functional observations

There were no treatment-related changes in the behavioural assessment parameters measured, the functional performance parameters measured and the sensory reactivity. Statistical analysis of the quantitative data revealed a minimum reduction in forelimb grip strength for males treated with 20000 or 5000 ppm when compared with controls. In the absence of any other evidence to suggest neurotoxicity the intergroup differences were fortuitous and of no toxicological importance.

Bodyweight

Males treated with 20000 ppm showed a slight reduction in bodyweight gain over the study period. No significant effect in bodyweight was detected at the remaining dose levels.

Food Consumption

A slight reduction in food consumption was detected for males treated with 20000 ppm throughout the study. No adverse effect on food efficiency was apparent in this sex at that dose level. Females treated with 20000 ppm and animals of either sex treated with the other dose levels showed food consumption and efficiency similar to that of controls.

Ophthalmoscopic Examination

No treatment-related ocular effects were detected. The incidental findings for a control, 20000 ppm female and 1000 ppm male animals were consistent with occasionally encountered findings in laboratory maintained rats of the strain and age employed.

*Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis*Haematology

Statistically significant reductions in haemoglobin, haemocrit, mean corpuscular haemoglobin and mean corpuscular volume were detected for animals of either sex treated with 20000 ppm compared with controls. A reduction in these parameters was also apparent at 5000 ppm but statistical significance was only achieved for male mean corpuscular haemoglobin and mean corpuscular volume. The statistically significant reduction in clotting time detected for 20000 and 5000 ppm males involved individual values that were well within normally expected range. The intergroup differences may not be toxicologically important due to the elevated control values. A statistically significant intergroup difference in the reduction in the lymphocyte count for 20000 ppm males was also observed.

Blood chemistry

A statistically significant increase in plasma alkaline phosphatase and cholesterol was detected for animals of either sex treated with 5000 ppm and 20000 ppm compared with controls. Plasma cholesterol was slightly but statistically significantly elevated for males treated with 1000 ppm, but, in the absence of any other treatment related changes detected at this dose level, this minimal intergroup difference may not be toxicologically



OECD TG 409 Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents was used as a source in the development of this method. Deviations include:  
 5 day per week dose regimen  
 The use of a control group instead of a vehicle control group i.e. the control group were not fed undosed gelatine capsules.

## RESULTS

| <i>Group</i>   | <i>Number and Sex of Animals</i> | <i>Dose mg/kg bw/day</i> | <i>Mortality</i> |
|----------------|----------------------------------|--------------------------|------------------|
| I (control)    | 4 male/4 female                  | 0                        | 0                |
| II (low dose)  | 4 male/4 female                  | 200                      | 0                |
| III (mid dose) | 4 male/4 female                  | 400                      | 0                |
| IV (high dose) | 4 male/4 female                  | 1000/700                 | 2 (1m, 1f)       |

### *Mortality and Time to Death*

One male in group IV was found dead immediately prior to the scheduled necropsy, and one female in group IV was euthanised on Day 42 due to moribundity.

### *Clinical Observations*

The majority of the findings related to faecal excretion of the animals and appeared likely to be dose dependent. These findings were diarrhoea, red diarrhoea, soft faeces, mucus or gel in faeces and decreased defecation. Sporadic salivation and vomiting, was also observed for animals in the test groups (groups II-IV). The female which was euthanised exhibited very slight to extreme activity decrease. Another group IV female exhibited very slight to moderate activity decrease from Day 42 to Day 86. The male that died began showing activity decrease on day 68 and it continued through study termination. He also showed signs of emaciation and ptosis, and had green urine the last two weeks of the study.

### Bodyweight and food consumption

There was little or no effect of treatment on bodyweights, weight gain or food consumption for low and mid dose animals. The differences in the male group IV bodyweights was not statistically significant as the weight of only one animals was affected. Group IV female mean body weights on day 84 were significantly lower than the control group even when the animal that had markedly reduced food consumption was excluded. There was no statistically significant difference in food consumption for male animals. Group IV female food consumption was statistically lower than that of control females at week 4 and also at week 12 if the animal that had markedly reduced food consumption was excluded.

### *Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis* Clinical Chemistry

The group IV male mean alkaline phosphatase and alanine aminotransferase (ALT) were significantly elevated as compared to the control group on Day 89 only. The group IV female alkaline phosphatase was elevated at all three time frames and ALT at day 60 but not at Day 89. The ALT and alkaline phosphatase values for the two females and one male that stopped eating during the study were excluded for the analysis. Although other differences were observed (Group IV males: elevated aspartate aminotransferase (AST), reduced potassium, Group IV females: reduced potassium), the values were still within normal limits and therefore not deemed of toxicological importance.

### Haematology

Although significant differences were observed (Group III females reduced lymphocyte (%), Group II and Group IV females, elevated and reduced MID cells (%)), the values were still within normal limits before and after treatment. MID cells include less frequently occurring and rare cells correlating to monocytes, eosinophils, basophils, blasts and other precursor white cells.

### *Pathology*

#### Organ weights

No difference was observed in the mean weights of the liver, spleen adrenals, testes/ovaries, thymus and brain in either male or female animals and in the mean weight of the kidney in female animals. Group II kidney weights in males were statistically lower than the control.

Macroscopic FindingsDied during study:

Internal findings in the male that died were enlarged salivary glands, engorged gall bladder, thickened stomach and small intestine, and no subcutaneous fat. The euthanised female had pale liver, stomach and intestines, a dark and shrunken spleen, and a discoloured area and dark gel on the occipital region of the brain.

All other animals

Findings for group I and II were similar, being cherry eye (1 group I male, 1 group II female) and pale lungs (2 group I males, 2 females (Group I and II). Group II findings were pale lungs (1 male), prominent mesenteric lymph nodes (2 females) and large nodes adjacent to trachea and abundant adipose tissue in abdomen (1 female). Group IV internal findings were much more numerous and included discoloured and/or thick spongy pancreas (3 males, 2 females), pale or discoloured lungs (1 male, 2 females), enlarged or discoloured lymph nodes (2 male, 3 female), spot on gall bladder (1 male), and discoloured liver, yellow gel in duo denum, small spleen and pale stomach (1 female).

Histopathology

Pigmentation was observed in the intestines, liver and kidneys of group III and Group IV animals. This pigmentation is a known cosmetic effect of silver (argyria) and is not considered toxicologically significant. A chronic/granulomatous inflammation was also observed in the liver of dogs in group III and IV. The inflammation was occasionally accompanied by hepatic vacuolation and/or necrosis in Group IV.

## Remarks – Results

Increases in serum ALT and alkaline phosphatase levels during the study suggest hepatic injury occurring in group IV animals only. In addition, adverse effects were observed in the liver of group IV animals during the histopathology study.

The necropsy findings were not supported by related histopathological changes and therefore are not considered of toxicological significance.

## CONCLUSION

Based on general toxicity and hepatic effects at the top dose, the No Observed (Adverse) Effect Level (NOAEL) was established as 400 mg/kg bw/day in this study. Based on minor effects at the mid dose, the NOEL was 200mg/kg bw/day.

TEST FACILITY                                      Stillmeadow Inc (2002)

**7.8. Genotoxicity - bacteria**

TEST SUBSTANCE                                      Alphasan RC 2000

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*:  
TA1538, TA1535, TA1537, TA98, TA100.  
*E. coli*: WP2 uvrA.  
Metabolic Activation System                      S9 fraction from Aroclor 1254 induced rat liver  
Concentration Range in                      Test 1  
Main Test                                      a) With metabolic activation:                      0- 2000 µg/plate.  
b) Without metabolic activation:                      0-50 µg/plate.  
Test 2  
a) With metabolic activation:                      0- 500 µg/plate.  
b) Without metabolic activation:                      0-50 µg/plate.  
Test 3  
a) With metabolic activation:                      0- 500 µg/plate.  
Vehicle                                      Dimethylsulphoxide  
Remarks - Method                                      No significant protocol deviations.

