File No: STD/1185

March 2006

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Organic peroxydic acid in Finish Powerball Quantum

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NICNAS

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1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Solvay Interox Pty Ltd (ABN 70 000 882 137) of 20-22 McPherson St, Banksmeadow, NSW, 2019

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

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:

Chemical Identity
Spectral Data
Purity and nature of impurities
Introduction volume
Details of use
Identity of Recipients

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:

Particle size
Acute toxicity – inhalation

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
None

NOTIFICATION IN OTHER COUNTRIES
EC, Italy, ELINCS 410-850-8, Registration 92-05-0185 (2002)
US EPA PMN P93-1607 (1995)

2. IDENTITY OF CHEMICAL

OTHER NAME(S)
Organic peroxydic acid

MARKETING NAME(S)
The notified chemical is introduced as a component of the finished good 'Finish Powerball Quantum'.

METHODS OF DETECTION AND DETERMINATION

Remarks High Performance Liquid Chromatography (HPLC) with UV detection is used for the quantitative recognition of the notified chemical.

The identity of the notified chemical was confirmed using infrared and UV/visible spectroscopy. The spectra provided were consistent with the proposed structure.

3. COMPOSITION

DEGREE OF PURITY
> 90%

IMPURITIES/RESIDUAL MONOMERS
Impurities present are not expected to contribute to the classification of the notified chemical as a hazardous substance.

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will not be manufactured in Australia, but will be imported as a component in a finished good.

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

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	< 30	< 30	< 30	< 30	< 30

USE
The notified chemical will be used as a bleaching agent component of a dishwashing tablet at a concentration of < 10%.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Sydney

IDENTITY OF MANUFACTURER/RECIPIENTS
The finished products containing the notified chemical will be sent to a customer in NSW before being distributed to retail outlets throughout Australia.

TRANSPORTATION AND PACKAGING
The finished product containing the notified chemical will be transported to Australia in refrigerated shipping containers. Only under exceptional circumstances would it be required to be air freighted into Sydney. Stock will then be transported, by road, to the warehouse facility. The finished product will then be distributed to numerous retail distribution outlets.

The dishwashing tablets containing the notified chemical are packaged in sealed polyethylene blisters in paperboard consumer cartons in a number of pack sizes (12, 24, 36 and 48).

5.2. Operation description
The notified chemical is imported in a finished product. No reformulation occurs in Australia.
Laboratory chemists may conduct in-house use tests on the finished product.

End use
The finished product containing the notified chemical will be sold to retail outlets.
Consumers will then use the finished product by placing one tablet per wash load in the appliance dispenser.

5.3. Occupational exposure
Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport and warehousing	10	6 - 8 hrs/day	200 days/year
Laboratory Chemist	2	1 - 2 hrs/day	2-3 days/year
Retail workers	> 10,000	0.5 hrs/day	100 days/year

Exposure Details
No occupational exposure to the notified chemical is expected for warehouse workers, transport workers and retail workers, since the handling will be limited to the packaged product and no direct contact with the dishwashing tablet is expected. Even in the event of a breach in packaging, the dishwasher tablet has a resin coating and as such direct contact with the notified chemical will be avoided.

Only occasional exposure is expected for laboratory chemists that will conduct in-use tests of the finished product. Direct exposure to the notified chemical from the handling of the dishwasher tablet is not expected due to the presence of the resin coating. Incidental dermal and ocular contact to notified chemical at a concentration of < 10% could occur with laboratory workers handling water solutions of the finished product. Laboratory chemists routinely wear lab coats, eye protection and gloves when working with chemicals.

5.4. Release

RELEASE OF CHEMICAL AT SITE
The notified chemical will not be manufactured in Australia, but will be imported as a component in finished formulation tablets used for dishwashing. Environmental release of the finished product, and thus the notified chemical, is unlikely during importation, transport and storage and an accidental spill with damage to the integrity of the packaging is the most likely reason for environmental release. Emergency clean up procedures (described in the MSDS) will limit the impact on the environment of such incidents.

RELEASE OF CHEMICAL FROM USE
During use the finished product will be diluted with 13 – 15 litre of water. The notified chemical in the product will undergo the following reaction(s):

- The notifier expects > 99% will react with the water and solids on the dishes to form its non-peroxidic degradation product.
- 1% maximum of the notified chemical will remain unreacted and enter the sewer, where biodegradation will readily occurs through reduction of the peroxidic group and partial hydrolysis of the resulting main degradation product.

5.5. Disposal
Should the event arise, bulk quantities in the warehouse would be disposed of appropriately through the local Waste Management Authority.

At the consumer level it is expected that all product be disposed of through use. However, some consumers may dispose of unwanted finished product with their household rubbish.

5.6. Public exposure
Since the notified chemical will be in products sold to the general public, widespread public exposure is expected. Typical use information is as follows (European Commission, 2003a):

Product	*Grams/Task*	*Use Frequency (tasks per week)*	*Duration of Task*
Dishwasher Tablet	19*	3-7	< 1 min

* provided by notifier.

Direct exposure to the notified chemical (at a concentration of < 10%) from the handling of the dishwasher tablet is not expected due to the presence of the resin coating.

Since the dishwasher powder will be stored and used in a domestic environment, there is the possibility of accidental ingestion by a child.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20ºC and 101.3 kPa Solid (White, odourless crystalline powder)

Melting Point/Freezing Point 81 ºC

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Determined using a melt microscope. Test conducted in compliance with Good Laboratory Practice standards.
TEST FACILITY Unpublished report provided by notifier

Density 1400 kg/m^3 at 23ºC

METHOD EC Directive 92/69/EEC A.3 Relative Density.
Remarks Determined by air comparison pycnometer. Test conducted in compliance with Good Laboratory Practice standards.
TEST FACILITY Unpublished report provided by notifier

Vapour Pressure < 1 x 10^{-3} kPa at < 87.9 ºC

METHOD EC Directive 92/69/EEC A.4 Vapour Pressure.
Remarks Determined using a vapour pressure balance. Test conducted in compliance with Good Laboratory Practice standards.

Vapour pressure was measured in the range 18-137 °C. Up to 87.9 °C, no increase in weight at the balance was observed. An evaluation of the raw data was only possible in the temperature range 130-137 °C with a vapour pressure ranging from 5.6 to 6.7 Pa. The measured values at these temperatures are considered to be due to impurities or decomposition products. The vapour pressure/temperature dependence of the substance could not be determined, although, up to 87.9 °C the vapour pressure is below the maximal limit of detection (1 Pa).
TEST FACILITY Unpublished report provided by notifier

Water Solubility 0.2 g/L at 20ºC

METHOD EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Determined using the Flask Method with the concentrations determined using high performance liquid chromatography. Test conducted in compliance with Good Laboratory Practice standards.

Saturated water solutions of the notified chemical were stirred for 24-72 hrs at 30°C and afterwards left to stand for 24 hrs at 20 °C prior to filtering and analysis. Under these conditions, partial degradation of notified chemical into its main degradation product occurred. The ratio of the notified chemical/main degradation product (27-37/73-63) resulting in a pH range of 3.6-3.8 was not affected by the stirring time. No significant differences were observed by adopting milder experimental procedures (stirring for 4 hrs at 20°C).

The concentration of notified chemical was estimated to be approximately 0.2 g/L at equilibrium.
TEST FACILITY Unpublished report provided by notifier

Fat Solubility 693 mg/100 g fat at 37°C

METHOD OECD TG 116 Fat Solubility of Solid and Liquid Substances.
Remarks Mixtures containing 0.5 g notified chemical and 25 g fat were stirred at 30ºC or 50ºC for 3 hours and 37ºC for 3 or 27 hours. The saturated liquid phase was separated from undissolved test substance by filtration through a filter at 37ºC. The final solution was analysed by HPLC to determine the concentration of test substance.

Results depend on the presaturation temperature and there seemed to be a slight

dependence on stirring time. The ratio of the notified chemical/main degradation product in fat stayed almost constant.

TEST FACILITY Unpublished report provided by notifier

Surface Tension 69.5 mN/m at 20°C

METHOD OECD TG 115 Surface Tension of Aqueous Solutions.
EC Directive 92/69/EEC A.5 Surface Tension.

Remarks Six measurements of the aqueous solutions of the substance at a temperature of 20^0C, every 5 minutes were done using a digital tensiometer. After correction with Harkins-Jordan correction table, the final value was observed. The notified chemical is not surface active.

TEST FACILITY Unpublished report provided by notifier

Hydrolysis as a Function of pH

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

pH	*T (°C)*	*t½ hours*
4	25	40 (estimation)
4	40	7.1
7	25	38.9
7	40	9.5
9	25	<24 (estimation)
9	50	<2.4

Remarks The optimal concentration of the test substance required for the HPLC analysis was about 100 mg/L. Because the low solubility the use of a solubility enhancing agent was necessary. Abiotic degradation tests were performed under exclusion of light as the test substance seems to degrade slowly in daylight. The HPLC ratios of the notified chemical/main degradation product found in the present investigation did not exactly correspond with the notified chemical/main degradation product ratios of earlier HPLC investigations, but according to quantitative ^{1}H NMR spectroscopy the composition of the test substance had not changed.

Preliminary Test:
A partial disappearance of the notified chemical was observed in the solutions with pH 4 and 7 treated at 50^0C for 2.4 hours. The notified chemical concentration decreased 47.9% and 44.9% at pH 4 and 7, respectively. An almost complete hydrolysis was observed for solutions at pH 9 (99.8% degradation). No further test was requested at pH 9 as the hydrolysis at 50^0C exceeded 50% in 2.4 hours. The degradation at 25^0C in this buffer can be estimated as being less than one day.

> 99.9% notified chemical was found to be hydrolysed at pH 4 and 7 after 5 days at 50^0C. A unique degradation product was identified at pH4 and 7 after 2.4 hours and at pH 4 after 5 days. Neither the notified chemical nor the main degradation product were detected at pH 9 after 2.4 hours and at pH 7 after 5 days at 50^0C.

Main test:
The half-life of the notified chemical at pH 4 and 7 was determined by measuring the degradation of the notified chemical as a function of time at 40^0C and 25^0C.
pH 7: 67% and 36.8% degradation were observed after 15.4 hours (40^0C) and 25.8 hours (25^0C), respectively.
pH 4: 51% degradation was observed after 7.3 hours.
Due to the similarities between the results obtained both in the preliminary and the main tests at pH 4 and 7, no further tests at pH 4 were considered necessary.

TEST FACILITY Unpublished report provided by notifier

Partition Coefficient (n-octanol/water) log Pow = 2.2 at 20°C (notified chemical)

log Pow = 2.0 at 20ºC (main degradation product)

METHOD OECD TG 117 Partition Coefficient (n-octanol/water).
Remarks HPLC Method:
- Column: Hypersil ODS, precolumn
- Mobile Phase: Distilled water/acetonitrile (50:50 v/v) adjusted to pH 3.9 with phosphoric acid (0.1 mole/L)
- Column temperature was 39ºC

The notified chemical (purity 92%) and its main degradation product (purity 99%) were injected in a HPLC chromatograph.
To meet the requirement of the guideline to measurements of ionisable substances in their non-ionised form, chromatography was performed at a pH of ca. 4, no dissociation of the notified chemical and its main degradation product occurred in the column. Six reference substances were used.
Calculations were also carried out using the program CLOGP 3.4 (Pomona Colloge Medicine Chemistry project, California) according to Leo and Hansch, resulting in log Pow of 1.48 and 2.17, respectively.
Results were extrapolated to 20ºC.
TEST FACILITY Unpublished report provided by notifier

Adsorption/Desorption log K_{oc} = 1.92 at 21°C

METHOD OECD TG 106 Adsorption - Desorption Using a Batch Equilibrium Method.
Remarks HPLC Method Comparable to OECD TG 121
- Column: Hypersil CPS, the stationary phase contains a moderate polar phase with lipophilic and polar moieties.
- Mobile Phase Methanol:Water (55:45 v/v)

Limit of quantification: for log Koc = 3 the log k' was 0.15 and for log Koc = 2 the log k' was -0.17.

The elution of the notified chemical, showed a capacity factor k', within those observed for the calibration substances assayed. As consequence, its calculated log Koc was within the limits of the method and resulted to be 1.916 ± 0.025.
The minor component, (main degradation product), was poorly retained in the column and was eluted under the test conditions with a lower retention time than atrazin (the first eluted of six reference substances). Its log Koc value was outside the limits of the method and below 1.5, namely 1.3 ± 0.004 corresponding to a Koc of 82.4 and therefore showing high soil mobility (McCall, 1980).
TEST FACILITY Unpublished report provided by notifier

Dissociation Constant pKa = 9.9

METHOD OECD TG 112 Dissociation Constants in Water.
Remarks The dissociation constant was determined by titration with 0.1 M NaOH. A constant of 1.26 x 10^{-10} was determined. The contribution of the dissociation of the main degradation product was not discussed. Test conducted in compliance with Good Laboratory Practice standards.
TEST FACILITY Unpublished report provided by notifier

Particle Size Not determined

Remarks The notifier reports that particles of < 600 µm are not expected. In addition, the notified chemical is imported as a component of a resin coated dishwasher tablet.

Flash Point Not determined

Remarks The notified chemical is a low volatility solid.

Flammability (Contact with Water) Does not evolve flammable gas

METHOD	EC Directive 92/69/EEC A.12 Flammability (Contact with Water).
Remarks	The notified chemical was placed in contact with water and the rate of evolution of gas was measured over a period of 7 hrs. No gas evolution was recorded. Test conducted in compliance with Good Laboratory Practice standards.
TEST FACILITY	Unpublished report provided by notifier

Autoignition Temperature > 400 ºC

METHOD	92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks	No self-ignition was observed up to a temperature of 400 ºC. Test conducted in compliance with Good Laboratory Practice standards.
TEST FACILITY	Unpublished report provided by notifier

Explosive Properties Not Explosive

METHOD	EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks	Explosive potential of the notified chemical was studied under heating, mechanical shock and friction conditions. Test conducted in compliance with Good Laboratory Practice standards. No explosion was recorded in any test.
TEST FACILITY	Unpublished report provided by notifier

Oxidizing Properties Not oxidising

METHOD	EC Directive 92/69/EEC A.17 Oxidizing Properties (Solids).
Remarks	Test conducted in compliance with Good Laboratory Practice standards. No flame propagation was observed in any mixture of notified chemical/cellulose. The notified chemical did not show oxidising properties under this test condition. However, organic peroxides are classified as Class 5.2 under the Australian Dangerous Good Codes (FORS, 1998)
TEST FACILITY	Unpublished report provided by notifier

Reactivity

Remarks	> 99% of the notified chemical is expected to be converted by means of hydrolysis to its main degradation product during the end use.