The dose levels in the second mutation test were reduced in the presence

of S-9 mix due to toxicity being observed at the three highest concentrations in the presence of S-9 in test 1.  
For strains TA 1535, TA 1537, TA 98. TA100 and WP2 *uvrA* insufficient non-toxic dose levels were observed in the presence of S-9 mix. Consequently a third mutation test was required for these strains.

## RESULTS

| <i>Metabolic Activation</i> | <i>Test Substance Concentration (µg/plate) Resulting in:</i> | <i>Cytotoxicity in Preliminary Test</i>                 | <i>Cytotoxicity in Main Test</i>                      | <i>Precipitation</i> | <i>Genotoxic Effect</i> |
|-----------------------------|--------------------------------------------------------------|---------------------------------------------------------|-------------------------------------------------------|----------------------|-------------------------|
| <i>Absent</i>               |                                                              | 50 (all strains)                                        |                                                       |                      |                         |
| Test 1                      |                                                              |                                                         | 25 (all strains)<br>12.5 (TA1538, TA98)               | >50                  | negative                |
| Test 2                      |                                                              |                                                         | 50 (all strains)<br>25 (all strains)<br>12.5 (TA1538) | >50                  | negative                |
| <i>Present</i>              |                                                              | 5000 (all strains)<br>500 (TA1538, TA98)<br>50 (TA1538) |                                                       |                      |                         |
| Test 1                      |                                                              |                                                         | 500 (all strains)<br>125 (TA1538)                     | >2000                | negative                |
| Test 2                      |                                                              |                                                         | 500 (all strains)<br>250 (TA1538)<br>125 (TA1538)     | >500                 | negative                |
| Test 3                      |                                                              |                                                         | 500 (all strains)                                     | >500                 | negative                |

## Remarks - Results

A reduced bacterial lawn was observed in all of the mutation tests. No substantial increases in revertant colony numbers of any of the tester strains were observed following treatment with the notified chemical at any dose level, in the presence or absence of S-9 mix, in either mutation test.

## CONCLUSION

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

## TEST FACILITY

Huntingdon Research Centre Ltd (1995b)

## 7.9.1. Genotoxicity – in vitro Mouse Lymphoma Assay

## TEST SUBSTANCE

Alphasan RC 2000

## 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  
Metabolic Activation  
System  
Vehicle  
Remarks - Method

L5178Y +/- 3.7.2c mouse lymphoma cell  
S-9 fraction from phenobarbitone/β-naphthoflavone induced rat liver

RPMI 1640 medium

No significant protocol deviations.  
A third experiment was performed to confirm weak mutagenic responses seen in test 1.

| <i>Metabolic Activation</i> | <i>Test Substance Concentration (µg/mL)</i> | <i>Exposure Period</i> | <i>Expression Time</i> | <i>Selection Time</i> |
|-----------------------------|---------------------------------------------|------------------------|------------------------|-----------------------|
| <i>Absent</i>               |                                             |                        |                        |                       |
| Test 1                      | 5,10, 20, 40*, 60*, 80*                     | 3 hour                 | 2 days                 | 10-14 days            |

|                |                            |         |        |            |
|----------------|----------------------------|---------|--------|------------|
| Test 2         | 1.25, 2.5, 5, 7.5, 10, 15* | 24 hour | 2 days | 10-14 days |
| Test 3         | 2.5, 5, 10, 15, 20, 30*    |         |        |            |
| <i>Present</i> |                            |         |        |            |
| Test 1         | 5, 10, 20, 40, 60, 80*     | 3 hour  | 2 days | 10-14 days |
| Test 2         | 10, 20, 40, 60, 70, 80*    | 3 hour  | 2 days | 10-14 days |

\*excluded from statistical analysis due to toxicity.

## RESULTS

| <i>Metabolic Activation</i> | <i>Cytotoxicity in Preliminary Test</i> | <i>Test Substance Concentration (µg/mL) Resulting in:</i><br><i>Cytotoxicity in Main Test</i> | <i>Precipitation</i> | <i>Genotoxic Effect</i> |
|-----------------------------|-----------------------------------------|-----------------------------------------------------------------------------------------------|----------------------|-------------------------|
| <i>Absent</i>               | 78.1 (3h exposure)<br>40 (24h exposure) |                                                                                               |                      |                         |
| Test 1                      |                                         | 40                                                                                            | >80                  | Weak Positive           |
| Test 2                      |                                         | 15                                                                                            | >15                  | equivocal               |
| Test 3                      |                                         | 30                                                                                            | >30                  | Weak Positive           |
| <i>Present</i>              | 78.1                                    |                                                                                               |                      |                         |
| Test 1                      |                                         | 80                                                                                            | >80                  | Weak Positive           |
| Test 2                      |                                         | 80                                                                                            | >80                  | equivocal               |

### Remarks - Results

#### Test 1

The test material induced a small but significantly significant and dose related increase in the mutant frequency in the presence of metabolic activation, and a small statistically significant increase in mutant frequency in the absence of S-9. The increase in mutant frequency was partly due to small colony formation.

#### Test 2

The test material did not induce any statistically significant or dose related increases in mutant frequency in either the absence or presence of activation. In the absence of activation, the only dose level with a marked increase was considered too be too toxic and in the absence of activation, although there was a slight indication of a dose related response, loss of the top dose level due to toxicity prevented any statistical significance. Therefore, this was taken to indicate that the mutagenic response was occurring at or around the onset of excessive toxicity.

#### Test 3

The test material induced a statistically significant dose-related increase in mutant frequency. The response observed, whilst modest, was accompanied by an increase in the absolute number of mutant colonies and therefore was considered to confirm the weak response seen in test 1.

#### General

The assay was hampered by the toxicity of the test material at relatively low doses. Nevertheless, the assay indicated a weak positive response with and without metabolic activation.

### CONCLUSION

The notified chemical was weakly clastogenic to L5178Y mouse lymphoma cells treated in vitro under the conditions of the test.

### TEST FACILITY

Safepharm (2000e)

### 7.9.2. Genotoxicity – in vitro Chromosomal Aberration Assay

#### TEST SUBSTANCE

Alphasan RC 2000

#### METHOD

OECD TG 473 In vitro Mammalian Chromosomal Aberration Test.

| Cell Type/Cell Line         | EC Directive 92/69/EEC B.10 In vitro Mammalian Chromosomal Aberration Test. |                        |                     |
|-----------------------------|-----------------------------------------------------------------------------|------------------------|---------------------|
| Metabolic Activation System | Human lymphocytes                                                           |                        |                     |
| Vehicle                     | S-9 fraction from phenobarbitone/ $\beta$ -naphthoflavone induced rat liver |                        |                     |
| Remarks - Method            | Dimethylsulfoxide                                                           |                        |                     |
|                             | No significant protocol deviations.                                         |                        |                     |
| <i>Metabolic Activation</i> | <i>Test Substance Concentration (<math>\mu\text{g/mL}</math>)</i>           | <i>Exposure Period</i> | <i>Harvest Time</i> |
| <i>Absent</i>               |                                                                             |                        |                     |
| Test 1                      | 0*, 78.13, 156.25*, 312.5*, 468.75*, 625, 937.5                             | 4 hours                | 24 hours            |
| Test 2                      | 0*, 39.07, 78.13, 156.25, 234.38*, 312.5*, 468.75*                          | 24 hours               | 24 hours            |
| <i>Present</i>              |                                                                             |                        |                     |
| Test 1                      | 0*, 78.13, 156.25, 234.75*, 312.5*, 468.75*, 625                            | 4 hours                | 24 hours            |
| Test 2                      | 0*, 39.07, 78.13, 156.25, 234.38*, 312.5*, 468.75*                          | 4 hours                | 24 hours            |

\*Cultures selected for metaphase analysis.