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Test Substance*	*Assessment Conclusion*
Rat, acute oral	notified chemical	low toxicity, LD50 2550 mg/kg bw/day
Rat, acute dermal	notified chemical	low toxicity, LD50 > 2000 mg/kg bw/day
Rat, acute inhalation	-	Not determined
Rabbit, skin irritation	notified chemical	non-irritating
Rabbit, eye irritation	notified chemical	severely irritating
Guinea pig, skin sensitisation – adjuvant test	notified chemical	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days days.	notified chemical	NOAEL100 mg/kg bw/day
Rat, repeat dose oral toxicity – 90 days.	notified chemical's main degradation product	NOAEL100 mg/kg bw/day
Genotoxicity – bacterial reverse mutation	notified chemical	non mutagenic
Genotoxicity – in vitro chromosome aberration test	notified chemical	non clastogenic
Genotoxicity – in vivo erythrocyte micronucleus test	notified chemical	non genotoxic
Genotoxicity – in vivo UDS test with mammalian liver cells	notified chemical	non genotoxic
Pharmacokinetic/Toxicokinetic studies	notified chemical/ notified chemical's main degradation product	Rapid breakdown in biological fluids and rapid excretion of metabolites mainly in the urine.
Developmental toxicity and reproductive effects	notified chemical's main degradation product	maternal NOAEL 50 mg/kg bw/day, foetal NOAEL 50 mg/kg bw/day
Reproductive toxicity – one generation study	notified chemical's main degradation product	F0 males NOAEL 100 mg/kg bw/day, F0 females NOAEL could not be established, LOAEL 50 mg/kg bw/day F1 generation NOAEL 50 mg/kg bw/day
Reproductive toxicity – one generation study	notified chemical's main degradation product	F0 female and F1 generation NOAEL 25 mg/kg bw/day

7.1. Acute toxicity – oral

TEST SUBSTANCE	Notified chemical
METHOD	In accordance with EEC guidelines-VI Amendment, Annex V, Directive 84/449/EEC.
Species/Strain	Rat/Sprague-Dawley
Vehicle	0.5% (w/v) methylcellulose water solution
Remarks - Method	No significant protocol deviations from OECD TG 401 Acute Oral Toxicity. Test conducted in compliance with the OECD principles of GLP.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5 per sex	1500	0
II	5 per sex	2000	0
III	5 per sex	2300	1 female

IV	5 per sex	2660	2 male, 5 female

LD50	2550 mg/kg bw (95% confidence limits)
Signs of Toxicity	Mortality: One female treated at 2,300 mg/kg was cannibalised on day 3. Two females treated at 2,660 mg/kg died on the day of administration (4 and 6 hours after the treatment). Two males and three females from the same treatment group died between day 2 and 3. Clinical signs (shallow breathing, piloerection, hypoactivity and hunched posture) observed at all dosage level starting from 30 minutes after the administration and lasting up to days 3-4 of the observation period. Ataxia and salivation were also noted at the two higher dosages. One animal treated at 2,660 mg/kg showed cyanosis, muscular tremors and palpebral closure on the treatment day. Another animal treated at 2,000 mg/kg showed red nasal discharge on day 2.
Effects in Organs	Congestion and erosion of the gastric mucosa, catarrhal content in the small intestine and lung congestion were observed in the rats that died before the end of the observation period. No appreciable finding was recorded during the gross pathology examination carried out at the end of the observation period on survived animals.
Remarks - Results	

CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Unpublished report provided by notifier

7.2. Acute toxicity – dermal

TEST SUBSTANCE	Notified chemical
METHOD	In accordance with EEC guidelines-VI Amendment, Annex V, Directive 84/449/EEC.
Species/Strain	Rat/Sprague Dawley
Vehicle	Test substance administered as supplied.
Type of dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations from OECD TG 402 Acute Dermal Toxicity – Limit Test. The moistening of the test substance in order to ensure good contact with the skin was not reported. Test conducted in compliance with the OECD principles of GLP.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
I	5 per sex	2000	0/10

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	No reactions were observed at the application site in any of the treated animals.
Signs of Toxicity - Systemic	There were no deaths or test substance-related clinical signs or remarkable body weight changes during the study period.
Effects in Organs	There were no remarkable necropsy findings.
Remarks - Results	

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

TEST FACILITY Unpublished report provided by notifier

7.3. Acute toxicity – inhalation

Not determined. Inhalation exposure to the notified chemical is not expected when it is used in the proposed manner.

7.4. Irritation – skin

TEST SUBSTANCE Notified chemical

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 84/449/EEC VI Amendment, Annex V, B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 males
Vehicle	Test substance moistened with saline.
Observation Period	72 hours
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations. Test conducted in compliance with the OECD principles of GLP.

RESULTS

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

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

Remarks - Results There were no deaths and no clinical signs or behavioural alterations noted. No signs of dermal irritation were observed.

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

TEST FACILITY Unpublished report provided by notifier

7.5. Irritation – eye

TEST SUBSTANCE Notified chemical

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 84/449/EEC VI Amendment, Annex V, B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3 males
Observation Period	21 days (animal 1), 7 days (animals 2 and 3)
Remarks - Method	No significant protocol deviations. Test conducted in compliance with the OECD principles of GLP. Sodium fluorescein was used to facilitate corneal observations. Due to humane reasons animals 2 and 3 were killed after the 7 day observation. Due to the difference in observation time and severity of reaction the individual results have been detailed below.

RESULTS

Lesion	*Mean Score**			*Maximum Value*			*Maximum Duration of Any Effect (days)*			*Maximum Value at End of Observation Period*		
Animal No.	1	2	3	1	2	3	1	2	3	1	2	3
Conjunctiva: redness	2	2	2	2	2	2	3–6	7	7	0	2	2
Conjunctiva: chemosis	2	3	3	3	3	3	7-13	7	7	0	3	3
Conjunctiva: discharge										-		
Corneal opacity	0.33	4	4	1	4	4	7-13	7	7	0	4	4
Iridial inflammation	1	**	**	1	**	**	3-6	7	7	0	**	**

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.
** iris not discernable

Remarks - Results

In animal 1, slight signs of epithelial defects were noted during examinations performed with sodium fluorescein.

In animals 2 and 3, at all the observation times the iris was not discernible owing to an irreversible severe corneal opacity. Corneal lesions were confirmed during examinations performed with sodium fluorescein.

CONCLUSION

The notified chemical is severely irritating to the eye.

TEST FACILITY

Unpublished report provided by notifier

7.6. Skin sensitisation

TEST SUBSTANCE

Notified chemical

METHOD

Skin Sensitisation – maximisation method of Magnusson and Kligman

Species/Strain

Guinea pig/Dunkin Hartley

PRELIMINARY STUDY

Maximum Non-irritating Concentration:
intradermal: not reported
topical: 100 % notified chemical

MAIN STUDY

Number of Animals

Test Group: 20 Control Group: 10

INDUCTION PHASE

Induction Concentration:
intradermal: 1% notified in paraffin oil
topical: Tested as supplied (undiluted)

Signs of Irritation

As the test compound did not show any irritating response in the preliminary test, 0.5 ml of 10 % sodium lauryl sulphate in vaseline were applied in animals from the treatment group before the topical induction phase. After the topical induction phase, slight necrosis and necrosis were observed in the control and treated animals, respectively.

CHALLENGE PHASE

1st challenge

topical: Tested as supplied (undiluted)

Remarks - Method

No significant protocol deviations from OECD TG 406 Skin Sensitisation – Magnusson and Kligman method. Test conducted in compliance with the OECD principles of GLP.

RESULTS

Animal	*Challenge Concentration*	*Number of Animals Showing Skin Reactions after:*			
		1st challenge		*2nd challenge*	
		24 h	*48 h*	*24 h*	*48 h*
Test Group	100 %	0/20	0/20	-	-
Control Group	100 %	0/10	0/10	-	-

Remarks - Results	There were no deaths or test substance-related clinical signs of toxicity or remarkable body weight changes during the study. There were no reactions indicative of sensitisation to the test substance following the challenge exposure.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Unpublished report provided by notifier

7.7.1. Repeat dose toxicity – 28-day Oral Toxicity Study in the Rat

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Sprague Dawley Crl:CD (SD) BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 28 days Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	0.5% (w/v) methylcellulose 400 cps water solution
Remarks - Method	Deviations from OECD TG 407: The weight of epididymis and thymus were not recorded. Test conducted in compliance with the OECD principles of GLP. Doses selected based on the results of a 14-day dose-range finding study where overt signs of toxicity were observed from 500 mg/kg bw/day and the NOEL was considered to be 100 mg/kg bw/day.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	10 per sex	0	0/20
II (low dose)	10 per sex	50	0/20
III (mid dose)	10 per sex	100	0/20
IV (high dose)	10 per sex	300	0/20

Mortality and Time to Death

No mortality was observed during the study.