## RESULTS

| <i>Metabolic Activation</i> | <i>Test Substance Concentration (<math>\mu\text{g/mL}</math>) Resulting in:</i> |                                   |                      |                         |
|-----------------------------|---------------------------------------------------------------------------------|-----------------------------------|----------------------|-------------------------|
|                             | <i>Cytotoxicity* in Preliminary Test</i>                                        | <i>Cytotoxicity* in Main Test</i> | <i>Precipitation</i> | <i>Genotoxic Effect</i> |
| <i>Absent</i>               | 625                                                                             |                                   |                      |                         |
| Test 1                      |                                                                                 | 625                               | >937.5               | negative                |
| Test 2                      |                                                                                 | 468.75                            | >468.75              | negative                |
| <i>Present</i>              | 312.5                                                                           |                                   |                      |                         |
| Test 1                      |                                                                                 | 312.5                             | >625                 | negative                |
| Test 2                      |                                                                                 | >312.5                            | >468.75              | negative                |

\*Approximate 50% mitotic inhibition

### Remarks - Results

#### Test 1

A 44% mitotic inhibition was achieved at 468.75  $\mu\text{g/mL}$  in the absence of S9. In the presence of S9, 56% mitotic inhibition was observed at 312.5  $\mu\text{g/mL}$  and an approximate 80% mitotic inhibition at 468.75  $\mu\text{g/mL}$ . However, the concurrent negative control was considered to have an unusually high index thereby giving an exaggerated mitotic inhibition profile. Therefore, 468.75  $\mu\text{g/mL}$  was selected as the maximum dose for metaphase analysis in both exposure groups.

The test material did not induce any statistically significant increases in the frequency of cells with aberrations either in the absence or presence of metabolic activation.

The test material did not induce a statistically significant increase in the number of polyploid cells at any dose level in either of the exposure groups.

#### Test 2

A 69% mitotic inhibition was achieved at 468.75  $\mu\text{g/mL}$  in the absence of S9. An approximate 40% mitotic inhibition was observed at 312.5  $\mu\text{g/mL}$  and 468.75  $\mu\text{g/mL}$ . It was considered that adequate toxicity had been achieved in both exposure groups. Therefore, 468.75  $\mu\text{g/mL}$  was selected as the maximum dose for metaphase analysis in both exposure groups.

The test material did not induce any statistically significant increases in the frequency of cells with aberrations either in the absence or presence of metabolic activation.

The test material did not induce a statistically significant increase in the number of polyploid cells at any dose level in either of the exposure groups.

|               |                                                                                                                   |
|---------------|-------------------------------------------------------------------------------------------------------------------|
| CONCLUSION    | The notified chemical was not clastogenic to human lymphocytes treated in vitro under the conditions of the test. |
| TEST FACILITY | Safepharm Laboratories (2002a)                                                                                    |

#### 7.10.1. Genotoxicity – in vivo Mouse Micronucleus Test

|                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TEST SUBSTANCE          | Alphasan RC 2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| METHOD                  | OECD TG 474 Mammalian Erythrocyte Micronucleus Test.<br>EC Directive 2000/32/EC B.12 Mutagenicity Mammalian Erythrocyte Micronucleus Test.                                                                                                                                                                                                                                                                                                                                                   |
| Species/Strain          | Mouse/albino CrI:CD-1 <sup>TM</sup> (ICR)BR                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Route of Administration | Oral –intraperitoneal injection.                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Vehicle                 | Arachis oil                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Remarks - Method        | No significant protocol deviations.<br>Bone marrow used for study.<br>A range finding study was conducted. Both male and female animals were dosed (2000 mg/kg) by oral gavage and intraperitoneal injection. As no marked difference in the test materials toxicity to male or female mice was observed, it was considered acceptable to use males only for the main study. The intraperitoneal route of administration was chosen in an attempt to maximise exposure to the test material. |

| <i>Group</i>                   | <i>Number and Sex<br/>of Animals</i> | <i>Dose<br/>mg/kg bw</i> | <i>Sacrifice Time<br/>hours</i> |
|--------------------------------|--------------------------------------|--------------------------|---------------------------------|
| I (vehicle control)*           | 7/male                               | 0                        | 48                              |
| II (vehicle control)*          | 7/male                               | 0                        | 24                              |
| III (positive control,<br>CP)* | 5/male                               | 50                       | 24                              |
| IV (high dose)                 | 7/male                               | 2000                     | 48                              |
| V (high dose)                  | 7/male                               | 2000                     | 24                              |
| VI (mid dose)                  | 7/male                               | 1000                     | 24                              |
| VII (low dose)                 | 7/male                               | 500                      | 24                              |

\* dosed orally. CP=cyclophosphamide.

|                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| RESULTS                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Doses Producing Toxicity | The high dose (2000 mg/kg bw) reached the limit dose for a non-toxic test substance. There were no premature deaths or clinical signs of toxicity observed in any of the dose groups                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Genotoxic Effects        | The test substance did not induce a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes (PCE) over the levels observed in the vehicle control. There was a statistically significant decrease in the PCE/NCE ratio in group VII when compared to the concurrent vehicle control group. However, this was part of an inverse dose-related response and was not considered to be treatment related. Results from the vehicle and positive control demonstrated that the test method was operating satisfactorily. Therefore, the test substance is considered negative in this micronucleus assay |
| Remarks - Results        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| CONCLUSION               | The notified chemical was not genotoxic in this in vivo mouse micronucleus assay under the conditions of the test.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| TEST FACILITY            | Safepharm Laboratories (2000f)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

#### 7.10.2. Genotoxicity – in vivo Liver Unscheduled DNA Synthesis Assay

|                         |                                                                                                                                                                                                                                                                                                        |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TEST SUBSTANCE          | Alphasan RC 2000                                                                                                                                                                                                                                                                                       |
| METHOD                  | OECD TG 486 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo.                                                                                                                                                                                                                   |
| Species/Strain          | Rat/Sprague-Dawley CD (CrI:CD®(SD) IGS BR)                                                                                                                                                                                                                                                             |
| Route of Administration | Oral – intraperitoneal route                                                                                                                                                                                                                                                                           |
| Vehicle                 | Arachis oil BP                                                                                                                                                                                                                                                                                         |
| Remarks - Method        | A range finding study was conducted. Both male and female animals were dosed (2000 mg/kg) by oral gavage and intraperitoneal injection. As no marked difference in the test materials toxicity to male or female mice was observed, it was considered acceptable to use males only for the main study. |

Deviations from protocol.

All animals were dosed via the intraperitoneal group. This could expose the liver directly to the test substance rather than via the circulatory system.

#### Experiment 1

| Group                  | Number and Sex of Animals | Dose mg/kg bw | Harvest Time hours |
|------------------------|---------------------------|---------------|--------------------|
| I (vehicle control)    | 6/male                    | 0             | 16                 |
| II (low dose)          | 4/male                    | 666.7         | 16                 |
| III (high dose)        | 4/male                    | 2000          | 16                 |
| IV (+ve control, 2AAF) | 4/male                    | 50            | 16                 |

2AAF=2-Acetamidofluorene

#### Experiment 2

| Group                  | Number and Sex of Animals | Dose mg/kg bw | Harvest hours |
|------------------------|---------------------------|---------------|---------------|
| I (vehicle control)    | 6/male                    | 0             | 2             |
| II (low dose)          | 4/male                    | 666.7         | 2             |
| III (high dose)        | 4/male                    | 2000          | 2             |
| IV (+ve control, NDHC) | 4/male                    | 20            | 2             |

NDHC=N,N'-Dimethylhydrazine dihydrochloride

#### RESULTS

Doses Producing Toxicity The high dose (2000 mg/kg bw) reached the limit dose for a non-toxic test substance. There were no premature deaths or clinical signs of toxicity observed in either of the two experiments. .