Clinical Observations

Hypersalivation was observed in animals (2 male, 4 female) from group IV immediately after the treatment, mainly in the last week of dosing. No treatment-related signs were recorded in group II and III animals. Body weight and food consumption values for control and treated animals were considered to fall within a normal range. No abnormalities were observed during the ophtalmoscopic examinations.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical Chemistry

A biologically significant (but not statistically significant) increase in alkaline phosphatase levels was observed in group IV males (16%) and females (26%) when compare to controls. A statistically significant decrease in serum glutamic oxaloacetic transaminase (SGOT) levels was observed in group III (25%, $P< 0.01$) and group IV (27%, $p<0.01$) males and group III (21%, $P<0.01$) and group IV (27%, $p<0.01$) females when compared to controls. A significant increase in alpha 1 globulin levels was observed in group IV males (27%, $p< 0.01$) and a significant decrease in total cholesterol levels was observed in group IV females (23%, $p<0.01$) when compared to controls. All other statistically significant differences in treated animals compared to

controls were either not dose related, not biologically significant or individual values were within the norm.

Haematology
A statistically significant increase in the total leukocyte count (25%, $p<0.05$) was observed in group II females when compared to controls. A similar increase was not observed in group III and IV females. There were no other statistically significant findings observed in any of the haematology parameters evaluated.

Urinalysis
There were no significant findings in any of the parameters in any of the treated animals

Effects in Organs
Organ Weights
A statistically significant ($p<0.01$) increase in mean absolute and relative liver weight was observed in group IV males (13% (abs), 16% (rel)) and females (15% (abs), 11% (rel)). Relative and absolute kidney weights were found to statistically increase in males (10%, $p<0.01$) and females (11%, $p<0.01$) of the group IV, respectively. A statistically ($p<0.05$) but not biologically (<10%) significant increased kidney absolute weight was also observed in females from groups II and III. A biologically but not statistically significant increase in absolute and relative adrenal weight was noted in group IV females (15%) and males (11%) respectively.

Macrosopic Findings
The following findings in group IV animals were considered to be treatment related: focal slight thickening of the gastric non-glandular mucosa (4/10 males, 2/10 females) and increase in size of the liver (5/10 males, 1/10 female). All other changes were considered to be incidental as they were seen with the same frequency among treated and control animals or are commonly seen in rats of this strain and age.

Histopathology
In group IV animals, slight to moderate focal areas of hyperplasia with hyperkeratosis were observed in the gastric non-glandular mucosa of 5/10 males and 3/10 females, associated with degeneration in most of them. Slight mucous neck cell hyperplasia and increased vacuolation with parietal cell atrophy and degeneration were observed at the glandular mucosa level in 4-5/10 group IV males. No treatment-related changes were observed in group II and III animals and no treatment-related histopathological changes were observed in the livers and kidneys of animals from any treatment group.

Remarks – Results
Clinical Chemistry
Elevated SGOT levels may indicate liver damage, however a decrease in SGOT levels is not regarded as toxicologically significant. The increase in alkaline phosphatase, decrease in cholesterol and increase in globulin levels may indicate damaged liver cells, although no treatment-related histopathological changes were observed in the liver.

Organ weights
In the absence of histopathological changes, the increase in kidney and adrenal weight was not considered to be toxicologically significant. Although the increase in liver weight was not accompanied by histopathological changes, the observation of possibly associated variations in clinical chemistry parameters and in the absence of evidence of this being a metabolic adaptation, these changes were considered to be treatment related.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 100 mg/kg bw/day in this study, based on the treatment related effects on the liver and stomach observed at 300 mg/kg bw/day.

TEST FACILITY Unpublished report provided by notifier

In order to avoid the local effects observed in the stomach of administered animals, attributable to the peroxidic moiety of the notified chemical, the following study was carried out using the main degradation product of the notified chemical.

7.7.2. Repeat dose toxicity – 90-day Oral Toxicity Study in the Rat

TEST SUBSTANCE	Main degradation product of the notified chemical
METHOD	OECD TG 408 Repeated Dose 90-Day Oral Toxicity Study in Rodents.
Species/Strain	Rat/Sprague Dawley Crl:CD (SD) BR
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 90 days Dose regimen: 7 days per week Post-exposure observation period: 6 weeks
Vehicle	0.5% (w/v) methylcellulose 400 cps water solution
Remarks - Method	Deviations from protocol: – functional observations were not performed; – the epididymides were not weighed; Test conducted in compliance with the OECD principles of GLP.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	10/sex	0	0/20
II (low dose)	10/sex	50	0/20
III (mid dose)	10/sex	100	0/20
IV (high dose)	10/sex	300	0/20
V (control recovery)	10/sex	0	0/20
VI (high dose recovery)	10/sex	300	0/20

Mortality and Time to Death

No mortality was observed during the treatment and recovery period.

Clinical Observations

Episodes of salivation were observed in group IV and group VI animals generally within 20 minutes of administration, starting from the 4th week of treatment but not observed in the recovery period. An increased incidence of fur loss possibly caused by increased grooming was also observed in group IV and group VI animals during the second half of the treatment period with fur loss still evident in some animals during the recovery period.

A slight but not significant decrease (6%) in body weight gain over the 90 day treatment was recorded in males from group IV and group VI when compared with controls. The difference in body weight gain started from week 3-4 upwards but was not observed in the last two weeks of treatment. With the exception of the first week after treatment bodyweight gain in the recovery period was comparable for both treated and control males. Other than a significant increase (9%, $P<0.05$) in mean body weight (at day 90) in group III females, no differences in body weight and body weight gain was observed in treated females when compared to controls during the treatment and recovery period.

No adverse effects on food consumption and feed efficiency were observed in any of the treated animals when compare to controls. Slightly increased water consumption (~12% over the treatment period) was observed in group III, IV and VI animals in comparison to controls. No abnormalities were observed during the ophtalmoscopic examinations.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical Chemistry

The clinical chemistry parameters were measured at week 6 and week 12 during the treatment period. A number of significant differences between control and treated animals were noted with main findings summarised below:

- A dose-related decrease in SGOT activity, recorded in both sexes at week 6 and 12 of treatment. Effects achieved statistical significance in group IV males (only at week 6, 23%, $p <0.01$) and in group II (16%, $p <0.05$), III (24%, $p < 0.01$) and IV females (24%, $p < 0.01$) at week 6 and in group II (14%, $p <0.01$), III (18%, $p < 0.01$) and IV females (21%, $p < 0.01$) at week 12. No statistically significant

changes were observed at the end of the recovery period.

- A dose-related increase in lactic dehydrogenase (LDH) activity recorded at week 12 in both sexes. The effect achieved statistical significance in group III (46%, p <0.01) and group IV (90%, p <0.01) males and in group III (52%, p <0.01) and group IV (44%, p <0.01) females. No statistically significant changes were observed at the end of the recovery period.
- A dose-related increase in creatinine levels measured at week 6 in females only and at week 12 in males only. The effect achieved statistical significance at ≥ 100 mg/kg/day in both males (50%, p<0.01) and females (31%, p <0.01). No significant changes were observed after the recovery period.
- Total bilirubin was found to slightly increase (~30%, p <0.01) without dose-response relationship in males from all treated groups at week 12. A statistically significant increase was noted in group IV females (46%, p <0.01) at week 12. A statistically significant decrease was observed in group VI males at the end of the recovery period (23%, p <0.05), in comparison to control. No statistically significant changes were observed in females at the end of the recovery period.
- A reduction in total cholesterol was observed in group IV males at week 6 (25%, p <0.01) and week 12 (23%, not statistically significant) of treatment and in group IV females at week 6 (9%, not statistically significant) at week 12 (12%, not statistically significant). A reduction but not statistically significant was also observed in group VI males (19%) and females (12%) at the end of the recovery period.
- A dose related increase in urea reaching statistical significance in group IV males (16%, p <0.01) was observed at week 12. No statistically or biologically significant changes were observed at the end of the recovery period.
- An increase (but not dose related) in glucose levels was observed in group III and IV females at week 6 and week 12. Effects achieved statistical significance at week 12 in group III (28%, p <0.01) and group IV (15%, p< 0.01). A statistically significant increase was observed in group VI females (15%, p <0.01) at the end of the recovery period.
- An increase (but not statistically significant) in alkaline phosphatase levels was observed in group IV females at week 6 (31%) and week 12 (47%) when compared to controls. No similar increase was observed at the end of the recovery period.

Haematology

The haematological parameters were measured at week 6 and week 12 during the treatment period. Although statistically significant differences were noted in lymphocyte percentage in males and erythrocyte indices (mean corpuscular haemoglobin concentration, decreased mean corpuscular haemoglobin and haematocrit) in females, these changes were considered incidental as they were either not biologically significant, only observed at the 6-week or post recovery measurement or not dose related.

Urinalysis

A dose related increase in frequency of animals with positive results for bilirubin was observed in treated females with 8/10 and 5/10 group IV females testing positive at week 6 and week 12 respectively. No positive results were found in group VI females at the end of the recovery period. No other changes from control values were considered to have toxicological relevance.

Effects in Organs

Organ Weights

A statistically significant increase in relative liver weights was observed in group IV males (13%, p< 0.01) compared to controls with a similar increase but not statistically significant (10%) observed in group IV females. No biologically or statistically significant differences in group VI animals compared to controls was observed at the end of the recovery period.

A statistically significant increase in absolute and relative adrenal weight was observed in most treated female groups compared to controls as follows: group II ((20%, p<0.05, abs), (22%, p <0.01, rel)), group III ((29%, p<0.01, abs), (16%, rel)), group IV ((28%, p<0.05, abs), (29%, p <0.01, rel)). No biologically or statistically significant differences in group VI animals compared to controls was observed at the end of the recovery period.

Macroscopic Findings

There were no remarkable necropsy findings.

Histopathology
A dose-related increase in the frequency of centrilobular hypertrophy of the liver was observed in group III (4/10) and group IV (5/10) males. These changes were not observed in group VI males at the end of the recovery period. Slight hypertrophy of the zona glomerulosa of adrenal glands was observed in group II (3/10), group III (4/10) and group IV (4/10) females. The incidence of this effect in the treated females (1/10) was similar to that found in controls at the end of the recovery period.

Remarks – Results
Clinical Chemistry
With the exception of reduced total cholesterol values in both sexes and increased glucose levels in females, none of the differences observed in the clinical chemistry parameters during treatment were observed at the end of the recovery period.

Organ Weight
The increase in liver weight, correlated with the changes in clinical chemistry parameters possibly indicative of hepatotoxicity (increased LDH, increased bilirubin, decreased cholesterol, increased alkaline phosphatase) and minimal hepatocellular hypertrophy observed microscopically is considered to be potentially adverse, although as effects appeared to reverse during the recovery period these changes may represent a metabolic adaptation. As the increase in adrenal weight were reported to be still within the range of historical controls and did not correlate with the incidence of slight hypertrophy of the zona glomerulosa, and the incidence of slight hypertrophy were not dose related, this effect is considered incidental. In addition, no effects were seen at the end of the recovery period.

CONCLUSION
The No Observed Adverse Effect Level (NOAEL) was established as 100 mg/kg bw/day in this study, based on the effects on the liver observed at 300 mg/kg bw/day

TEST FACILITY	Unpublished report provided by notifier

7.8.1 Genotoxicity – bacteria

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 471 Bacterial Reverse Mutation Test. EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria. Plate incorporation procedure
Species/Strain	*S. typhimurium*: TA1538, TA1535, TA1537, TA98, TA100 *E. coli*: WP2uvrA
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver.
Concentration Range in Main Test	a) With metabolic activation: 10 - 5000 µg/plate b) Without metabolic activation: 1.0 – 333.3 µg/plate
Vehicle	Acetone
Remarks - Method	There were no significant deviations from the protocol other than the choice of positive controls. 2-Aminoanthracene was used as the sole indicator of the efficacy of the S9-mix. In the absence of activation, 4-nitro-o-phenylendiamine was used as the positive control for strains TA1537, TA1538 and TA98 and methyl methane sulphonate for strain WP2uvrA. Test conducted in compliance with GLP regulations. The preliminary cytotoxicity test was conducted on strains TA98, TA100 and WP2uvrA.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	33.3 (TA98), 100 (TA100), 333.3 (WP2uvrA)			
Test 1		33.3 (TA1535, TA98), 66.6 (TA1538, TA100), 100 (TA1537), 333.3 (WP2uvrA)	> 333.3	negative
Test 2		33.3 (TA1537, TA100), 66.6 (TA98, TA1535, TA1538), 333.3 (WP2uvrA)	> 333.3	negative
Present	1000 (TA100), 5000 (TA98, WP2uvrA)			
Test 1		1000 (TA1535, TA1537, TA1538 TA100), 5000 (TA98, WP2uvrA)	> 5000	negative
Test 2		1000 (TA1535, TA1537, TA98, TA100), 5000 (TA1538, WP2uvrA)	> 5000	negative

Remarks - Results

The test substance did not cause a reproducible dose-related increase in the number of revertants per plate of any of the tester strains either in the presence or absence of activation. Positive controls confirmed the sensitivity of the test system. Although for strain WP2uvrA the number of colonies was lower than the historical control ranges in Test 1, this is not considered to impact the outcome of the study

CONCLUSION

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

TEST FACILITY

Unpublished report provided by notifier

7.8.2 Genotoxicity – bacteria

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure and Pre incubation procedure

Species/Strain

S. typhimurium: TA1535, TA1537, TA98, TA100
E. coli: WP2uvrA

Metabolic Activation System

S9 fraction from Phenobarbital Na/β-Naphthoflavone induced rat liver.

Concentration Range in Main Test

Test 1
a) Without metabolic activation: 5-5000 µg/plate
b) With metabolic activation: 5-5000 µg/plate

Test 2
a) Without metabolic activation: 0.5-50 µg/plate

b) With metabolic activation: 1.5-150 µg/plate

Test 3
a) Without metabolic activation: 0.5-50 µg/plate
b) With metabolic activation: 1.5-150 µg/plate

Vehicle: Ethanol

Remarks - Method: There were no significant deviations from the protocol other than the choice of positive controls. In the absence of activation 2-Aminofluorene was used for strains TA98 and TA100. In the absence of activation, Hydrazine sulphate was used as the positive control for strain TA1535, Doxorubicine for strains TA98 and TA100 and methyl methane sulphonate for strain WP2uvrA.

Test conducted in compliance with the OECD principles of GLP.

Three independent tests were performed. The preliminary toxicity test was performed as part of test 1 using the plate incorporation method. Since there were fewer than five valid concentrations in test 1, this test was repeated using the plate incorporation method with a different concentration range. Test 3 was carried out using the plate incorporation method without metabolic activation and the pre-incubation method with metabolic activation.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	*Cytotoxicity in Preliminary Test**	*Cytotoxicity in Main Test**	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	50 (all strains)	See preliminary test	> 5000	negative
Test 2	-	50	> 50	negative
Test 3	-	50	> 50	negative
Present				
Test 1	150 (all strains)	See preliminary test	> 5000	negative
Test 2	-	150	> 150	negative
Test 3	-	150	> 150	negative

* see remarks

Remarks - Results: In the preliminary toxicity test, zero to very low colony growth and severe thinning of background lawn was observed in all strains tested at 50 and 150 µg/plate without and with metabolic activation, respectively. There was also less marked toxicity in all strains tested at 50 and 150 µg/plate, without and with metabolic activation, respectively, causing a decrease in colony growth and a slight decrease in background lawn. The toxicity observed in test 1 was confirmed in test 2 and 3.