#### Genotoxic Effects

##### Experiment 1

With the exception of one vehicle control group, all animals were processed to provide scorable slides. The test material did not induce any marked increases in the incidence of cells in repair at either dose level. Results from the vehicle and positive control demonstrated that the test method was operating satisfactorily.

##### Experiment 2

With the exception of one vehicle control group, all animals were processed to provide scorable slides. The test material did not induce any marked increases in the incidence of cells in repair at either dose level. Results from the vehicle and positive control demonstrated that the test method was operating satisfactorily

#### Remarks - Results

No significant increase in the incidence of cells undergoing unscheduled DNA synthesis in isolated rat hepatocytes was observed after 2 and 16 hour exposures in vivo.

#### CONCLUSION

The notified chemical was not genotoxic in this in vivo UDS test under

the conditions of the test.

TEST FACILITY

Safepharm Laboratories (2002b)

## ADDITIONAL INVESTIGATIONS

## 7.11. Developmental toxicity

## TEST SUBSTANCE

|                         |                                                                                                                                                                                                                                                                                                                                 |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| METHOD                  | Oral Gavage Teratology Study in Rats (In house)                                                                                                                                                                                                                                                                                 |
| Species/Strain          | Rat/ Sprague-Dawley CD                                                                                                                                                                                                                                                                                                          |
| Route of Administration | Oral – gavage                                                                                                                                                                                                                                                                                                                   |
| Exposure Information    | Total exposure days: 10 days;<br>Dose regimen: 7 days per week;<br>Pre-exposure observation period: 3-5 days;<br>Post-exposure observation period: 5 days                                                                                                                                                                       |
| Vehicle                 | 1% carboxymethyl cellulose                                                                                                                                                                                                                                                                                                      |
| Remarks - Method        | The study was designed to reflect the requirements of OPPTS test guideline 870.8300 (Prenatal Developmental Toxicity Study), and OECD Guidelines for the Testing of Chemicals.<br>Deviations from OECD TG 414 Teratogenicity are as follows:<br>The animals were delivered post mating.<br>Dosing period: Day 6 to Day 15 only. |

## RESULTS

| Group          | Number and Sex of Animals | Dose Level mg/kg bw/day | Dose Concentration mg/mL | Mortality |
|----------------|---------------------------|-------------------------|--------------------------|-----------|
| I (control)    | 25/female                 | 0                       | 0                        | 0         |
| II (low dose)  | 25/female                 | 10                      | 13                       | 0         |
| III (mid dose) | 25/female                 | 300                     | 30                       | 1         |
| IV (high dose) | 25/female                 | 1000                    | 100                      | 0         |

*Mortality and Time to Death*

One female in Group III was killed *in extremis* on study Day 15 with clinical signs of respiratory distress. At post mortem examination there was clear fluid and fibrinous adhesions present within the thorax. The lungs were congested. These findings are consistent with dosing trauma.

*Effects on Dams*

| Group          | Number pregnant | Mean number of Corpora Lutea | Mean total number of Implants | Mean Embryonic/Foetal deaths |      | Mean Implantation loss % |      |
|----------------|-----------------|------------------------------|-------------------------------|------------------------------|------|--------------------------|------|
|                |                 |                              |                               | Early                        | Late | Pre                      | Post |
| I (control)    | 22              | 15.7                         | 14.3                          | 0.91                         | 0.27 | 7.9                      | 7.9  |
| II (low dose)  | 23              | 15.1                         | 13.3                          | 0.39                         | 0.13 | 12.1                     | 4.2  |
| III (mid dose) | 23              | 15.2                         | 13.3                          | 0.74                         | 0    | 12.1                     | 5.5  |
| IV (high dose) | 21              | 15.6                         | 14.2                          | 0.76                         | 0.05 | 9.2                      | 5.6  |

With the exception of the one female (detailed above), there were no clinical signs of ill-health or reaction to dosing during the course of the study. There were no significant differences in bodyweight gain and food consumption for treated groups when compared to controls. The necropsy findings observed (increased renal pelvic cavitation, follicular cyst on ovary) are commonly observed in this strain of rat and are considered to be incidental and not attributed to the test material. There were no significant treatment related differences in the uterine implantation data reported. The pre and post implantation losses were comparable for all dose groups when compared to controls.

*Effects on Foetus*

| Group          | Mean number of Live Foetuses | Mean % Male Foetuses | Mean Foetal weight (g) | Mean total Litter Weight (g) |
|----------------|------------------------------|----------------------|------------------------|------------------------------|
| I (control)    | 13.1                         | 43                   | 3.71                   | 48.65                        |
| II (low dose)  | 12.7                         | 46.9                 | 3.80                   | 48.11                        |
| III (mid dose) | 12.6                         | 50.4                 | 3.74                   | 46.84                        |

|                |      |      |      |       |
|----------------|------|------|------|-------|
| IV (high dose) | 13.4 | 56.8 | 3.77 | 49.95 |
|----------------|------|------|------|-------|

The group IV mean percentage of males per litter was statistically significantly higher than the control value. This is considered a chance result within the context of this study. The live litter size, mean foetal weights and total litter weights were comparable for all groups. Foetal visceral and skeletal evaluation showed no significant differences in the proportion of foetuses with anomalies/variances in development and also the incidence and type of anomalies/variances found.

#### Remarks - Results

#### CONCLUSION

Females dosed with the notified chemical from Day 6 to Day 15 of gestation at dose levels up to and including 1000 mg/kg showed no evidence of maternal toxicity and no significant effects on the growth and development of offspring. Therefore, 1000mg/kg bw/day is considered the maternal and developmental NOAEL of the study.

TEST FACILITY                                      SafePharm Laboratories (1999)

#### 7.12.              Toxicity to reproduction – two (three) generation study

|                         |                                                                                                                                                   |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| TEST SUBSTANCE          | Alphasan RC 2000                                                                                                                                  |
| METHOD                  | OPPTS 870.8300 Reproduction and Fertility effects                                                                                                 |
| Species/Strain          | Rat/Sprague-Dawley Crl: CD® IGS BR                                                                                                                |
| Route of Administration | Oral –diet                                                                                                                                        |
| Exposure Information    | F <sub>0</sub> and F <sub>1</sub> males and females were dosed during maturation (75 days), mating (up to 21days), gestation and weaning (21days) |
| Vehicle                 | Diet                                                                                                                                              |
| Remarks - Method        | No significant deviations from OECD TG 416 Two Generation Reproduction Toxicity Study                                                             |

| Generation     | Group          | Number and Sex of Animals | Dose/Concentration |                                    |
|----------------|----------------|---------------------------|--------------------|------------------------------------|
|                |                |                           | Nominal (ppm)      | Mean actual pre mating (mg/kg/day) |
| F <sub>0</sub> | I (control)    | 28 male/28 female         | 0                  | 0                                  |
|                | II (low dose)  | 28 male/28 female         | 1000               | 75.4                               |
|                | III (mid dose) | 28 male/28 female         | 5000               | 381.3                              |
|                | IV (high dose) | 28 male/28 female         | 20000              | 1538.6                             |
| F <sub>1</sub> | I (control)    | 24 male/ 24 female        | 0                  | 0                                  |
|                | II (low dose)  | 24 male/ 24 female        | 1000               | 102.4                              |
|                | III (mid dose) | 24 male/ 24 female        | 5000               | 515.5                              |
|                | IV (high dose) | 24 male/ 24 female        | 20000              | 2124.8                             |

#### RESULTS

##### *Mortality and Time to Death*

F<sub>0</sub> Generation: No mortalities occurred in groups III and IV. At 1000 ppm one female was killed in extremis during pregnancy on day 85 because of possible dystocia. Two females from the control group were found dead on day 102 and 117.

F<sub>1</sub> Generation: At 20000 ppm three males were found dead on days 123, 143 and 195 and one was killed in extremis on Day 234. Macroscopic findings on the latter included dark contents in the intestines and gaseous distension of the caecum. Two females were killed in extremis on days 196 and 219. One due to suspected dystocia and the other due to clinical signs of ataxia, hunched posture, dehydration and emaciation. Macroscopic findings on the latter indicated gastrointestinal changes. At 5000 ppm one female was killed in extremis on day 170 due to suspected haemaphroditism. At 1000 and 0 ppm there were no mortalities.

*Effects on Parental (F<sub>0</sub>) animals:*

There were no significant treatment related clinical signs of toxicity for males and females during the course of the study. At high dose a slight increase in the incidence of fur loss was noted but due to a lack of correlation of time and duration of appearance between animals, this was not thought to be treatment related.

There were no significant treatment related differences in mating and pregnancy indices, gestation length, litter size, viability and incidents of suspected dystocia. There were no significant treatment related differences in sperm motility or numbers of homogenisation resistant spermatids for either testis or epididymis

At 20000 ppm the majority of animals showed darkened or discoloured pancreas and there was a reduction in the group mean seminal vesicle/coagulating gland weight and thymus weight and an increase in group mean spleen weight. At 5000 ppm there was a reduction in the group mean seminal vesicle/coagulating gland weight and an increase in group mean spleen weight. The margin of difference compared to control showed no dose related response. No effects were observed at 1000 ppm except a slight reduction in epididymis weight.

*Effects on 1<sup>st</sup> Filial Generation (F<sub>1</sub>)*

Offspring (from F<sub>0</sub>):

At 20000 ppm there was a statistically significant reduction in mean individual offspring weight. There were no significant treatment related effects upon reflexological responses, sex ratio and time to completion of sexual maturation. At 20000 and 5000 ppm there was a reduction in both male and female offspring group mean thymus weight, however, at 5000 ppm the values were comparable to historical control values.

Adult:

At 20000 ppm there was a reduction in adult bodyweight gain for F<sub>1</sub> males and females only during maturation. Starting weights for males and females were lower than control values. Male food consumption values were lower during maturation and female food consumption was reduced during gestation and lactation period. No significant findings for 5000 and 1000 ppm.

There were no significant treatment related differences in mating and pregnancy indices, gestation length and incidents of suspected dystocia. At 20000 ppm there was a reduction in the group mean litter size. There were no significant treatment related differences in sperm motility or numbers of homogenisation resistant spermatids for either testis or epididymis.

There were no significant effects upon reproductive organs either macroscopically or microscopically and no effects on semen characteristics or oocyte numbers. Darkened or discoloured pancreas and mesenteric lymph nodes was observed in animals dosed with 20000 and 5000 ppm. A lower incidence was observed at 5000 ppm. At 20000 ppm, there was a statistically significant reduction in both absolute weight and as a percentage of bodyweight in prostate and uterus weight, a significant reduction in the group mean absolute male adrenal, male kidney and seminal vesicle/coagulating gland weight and a statistically significant increase in group mean male organ weights as a percentage of body weight for brain, left testis and left and right epididymis. At 5000 ppm, there was a reduction in group mean male kidney weight, a slight increase in the group mean absolute weight for the left epididymis and an increase in the thymus weight (both absolute and as a percentage of body weight). No corresponding histopathological changes were noted in any of the organs shown to have weight differences.

*Effects on 2<sup>nd</sup> Filial Generation (F<sub>2</sub>)*

At 20000 ppm there was a reduction in the mean offspring bodyweight. There were no significant treatment related effects upon reflexological responses, sex ratio and offspring development at any dose.

At 20000 and 5000 ppm there was a reduction in both male and female offspring group mean thymus weight, however, at 5000 ppm the values were comparable to historical control values.

*Remarks – Results*

General toxicity at 20000 ppm, evidenced by mortality incidence (F<sub>1</sub> generation), reduction in body weight gain and reduction in absolute organ weights. Based on the minor effects at the mid dose the No Observed Effect Level (NOEL) was established in this study as 1000 ppm.

No evidence of significant effects on reproductive organs or performance at any dose.

Effects associated with the pancreas and mesenteric lymph nodes were related to the accumulation of pigment within the tissues. This effect was not associated with adverse histopathological changes. Pigmentation is a known cosmetic effect of silver (argyria) and is not considered toxicologically significant.

CONCLUSION. Based on the toxicity at 20000 ppm, the No Observed (Adverse) Effect Level (NOAEL) was established in this study as 5000 ppm

TEST FACILITY                                      Safepharm Laboratories (2002c)

## 8. ENVIRONMENT

### 8.1. Environmental fate

No environmental fate data were submitted. The notified chemical is a microbiocide and is unlikely to biodegrade rapidly in the environment. It is a mineral and may exchange silver for other metals. It is unlikely to bioaccumulate in aquatic organisms. Leachability data from various products containing RC2000 or RC5000 (note no test reports provided) are as follows:

- RC5000 powder (3.8% Ag) - 17 ppm Ag
- 0.2% RC2000 incorporated into dried latex polymer used for coatings – 0 ppm Ag
- Carpet with latex polymer backing containing 0.2% RC2000 – 0 ppm Ag
- Fabric coated with polymer containing 0.5% RC5000 – 3.3 ppm Ag
- Polyester microdenier fibre containing 1.5% RC5000 – 0.14 ppm Ag
- Nylon 6,6 fibre containing 0.8% RC5000 – 0.26 ppm Ag
- Pelletised nylon masterbatch containing 30% RC5000 – 0.98 ppm Ag
- Wastewater treatment sludge containing 0.8% Ag – 0.08 ppm Ag.

### 8.2. Ecotoxicological investigations

#### 8.2.1. Acute toxicity to fish

|                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TEST SUBSTANCE        | Alphasan RC2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| METHOD                | OECD TG 203 Fish, Acute Toxicity Test – Static.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Species               | Rainbow trout ( <i>Oncorhynchus mykiss</i> )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Exposure Period       | 96 h                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Auxiliary Solvent     | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Water Hardness        | 56 mg CaCO <sub>3</sub> /L (soft)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Analytical Monitoring | Test conditions were monitored at 0, 24 and 96 h: temperature 11-13.8°C, pH 7.8-8.2, dissolved oxygen 9.4-10.6 mg/L (acceptable).                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Remarks – Method      | Aliquots of test substance were weighed and added to dilution water (40 L) at nominal concentrations of 78, 160, 310, 630, 1300 and 2500 µg/L. Test suspensions were mixed for 1 h prior to introduction of the test organisms. The negative control, 78, 160 and 310 µg/L were clear and colourless throughout while higher test suspensions were slightly cloudy in appearance throughout the tests, with the cloudiness increasing with increasing concentration, suggesting effects may have been due to physical as well as toxicological responses. |

#### RESULTS

| Concentration mg/L |        | Number of Fish | Mortality |      |      |      |      |
|--------------------|--------|----------------|-----------|------|------|------|------|
| Nominal            | Actual |                | 3.5 h     | 24 h | 48 h | 72 h | 96 h |
| 0                  | <LOQ   | 20             | 0         | 0    | 0    | 0    | 0    |
| 0.078              | 0.047  | 20             | 0         | 0    | 0    | 0    | 0    |
| 0.160              | 0.126  | 20             | 0         | 0    | 0    | 0    | 0    |
| 0.310              | 0.236  | 20             | 0         | 0    | 0    | 0    | 0    |
| 0.630              | 0.501  | 20             | 0         | 0    | 1    | 1    | 2    |
| 1.300              | 0.948  | 20             | 0         | 3    | 20   | 20   | 20   |
| 2.500              | 2.290  | 20             | 0         | 20   | 20   | 20   | 20   |

|                   |                                                                                                                                                                                              |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| LC50              | 1.292 mg/L at 24 hours (95% CI 0.948-2.290).<br>0.661 mg/L at 48 hours (95% CI 0.501-0.948).<br>0.661 mg/L at 72 hours (95% CI 0.501-0.948).<br>0.643 mg/L at 96 hours (95% CI 0.501-0.948). |
| NOEC              | 0.236 mg/L at 96 hours.                                                                                                                                                                      |
| Remarks – Results | Sublethal effects (lying on bottom of test container) were observed at 3.5 h exposure to 0.948 mg/L.                                                                                         |

|               |                                                                                        |
|---------------|----------------------------------------------------------------------------------------|
| CONCLUSION    | The notified chemical is very toxic to fish (96 h LC50 <1 mg/L; Mensink et al., 1995). |
| TEST FACILITY | Wildlife International, Ltd (2000a).                                                   |