The test substance did not cause a reproducible dose-related increase in the number of revertants per plate of any of the tester strains either in the presence or absence of activation. Positive controls confirmed the sensitivity of the test system. Negative controls were within historical limits.

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

TEST FACILITY: Unpublished report provided by notifier

7.9. Genotoxicity – in vitro

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
Species/Cell Type	Human Lymphocytes
Metabolic Activation System	S9 fraction from Aroclor 1254 induced rat liver.
Vehicle	Ethanol
Remarks - Method	No significant protocol deviations. Test conducted in compliance with the OECD principles of GLP

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	5*, 15*, 50*, 150*, 500*	24	24
Test 2	5, 15, 50, 150*, 500*	24	48
Present			
Test 1	5*, 15*, 50*, 150*, 500*	3	24
Test 2	5, 15, 50, 150*, 500*	24	48

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent	-			
Test 1	-	150/500*	> 500	negative
Test 2	-			negative
Present	-			
Test 1	-	150/500*	> 500	negative
Test 2	-			negative

* see remarks

Remarks - Results	In test 1, the suppression of the mitotic index was about 70%, both with and without activation at 500 µg/mL, while at 150 µg/mL, the suppression of the mitotic index was 22% and 32%, with and without activation, respectively. Due to the test substance cytotoxicity, it was possible to score only approximately 100 metaphases in the samples at 500 µg/mL in test 1 and at 150 µg/mL in test 2, both with and without metabolic activation. No metaphases could be analysed at 500 µg/mL in test 2, both with and without metabolic activation. In both tests, no statistically or biologically significant increases in the percentage of aberrant cells, above the vehicle control values, were recorded for any cultures treated with the test substance either with or without metabolic activation. Positive controls confirmed the sensitivity of the test system. Negative controls were within historical limits.
CONCLUSION	The notified chemical was not clastogenic to Human Lymphocytes treated in vitro under the conditions of the test.
TEST FACILITY	Unpublished report provided by notifier

7.10.1 Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 474 Mammalian Erythrocyte Micronucleus Test.
Species/Strain	Mouse/Crl:CD-1 (ICR) BR

Route of Administration	Oral – gavage
Vehicle	0.5% methylcellulose water solution
Remarks - Method	A preliminary toxicity test was carried out, in which 2 mice/sex/dose were administered with 500, 1000, 2000, 3000, 4000 and 5000 mg/kg bw by gavage. 4000 mg/kg was selected as the suitable dose for the main test on the basis of the severe clinical effects observed at the highest dose. Deviations from protocol The bone marrow was sampled 18 hours, 42 hours and 66 hours after treatment. The guidelines state that samples of bone marrow should be taken at least twice, starting not earlier than 24 hours after treatment, but not extending beyond 48 hours after treatment with appropriate interval(s) between samples. Test conducted in compliance with the OECD principles of GLP.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time Hours*
I (vehicle control)	15/sex	0	18, 42 and 66
II	15/sex	4000	18, 42 and 66
III (positive control, M)	5/sex	8	42

M=mitomycin C.

RESULTS

Doses Producing Toxicity	One female died on 16 hrs after the treatment although no evident signs of toxicity were identified at the autopsy. 4000 mg/kg did not induce any significant toxicity in the bone marrow, expressed as the ratio polychromatic/normochromatic erythrocytes. There was no decrease in ratio of polychromatic (PCE)/normochromatic erythrocytes (NCE) in the treated group indicating that the test substance was not toxic to the bone marrow.
Genotoxic Effects	The test substance did not induce a statistically significant increase in the frequency of micronucleated PCE over the levels observed in the vehicle control. Positive controls confirmed the sensitivity of the test system.
Remarks - Results	

CONCLUSION	The notified chemical was not clastogenic under the conditions of this in vivo erythrocyte micronucleus test.
TEST FACILITY	Unpublished report provided by notifier

7.10. Genotoxicity – in vivo

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 486 Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells in vivo.
Species/Strain	Rat/CDF Fischer 344
Route of Administration	Oral – gavage
Vehicle	0.5% (w/v) methylcellulose aqueous solution
Remarks - Method	There were no significant deviations from the protocol other than the choice of positive controls. Test conducted in compliance with the OECD principles of GLP. Four separate tests were conducted at each dose. In each test, two animals per groups were treated at the relevant dose. In test 1 and 3 the animals were sacrificed 2 hours after dosing. In test 2 and 4 the animals were sacrificed 16 hours after dosing.

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Sacrifice Time Hours*
I (vehicle control)	8 males*	0	2 and 16
II (low dose)	8 males*	500	2 and 16
III (mid dose)	8 males*	1000	2 and 16
IV (high dose)	8 males*	2000	2 and 16
V (positive control, Me)	4 males	300	2
V (positive control, AAF)	4 males	50	16

Me= Methyl methane sulphonate; AAF = 2-acetylaminofluorene.
* see remarks - method

RESULTS

Doses Producing Toxicity	At the doses tested no significant cytotoxic effect was observed on the slides.
Genotoxic Effects	The test substance did not induce a statistically significant increase in either the gross nuclear grain count or the net nuclear grain count (i.e. the gross nuclear grain count minus the cytoplasmic grain count) at any dose level at either sampling time. No difference was observed in the % of cells under repair in the treated groups in comparison to controls at any sampling time. Positive controls confirmed the sensitivity of the test system.
Remarks - Results	

CONCLUSION The notified chemical did not elicit any evidence of DNA-damage under the conditions of this in vivo UDS in rat liver cells test.

TEST FACILITY Unpublished report provided by notifier

7.11. Developmental toxicity

TEST SUBSTANCE Main degradation product of the notified chemical

METHOD In house – Teratogenisis study in rabbits

Species/Strain	Rabbit/New Zealand white
Route of Administration	Oral – gavage
Exposure Information	Exposure days: days 6-18 of gestation Dose regimen: daily Post exposure period: up to day 29 post mating.
Vehicle	0.5% (w/v) methylcellulose 400 cps water solution
Remarks - Method	Deviation from OECD 414 Teratogenicity • Dosing only occurred solely during the period of organogenesis (days 6-18) and not up to the day before termination. Test conducted in compliance with the OECD principles of GLP. In order to avoid the local effects in the stomach of administered animals, attributable to the peroxidic moiety of the notified chemical, the study was carried out using the main degradation product of the notified chemical.

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (vehicle control)	20	0	1
II (low dose)	20	50	1
III (mid dose)	20	100	2
IV (high dose)	20	300	1

Mortality and Time to Death

Five animals (one from group I (day 17), one from group II (day 19), two from group III (day 12 and day 24 and one from group IV (day 12)) died during the study. Based on the histopathology findings, the group II animal was considered to have died of acute pneumonia. Tubular dilatation atrophy and basophilia or cortical fibrosis and hepatocellular steatosis were observed in the dead group III and IV with centrilobular necrosis and degeneration in one group III animal. The causes of the death of the one control animal were not investigated but were contributed to wrong gavage. All deaths were considered as incidental, although it could be possible that treatment induced a worsening of effects.

Effects on Dams

A statistically significant and dose related decrease in bodyweight gain over the dosing period (day 6-19) (46% over study period) was observed in all treatment groups compared to controls (group II (50%, $p < 0.05$), group III (70%, $p < 0.01$) and group IV (lost bodyweight)). This decrease in bodyweight corresponded to a decrease in food consumption in these animals during this period. A similar trend was observed also for water intake.