### 8.2.2. Acute toxicity to aquatic invertebrates

|                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TEST SUBSTANCE        | Alphasan RC 2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| METHOD                | OECD TG 202 <i>Daphnia</i> sp. Acute Immobilisation Test - Static.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Species               | <i>Daphnia magna</i> (neonates <24 h old)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Exposure Period       | 48 hours                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Auxiliary Solvent     | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Water Hardness        | 56 mg CaCO <sub>3</sub> /L                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Analytical Monitoring | Test parameters monitored 0 and 48 h: Temperature 20.4-20.5 °C, dissolved oxygen 8.6-8.8 mg/L, pH 8.2-8.8, light 16 h:8 dark, total organic carbon (TOC) 0.6-1.5 mg/L.                                                                                                                                                                                                                                                                                                                                                                                     |
| Remarks - Method      | Primary stock (1 mg/L), containing 0.01 g of test substance in 10 L of dilution water, was added to dilution water in test chambers to prepare test concentrations of 20, 40, 80, 160 and 320 µg/L. Test suspensions were stirred (30 min) prior to addition of test organisms. Test suspensions were mixed continuously throughout the tests. All suspensions appeared clear and colourless at test initiation, after ~24 h and at test termination. This indicates effects in the test organisms were toxicological, rather than from a physical effect. |

### RESULTS

| Concentration mg/L |        | Number of <i>D. magna</i> | Number Immobilised |      |
|--------------------|--------|---------------------------|--------------------|------|
| Nominal            | Actual |                           | 24 h               | 48 h |
| 0                  | <LOQ   | 20 (4 reps)               | 0                  | 0    |
| 0.020              | 0.015  | 20 (4 reps)               | 0                  | 0    |
| 0.040              | 0.018  | 20 (4 reps)               | 0                  | 4    |
| 0.080              | 0.042  | 20 (4 reps)               | 8                  | 20   |
| 0.160              | 0.093  | 20 (4 reps)               | 20                 | 20   |
| 0.320              | 0.158  | 20 (4 reps)               | 20                 | 20   |

|                   |                                             |
|-------------------|---------------------------------------------|
| EC50              | 0.023 (95% CI 0.018-0.042) mg/L at 48 hours |
| NOEC              | 0.015 mg/L at 48 hours                      |
| Remarks - Results |                                             |

|               |                                                                                                         |
|---------------|---------------------------------------------------------------------------------------------------------|
| CONCLUSION    | The notified chemical is very toxic to aquatic invertebrates (48 h EC50 <1 mg/L; Mensink et al., 1995). |
| TEST FACILITY | Wildlife International, Ltd (2000b).                                                                    |

### 8.2.3. Algal growth inhibition test

|                     |                                                                                                |
|---------------------|------------------------------------------------------------------------------------------------|
| TEST SUBSTANCE      | Alphasan RC 5000                                                                               |
| METHOD              | OECD TG 201 Alga, Growth Inhibition Test and EC Directive 92/69/EEC C.3 Algal Inhibition Test. |
| Species             | Green algae <i>Selenastrum capricornutum</i>                                                   |
| Exposure Period     | 72 hours                                                                                       |
| Concentration Range |                                                                                                |
| Nominal             | 0.078, 0.156, 0.313, 0.625, 1.25, 2.5 and 5.0 mg/L                                             |
| Auxiliary Solvent   | None                                                                                           |
| Water Hardness      | Not stated                                                                                     |

Analytical Monitoring  
Remarks - Method

Test temperature 24 °C  
Continuous illumination (~7000 lux). Initial cell densities  $5.1 \pm 10^4$  cells per mL. Seven test concentrations plus one untreated control (each in triplicate). Test substance was dispersed directly in sterile medium to produce a series of stock solutions exactly twice the concentration of the intended exposure levels. 500 mL of algal pre-culture was mixed with 500 mL of each of these solutions to give the final test series. The control was prepared by adding 500 mL of algal pre-culture to 500 mL of sterile nutrient medium. The highest test exposure level (without the presence of algal cells) was prepared by adding 500 mL of the highest stock solution to 500 mL of sterile nutrient medium. Test concentrations were verified by chemical analysis of unfiltered test solution samples collected at 0 and 120 h.

## RESULTS

| <i>Biomass</i>               |                               | <i>Growth</i>                | <i>72 h NOEC</i> |
|------------------------------|-------------------------------|------------------------------|------------------|
| <i>72 h E<sub>b</sub>C50</i> | <i>120 h E<sub>b</sub>C50</i> | <i>72 h E<sub>r</sub>C50</i> |                  |
| <i>95% CI (mg/L)*</i>        | <i>95% CI (mg/L)*</i>         | <i>95% CI (mg/L)*</i>        | <i>mg/L</i>      |
| 0.313-0.625                  | 0.156-0.625                   | 0.313-0.625                  | 0.156            |

\*Determination of precise EC50 values was not possible due to the high variability in the test data between replicates, indicating that the results should be interpreted with caution particularly as they are based on nominal concentrations.

## Remarks - Results

Regrowth occurred in cultures, indicating an algistatic effect.

## CONCLUSION

The notified chemical is very toxic to algae (EC50 <1 mg/L; Mensink et al., 1995).

## TEST FACILITY

Huntington Research Centre (1995c).

## 8.2.4. Inhibition of microbial activity

## TEST SUBSTANCE

Alphasen RC 2000

## METHOD

OECD TG 209 Activated Sludge, Respiration Inhibition Test.  
EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test

## Inoculum

Activated sewage sludge (200 mL) in synthetic sewage (16 mL) and notified chemical in water to a volume of 500 mL.

## Exposure Period

3 hours

## Concentration Range

## Nominal

0, 10, 32, 100, 320, 1000 mg/L

## Remarks – Method

Test temperature 21 °C, pH 7.3, suspended solids 3900 mg/L. Reference material 3,5-dichlorophenol validated the test results (3 h EC50 = 10 mg/L). Test concentrations were made by adding test material (5.0, 16, 50, 160, 500 mg) to 250 mL water and subjected to ultrasonication.

## RESULTS

## 3 h EC50

160 mg/L

## NOEC

32 mg/L

## CONCLUSION

Inhibitory to sludge microbes at concentrations > 32 mg/L under the conditions of the tests (eg. 3 h exposure). The notifier indicates that due to the low water solubility and very low migration rate, the notified chemical in products are not rapid sterilants and often require >24 hours before their antimicrobial properties are realised. Therefore, the results should be interpreted with caution.

## TEST FACILITY

Safepharm Laboratories Limited (2002d).

**8.5E. Avian acute oral toxicity**

TEST SUBSTANCE                      Alphasan RC 2000

METHOD                              USEPA Ecological Effects Test Guidelines OPTS 850.2100 Avian Acute Oral Toxicity Test (EPA-712-C-96-136) April 1996. Public draft.

Species/Strain                      Bobwhite quail (*Colinus virginianus*) 21 weeks old

Vehicle                                Gelatin capsule by gavage

Remarks - Method                Test duration 14 days.