Effects on Foetus

An increase in the incidence of does with early resorptions was observed in all treated groups (30-35%) compared to controls (8.33%). This included two does, one in group II and another in group III with only resorptions present. In addition, a statistically significant ($p < 0.01$) increase in the percentage of early resorptions (group total number of early resorptions/group total number of implantations) was observed in groups III (12%) and IV (11%) (even with the two cases of only resorptions excluded) .

The mean viable foetal weight of group IV was significantly lower (16%, $p < 0.01$) than the respective controls. No other effects were observed in litter parameters. No treatment-related malformations, anomalies and variants were observed at any tested dose.

Remarks - Results

The incidence of does with early resorptions and does with only resorptions was in the range of normal variability seen in this strain. The group mean number of early resorptions in group III and IV was also in the range of normal variability and the increase in the percentage of early resorption observed in group III and IV was considered to be due to a high individual value. Although in light of the increased post-implantation loss observed in the one-generation reproduction study in rats (see 7.12.1), this should be treated with caution.

CONCLUSION

The Maternal No Observed Adverse Effect Level (NOAEL) was established as 50 mg/kg bw/day in this study, based on significantly lower bodyweight gain and food and water intake observed at doses ≥ 100 mg/kg bw/day. The Foetal No Observed Adverse Effect Level (NOAEL) was established as 50 mg/kg bw/day in this study, based on the decreased foetal weight observed at 300 mg/kg bw/day and the possible treatment related increase in the number of early resorptions at doses ≥ 100 mg/kg bw/day. No evidence of teratogenic potential was indicated by this study.

TEST FACILITY Unpublished report provided by notifier

7.12.1 Toxicity to reproduction – one generation study

TEST SUBSTANCE Main degradation product of the notified chemical

METHOD OECD 415 One-Generation Reproduction Toxicity Study
Species/Strain Rat/ Crl:CD (SD) BR
Route of Administration Oral – gavage

Exposure Information	Exposure period - female: from 14 days prior the mating period to day 21 of lactation Exposure period - male: 70 days prior to the mating phase and throughout the mating period Dose regimen: 7 days per week;
Vehicle	0.5% (w/v) methylcellulose 400 cps water solution
Remarks – Method	No significant protocol deviations. Test conducted in compliance with the OECD principles of GLP. In order to avoid the local effects in the stomach of administered animals, attributable to the peroxidic moiety of the notified chemical, the study was carried out using the main degradation product of the notified chemical.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (vehicle control)	24/sex	0	1 male
II (low dose)	24/sex	50	0
III (mid dose)	24/sex	100	1 male
IV (high dose)	24/sex	300	1 male, 1 female

Mortality and Time to Death

There were no treatment related deaths. Three males (1 from group I, group III and group IV) died during the mating period due to erroneous gavage. A female from group IV died during the mating period owing to flooding of the cage.

Effects on Parental (P) animals:

Pre-mating period: An overall decrease in mean body weight gain (10%) of group IV males was observed in the pre-mating period, achieving statistical significance during week 1, 2 and 4 of treatment. Bodyweight gain in the second half of the pre-mating period was similar to controls. A statistically significant decrease in overall bodyweight gain was observed in group IV females (58%), with group III and IV females losing weight in the first week of treatment. Bodyweight gain in the second half of the pre-mating period was similar to controls. The decreased bodyweight gain appeared to correspond to a similar trend in decreased food consumption. No treatment related changes were observed in males sacrificed at the end of the mating period.

Pregnancy: A dose related decrease in mean bodyweight gain was noted in treated females, with a statistically significant decrease in group IV during days 7-14 (18%, $p < 0.05$) and in group III (13%, $p < 0.05$) and group IV (16%, $p < 0.01$) during days 14-20 of pregnancy. A statistically significant decreased food consumption (12-13%, $p < 0.01$) was still noted in group IV females in comparison to controls, limited to the first 2 weeks of pregnancy.

No treatment related differences were noted in oestrus cycle, mating and fertility indices. A dose related statistically significant ($p < 0.01$) longer pregnancy period was observed in all the treated females in comparison to controls, although the pregnancy duration was within historical control values in group II. There were no associated signs of dystocia or subsequent mortalities associated with the prolonged pregnancy period. A decreased mean number of implantations per litter was observed in group IV (10%) in comparison to controls.

Lactation period: The mean bodyweight of females from group IV continued to be statistically significantly lower than the control group, however, as there appeared to be no treatment related effects on bodyweight gain and food consumption during this period, this difference is considered to be due to earlier effects.

No treatment related findings were noted at the autopsy of F0 females at the end of the exposure period.

Effects on 1st Filial Generation (F1)

An increased (but not dose related) post implantation loss was observed in all treated animals (group II (11%, not significant), group III (18%, p <0.01) and group IV (14%, not significant) when compare to controls (8%). A decreased number of live born per litter (12-13%) was observed in group III and IV, in comparison to controls. In particular in group IV there was a significantly decreased (28%, p < 0.01) number of live males per litter. There were no significant treatment related effects on pup survival.

A significantly higher mean bodyweight (5-10%) was noted at birth and through weaning in group II and III males and females. This finding may be related to the longer pregnancy period of the treated groups, with no difference observed in group IV animals due to a counter decreased bodyweight treatment related effect. No treatment-related external abnormalities were observed in F1 pups. 2 cases of umbilical hernia, observed in 2/266 pups from group IV were considered as incidental, due to the low incidence and to the relatively common presence of this malformation in the selected rat strain. No other treatment-related finding was observed in F1. No important differences were noted in the mean time of vaginal opening and in the mean time of cleavage of the balanopreputial gland among the various experimental groups.

Remarks - Results

The post-implantation loss observed in group II was not significant, was within the range of historical controls and did not lead to a decreased number of live born per litter and therefore is considered to be incidental.

CONCLUSION

The NOAEL for F0 males was set at 100 mg/kg/day, due to the decreased bodyweight gain observed at 300 mg/kg/day.

No NOAEL could be established for F0 females, due to the elongation of the gestation period, although 50 mg/kg bw/day could be considered as the LOAEL (Low Observed Adverse Effect Level) as gestation length was still within historical controls and was the only effect observed at this dose.

50 mg/kg/day was considered as a NOAEL for the F1 generation, due to the significant increase in post implantation loss and decrease in number of live born per litter observed at doses ≥ 100 mg/kg bw/day.

TEST FACILITY	Unpublished report provided by notifier

7.12.2 Toxicity to reproduction – one generation study

TEST SUBSTANCE	Main degradation product of the notified chemical
METHOD	OECD 415 One-Generation Reproduction Toxicity Study
Species/Strain	Rat/ Crl:CD (SD) BR
Route of Administration	Oral – gavage
Exposure Information	Exposure period - female: from 14 days prior the mating period to day 21 of lactation Dose regimen: 7 days per week;
Vehicle	0.5% (w/v) methylcellulose 400 cps water solution
Remarks – Method	Only two treatment groups were used, however, this study was conducted as a follow-up to another one generation study (see 7.12.1). As a NOAEL effect level was established in the previous study for F0 males, only females were treated in this study. There were no other significant protocol deviations. Test conducted in compliance with the OECD principles of GLP. In order to avoid the local effects in the stomach of administered animals, attributable to the peroxidic moiety of the notified chemical, the study was carried out using the main degradation product of the notified chemical.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (vehicle control)	24 females	0	0
II (low dose)	24 females	12.5	0
III (high dose)	24 females	25	0

Mortality and Time to Death
No mortality was observed during the study.

Effects on Parental (P) animals:
Pre-mating period: A dose related (but not statistically significant), decrease in mean body weight gain of females from group II (20%) and III (40%) was recorded in the first week of treatment in comparison to controls. A complete recovery was observed starting from the second week of exposure. A slight decrease in food consumption (3-5%) was observed in the first week of exposure in females from both treatment group. No other treatment related findings were recorded.