**RESULTS**

| <i>Group</i> | <i>Number and Sex<br/>of Animals</i> | <i>Dose<br/>mg/kg bw</i> | <i>Mortality</i> |
|--------------|--------------------------------------|--------------------------|------------------|
| 0            | 10 male, 10 female                   | 0                        | Nil              |
| 1            | 10 male, 10 female                   | 2000                     | Nil              |

LD50                                      >2000 mg/kg bw

Signs of Toxicity                      Diarrhoea was noted at 7.5 h post-dosing and on Test Day 3 of the study in the 2000 mg/kg bw group. A sublethal NOEL was not calculated. A NOEL (mortality) of 2000 mg/kg bw has been derived from this study.

Effects in Organs                      Enlarged gall bladder (1.5 times). Gaseous intestines.

Remarks - Results

CONCLUSION                            The notified chemical is practically non-toxic to birds via the oral route.

TEST FACILITY                        Bio-Life Associates, Ltd (1998).

## 9. RISK ASSESSMENT

### 9.1. Environment

#### 9.1.1. Environment – exposure assessment

The notified chemical is non-volatile and atmospheric losses following environmental releases are expected to be low. Furthermore, it is not readily dissolved in water. Being inorganic, mineral and microbiocidal, it is unlikely to be readily or inherently biodegradable.

The notified chemical is unlikely to leach or migrate within the landfill environment from landfilled products, and is more likely to absorb to landfill wastes and soils.

There is a low potential for environmental release of the notified chemical to waters based on its very low leachability from carpet, their use patterns and disposal methods. According to the notifier, activities involving application of the notified chemical will not result in any discharges of the notified chemical to sewer.

However, through use of the notified chemical in a possible wide range of products, leaching of the notified chemical to sewer may occur. If it is assumed that 5% of the notified chemical leached to sewer (diffuse use), a predicted sewer effluent concentration (assuming no sewerage system attenuation) of 0.34 µg/L. This is estimated using a per capita water usage of 200 L/d and a population of 20 million people. Predicted environmental concentrations (PECs) for freshwater and marine receiving environments of 0.34 µg/L and 0.034 µg/L have been derived assuming dilution factors of 1 and 10, respectively.

#### 9.1.2. Environment – effects assessment

The results of the aquatic toxicity tests available indicate that the lowest available toxicity data is for *Daphnia magna*, with a 48 h EC50 0.023 mg/L. A predicted no effect concentration for aquatic organisms (PNEC<sub>aquatic</sub>) of 0.00023 mg/L (0.23 µg/L) has been derived by dividing this value by a safety factor of 100. The notified chemical is likely to have a low toxicity to wildlife, and the potential for exposure is low.

#### 9.1.3. Environment – risk characterisation

The notified chemical will interact with other components to form a stable chemical matrix and, once dry, is expected to be immobile within products and pose little risk to the environment. No aquatic release is expected and no PEC/PNEC ratio has been derived for the intended use pattern (i.e. a component of latex carpet backing). The notified chemical is not likely to present a risk to the environment when it is stored, transported, used, recycled and disposed of in the proposed manner.

However, possible uses other than the intended use pattern may potentially pose a risk to the environment, with a potential PEC/PNEC ratio of ~1.5 for freshwater environments, assuming 5% of the notified chemical was discharged to sewer. It is known from leaching tests using other products that the notified polymer can leach from these other types of materials. In addition, although no chronic toxicity data were available, the notified chemical may display chronic toxicity due to its likely environmental persistence.

### 9.2. Human health

#### 9.2.1. Occupational health and safety – exposure assessment

##### *Formulation*

The greatest potential for exposure is during the weighing and transfer processes. Both dermal and inhalation exposure could occur.

The estimated dermal exposure during formulation is 0.1-1 mg/cm<sup>2</sup>/day, based on EASE model. (HSE, 1994) Therefore, for a 70 kg worker with surface area for hands at 820 cm<sup>2</sup> and forearms at 1140 cm<sup>2</sup> and a default dermal absorption factor of 10%, systemic exposure is estimated to be 0.28-2.8 mg/kg bw/day.

The estimated atmospheric concentration of notified chemical during formulation is 0.2 – 0.5

mg/m<sup>3</sup> based on EASE model (HSE, 1994). Therefore for a 70 kg worker, assuming an inhalation rate of 1.3 m<sup>3</sup>/hour, a 4 hour exposure time and 100% bioavailability, inhalation exposure is estimated to be 0.015 – 0.037 mg/kg bw/day.

Exposure to the notified chemical would be reduced by the use of local exhaust ventilation and the use of PPE.

#### *End use*

In the final articles the notified chemical is bound in the polymer matrix and therefore exposure to the notified chemical due to contact with the finished article is expected to be negligible. However, there is potential for exposure to silver due to its migration from the notified chemical.

The notifier submitted the reports from three studies to determine the migration of silver from low density polyethylene (LDPE) containing Alphasan RC 2000 (Covance (1998), TNO (1999), Milliken (2000)). The results of which are summarised below:

| <i>Study Number</i> | <i>% Alphasan RC 2000</i> | <i>Extraction Solvent</i>                       | <i>Conditions</i>                        | <i>Migration (µg/6dm<sup>2</sup>)</i> |
|---------------------|---------------------------|-------------------------------------------------|------------------------------------------|---------------------------------------|
| 1                   | 2                         | 10% ethanol                                     | 100°C for 2 hours, then 40°C for 10 days | <10                                   |
| 1                   | 2                         | 95% ethanol                                     | 100°C for 2 hours, then 40°C for 10 days | <10                                   |
| 2                   | 2                         | 3% acetic acid                                  | 40°C for 10 days                         | <10                                   |
| 2                   | 2                         | 95% acetic acid                                 | 40°C for 10 days                         | <10                                   |
| 3                   | 1.78                      | 40mM sodium acetate buffer solution, pH 5.0     | 40°C for 10 days                         | 20                                    |
| 3                   | 1.78                      | 50mM sodium phosphate buffer solution at pH 7.0 | 40°C for 10 days                         | 23                                    |
| 3                   | 1.78                      | 35mM sodium phosphate buffer solution at pH 9.0 | 40°C for 10 days                         | <14.5                                 |

Since the notified chemical can be considered an ion-exchange complex, the solvents used in study three were thought to represent worst-case extraction conditions. Even assuming that silver would migrate as readily to skin as to these solvents, potential dermal exposure to silver would be 0.06 µg/kg bw/day. Assumptions used include: skin contact occurs to the hands and arms only, exposure duration is 8 hours a day and the average bodyweight of workers is 70kg.

#### **9.2.2. Public health – exposure assessment**

In the final articles the notified chemical is bound in the polymer matrix and therefore exposure to the notified chemical due to contact with the finished article, is expected to be negligible. There is potential for exposure to silver due to its migration from the notified chemical.

For the current intended use of carpet backing, dermal contact is expected to occur less frequently than with workers (discussed above) therefore exposure is expected to be negligible. Future uses of the notified chemical such as in food contact materials may result in a different pattern of public exposure.

#### **9.2.3. Human health - effects assessment**

Alphasan RC 2000 was the test substance used in all of the toxicity studies. Alphasan RC 2000 contains a higher level of silver than Alphasan RC 5000, and, thus would possess the highest potential for toxicological response.

*Acute toxicity.*

The notified chemical was of low oral, dermal and inhalation toxicity in acute rat studies.

#### **Irritation and Sensitisation.**

In the skin irritation study, very slight erythema was observed in at the abraded sites of 3 of the six rabbits but no dermal reactions were observed at any of the intact skin sites. The notified chemical is considered to be a slight irritant to abraded skin and a non-irritant to intact skin. In the eye irritation study, minimal to moderate irritation was observed in all rabbits. Treated animals appeared normal 48 or 72 hours after treatment. The notified chemical is considered to be a slight eye irritant. The notified chemical was negative in a skin sensitisation adjuvant test in guinea-pigs.

The notifier's MSDS states that dust may be, irritating to the eye and slightly irritating to the respiratory tract.

#### **Repeated Dose Toxicity**

In the 90 day oral repeat study in rats, in high-dose animals the decrease in haemoglobin, haematocrit, mean corpuscular haemoglobin and mean corpuscular volume along with the increase in extramedullary haemopoiesis in the spleen were considered to be treatment-related. In addition, in the high dose male rats, the increase in the relative liver weight, together with the supporting blood chemical changes were indicative of hepatic effects. Based on the increased liver weight in males and haemopoiesis in the spleen at 20000 ppm, the No Observed (Adverse) Effect Level (NOAEL) was established in this study as 389mg/kg bw/day (equivalent to 5000 ppm). Based on minor haematological and clinical changes and accumulation of pigment in a number of organs, no NOEL was established.

In the 90-day oral repeat study in dog, the increase in serum ALT and alkaline phosphatase in the high dose animals as well as the adverse effects observed in the liver of these animals were considered to be treatment-related. Based on general toxicity and hepatic effects at the top dose, the No Observed (Adverse) Effect Level (NOAEL) was established as 400 mg/kg bw/day in this study. Based on minor effects at the mid dose, the NOEL was 200mg/kg bw/day.

#### **Mutagenic**

A small but significantly significant increase in mutant frequency was observed in the absence of metabolic activation in an in vitro mammalian cell gene mutation test. The notified chemical was weakly clastogenic to L5178Y mouse lymphoma cells treated in vitro in this study. The notified chemical was negative in an Ames test and found not to be clastogenic in a chromosomal aberration study in human lymphocytes. Two in vivo genotoxicity studies were conducted, an erythrocyte micronucleus test in mice and an unscheduled DNA synthesis (UDS) test with rat liver cells. The notified chemical was found not to be genotoxic in these studies. On balance, the notified chemical is either weakly genotoxic or not genotoxic.

#### **Developmental/Reproduction Toxicity**

No evidence of maternal toxicity and no significant effects on the growth and development of offspring were observed in any of the rats dosed with levels up to 1000mg/kg from Day 6 to Day 15 of gestation. The maternal and developmental NOAEL was established to be 1000 mg/kg bw/day in this study.

In a two generation reproduction study, general toxicity in F<sub>1</sub> adults and a reduction in mean offspring bodyweight were observed at 20000 ppm. There were no effects in offspring development and reproductive organs or performance. The NOAEL was established to be 5000 ppm.

#### **Hazard classification for health effects.**

Based on the available toxicological data, the notified chemical is not classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999).

#### **Exposure Guidelines**

Relevant exposure standards for atmospheric contaminants in the occupational environment (NOHSC, 1995) are:

Silver compounds (as Ag) 0.01 mg/m<sup>3</sup> (TWA and STEL)

Zirconium compounds (as Zr) 5 mg/m<sup>3</sup> (TWA), 10 mg/m<sup>3</sup> (STEL)

The limit for silver in the Australian Drinking Water Guidelines is 0.1 mg/L (NHMRC, 1996).

The US EPA established an oral Reference Dose (RfD), or daily intake limit, of 0.005 mg/kg/day for silver in 1991.

#### *Other*

The one clinical condition that is known in humans to be attributable to long-term exposure to silver and silver compounds is a gray or blue-gray discoloring of the skin (argyria). Argyria may occur in an area of repeated or abrasive dermal contact with silver or silver compounds, or more extensively over widespread areas of skin and the conjunctiva. This condition is considered cosmetic, and not health related.

#### **9.2.4. Occupational health and safety – risk characterisation**

The notified chemical is a slight irritant to eyes and abraded skin and the notified MSDS states that dust may be, irritating to the eye and slightly irritating to the respiratory tract. Exposure to the notified chemical is most likely during the weighing and transfer, therefore these activities should take place in the presence of adequate ventilation and workers should wear overalls and safety glasses. Workers should 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 also reduce prolonged exposure to the notified chemical. Exposure to the notified chemical was estimated to be 0.29 – 2.8 mg/kg bw/day. The margin of exposure (MOE) was based on a NOAEL of 389 mg/kg bw/day. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Based on the above, the MOE is calculated as 1341- 138. Therefore, the risk using modelled worker data is acceptable for formulation workers handling the neat notified chemical.

Following incorporation into the final article, exposure to the notified chemical is expected to be negligible. Worst case exposure to silver was estimated to be 0.06ug/kg bw/day. This value is nearly 100 times lower than the US EPA daily intake limit and over 3000 times lower than the average persons intake from drinking water (assuming consumption 2L/day and silver present at limit). Therefore, the risk of adverse effects is negligible.

#### **9.2.5. Public health – risk characterisation**

With the current intended use of the notified chemical the public exposure to the notified chemical is expected to be negligible and therefore the risk to public health is also expected to be negligible.

Future uses of the notified chemical such as in food contact materials may result in a different pattern of public exposure

### **10. CONCLUSIONS – ASSESSMENT LEVEL OF CONCERN FOR THE ENVIRONMENT AND HUMANS**

#### **10.1. Hazard classification**

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

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.

**Chronic Hazard 1 Very Toxic to Aquatic Life with Long Lasting Effects**

The notified chemical has microbiocidal properties and is not expected to be readily or inherently biodegradable

#### 10.2. Environmental risk assessment

The chemical is not considered to pose a risk to the environment based on its reported use pattern (i.e. a component in latex carpet backing).

#### 10.3. Human health risk assessment

##### 10.3.1. Occupational health and safety

There is Low Concern to occupational health and safety under the conditions of the occupational settings described.

##### 10.3.2. Public health

There is Negligible Concern to public health based on its reported use pattern (i.e. a component in latex carpet backing).

### 11. MATERIAL SAFETY DATA SHEET

#### 11.1. Material Safety Data Sheet

The MSDS of the notified chemical Alphasan RC 2000 provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994a). It is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

#### 11.2. Label

The label for the notified chemical Alphasan RC 2000 provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994b). The accuracy of the information on the label remains the responsibility of the applicant.

### 12. RECOMMENDATIONS

#### CONTROL MEASURES

##### Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical as introduced.
  - Ensure adequate ventilation
- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Protective eyewear, chemical resistant industrial clothing and footwear and impermeable gloves; where engineering controls and work practices do not reduce vapour and particulate exposure to safe levels, an air fed respirator should also 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.

##### Environment

- The following concentration limit should be considered by environment protection agencies for release of the notified chemical to the aquatic environment:
  - 0.23 µg/L

#### Disposal

- The notified chemical (neat powder) should be recycled or disposed of as a special waste due to its leachability in accordance with by State/Territory waste management regulations, guidelines and codes of practice. Products containing the notified chemical should be recycled or sent to landfill for disposal.

#### Emergency procedures

Spills/release of the notified chemical should be handled by collecting spilled powder into sealable labelled containers. Do not attempt to clean up with water. Avoid disposal into wastewater treatment facilities or waterways.

### 12.1. Secondary notification

The Director of Chemicals Notification and Assessment must be notified in writing within 28 days by the notifier, other importer or manufacturer:

- (1) Under Sub Section 64(1) of the Act; if
  - uses are proposed other than incorporation of the notified chemical in latex carpet backing.or
- (2) Under Sub Section 64(2) of the Act:
  - if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

Any Secondary Notification should include

- leaching tests for the products manufactured containing the notified chemical.
- chronic *Daphnia* study (for uses which will result in a more significant release to the aquatic compartment, including via the sewer, eg. shower curtains, scouring pads, water pipes).

Any proposed use in Food Contact Materials should also be notified to the Standards Liaison Officer at Food Standards Australia New Zealand.

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Attachment: Section of label for Alphasan RC2000 detailing possible uses for the notified chemical.