Pregnancy: There were considered to be no treatment related effects to bodyweight gain and food consumption during the pregnancy period. No treatment related differences were noted in oestrus cycle, mating and fertility indices were observed. The length of pregnancy was similar between control and treated groups and there were considered to be no effects on the number of implantations and incidence of post implantation losses.

Lactation period: There were considered to be no treatment related effects to bodyweight gain and food consumption during the pregnancy period.

No treatment related findings were noted at the autopsy of F0 females at the end of the exposure period.

Effects on 1st Filial Generation (F1)
There were no external malformations in any experimental group. No differences were observed among the treatment groups and the controls with the number of implantations and incidence of post implantation losses, number of live born per litter and pup survival. No treatment-related differences were observed in the bodyweights of pups from both treatment groups in comparison to controls. No important differences were noted in the mean time of vaginal opening and in the mean time of cleavage of the balanopreputial gland among the various experimental groups.

Remarks - Results
Only a transient decrease in bodyweight gain of F0 females from group II and II was observed during the first week of the pre-mating period. Bodyweight gain was completely recovered afterwards and was not considered as a clearly adverse effect. No other treatment-related changes were observed in F0 animals.
No treatment-related effects were observed in the F1 generation.

CONCLUSION
The Maternal and Foetal No Observed Adverse Effect Level (NOAEL) was established as 25 mg/kg bw/day in this study, based on the absence of adverse treatment related effects.

TEST FACILITY Unpublished report provided by notifier

7.13.1 Pharmacokinetic/toxicokinetic

TEST SUBSTANCE Notified chemical

METHOD Fate in biological Fluids – in house

STUDY DESIGN AND OBJECTIVE
The study aimed to analyse the degradation of the notified chemical in biological fluids (stomach contents,

blood plasma and urine). The biological fluids were collected from a single Wistar rat. Solutions of the notified chemical were made with every biological fluid and their degradation was followed by means of HPLC analysis using UV detection.

In the following 'a solution of the notified chemical' and 'a solution of the notified chemical's main breakdown product' refers to 'a 0.1 g/L solution of the notified chemical and notified chemical's main breakdown product in 5% acetonitrile", respectively.

Urine: Fresh urine was collected and filtered. A solution of the notified chemical was prepared in filtered urine and an aliquot was injected into HPLC within one minute of dissolution. A second injection was carried out after 30 minutes. Control samples of filtered urine only and a solution of the notified chemical's main breakdown product in filtered urine were also analysed. Solutions of the notified chemical in diluted urine (1:10 and 1:100 in water) were also analysed. A time-course study of the notified chemical in 1% (v/v) urine in distilled water was carried out up to 24 hrs.

Stomach contents: Stomach contents were removed and collected from the rat at the sacrifice. A solution of the notified chemical was added at a level of 0.5 mL/g of stomach content. This solution was filtered and HPLC analyses were carried out within 5 minutes and 90 minutes after the solution preparation. Control samples of stomach contents in 5% aqueous acetonitrile solution and a filtered solution of the notified chemical's main breakdown product in an aqueous solution of stomach contents were also analysed. In addition, 10 µL of a solution of the notified chemical was added to a filtered solution of the notified chemical's main breakdown product in stomach contents. HPLC analyses of this solution were carried out immediately and after 60 minutes.

Blood plasma: Heart blood was collected and centrifuged to separate the plasma. A solution of the notified chemical in 1:10 phosphate buffered saline diluted plasma was prepared. HPLC analysis was carried out within 1 minute and 60 minutes after the solution preparation. Control samples of 10% plasma only and a solution of the notified chemical's main breakdown product in 10% plasma were also analysed. A solution of the notified chemical in 1% plasma was also analysed.

The notified chemical's stability at 37°C was also studied by analysing an incubated solution of the notified chemical at hourly intervals for 6 hours and after 24 hours.

RESULTS

At a concentration of 0.1 g/L notified chemical, no HPLC peak attributable to notified chemical was detected (the limit of detection of the method was estimated to be 5 µg/ml notified chemical) within 1 minute of contact with urine and plasma and within 5 minutes of contact with stomach contents. The half-life of the notified chemical was thus estimated to be less than 15 seconds in urine and plasma and less than 1.25 minutes in stomach contents. Due to the experimental procedures followed for the preparation of the stomach contents solution, the notified chemical's half-life in stomach contents was considered to be overestimated. The main degradation products of the notified chemical was identified by comparison with the control samples
No degradation of the notified chemical's main breakdown product was observed.

A slower degradation was observed for 0.1 g/l notified chemical in 5% acetonitrile in water at 37°C, in comparison to the rates observed in the presence of biological fluids. Accurate determination of the half-life could not be carried out because some hydrolysis had already occurred during the first HPLC run. A literature value of 9.5 hours was reported for the notified chemical in 1% acetonitrile (pH7) at 40 °C.

CONCLUSION

The notified chemical breaks down rapidly in biological fluids (urine, stomach contents and plasma) to one main degradation product. The main degradation product was shown to be stable under similar conditions.

TEST FACILITY Unpublished report provided by notifier

7.18.2 Pharmacokinetic/toxicokinetic

TEST SUBSTANCE Main degradation product of the notified chemical

METHOD Toxicokinetics in the rat after administration by gavage – in house

STUDY DESIGN AND OBJECTIVE
The toxicokinetics of the main degradation product of the notified chemical was tested rather than the notified chemical due to the rapid breakdown of the notified chemical in biological fluids.

Eight male and eight female CD rats were administered via gavage with approximately 2.56 mg ^{14}C-labelled test substance. Expired air, urine and faeces were collected/sampled as follows:
Urine: At 8, 24, 72 and 96 hours
Faeces: At 24, 48, 72 and 96 hours
Expired air: At 2, 4, 8 and 24 hours.

At 4, 8, 24, 48 and 96 hours one male and one female rat were weighed and sacrificed and prepared for whole body autoradiography (WBA). After 96 ours, heart blood was withdrawn from the remaining animals, whose carcasses were prepared for ^{14}C analysis.

Throughout the study ^{14}C activity was determined by liquid scintillation counting. Urine samples were analysed by TLC and HPLC for the detection of metabolites.

RESULTS
The ^{14}C was extensively and rapidly absorbed from the gut, then rapidly excreted. The major route of excretion was in the urine, with approximately 90 - 92 % (males - females) of the dose accounted for in 96 hours with the majority excreted in the first 24 hours. Excretion via the faeces in 96 hours accounted for another 8 - 5 % (males - females) of the dose. The majority of the faecal ^{14}C was in the first 24 hours in the male rats and in the 24 -72 hour period in the female rats. No exhalation of ^{14}C CO2 was detected and no radioactivity was detected in samples of circulating blood. Only 1-2% of the administered dose was present in the carcase after 96 hours. WBA showed similar tissue distribution. The tissues showing the highest levels of ^{14}C were those associated with the major routes of excretion (liver - including bile ducts, kidney, bladder and intestinal tract). Other tissues showing low levels of radioactivity were the lungs, heart, muscle, testis, nasal turbinates, salivary gland and brown fat. After 24 hours only low levels of radioactivity remained, being confined to the liver, kidney and intestine At 48 and 96 hours all the organs and tissues are at background levels indicating that there is not accumulation or retention of the chemical. Chromatographic analysis (HPLC and TLC) of urine showed there to be at least six products of metabolism of which two accounted for approximately 80% of total urinary ^{14}C. There did not appear to be any parent material present. The identity of the metabolism products was not established but they appeared to be the same as the test substance's degradation products in urine.

CONCLUSION
The test substance was rapidly and extensively absorbed from the intestinal tract, followed by rapid and virtually complete elimination within 24 hours.

TEST FACILITY Unpublished report provided by notifier

7.18.3 Pharmacokinetic/toxicokinetic

TEST SUBSTANCE Main degradation product of the notified chemical

METHOD Toxicokinetics in the rat after topical administration – in house

STUDY DESIGN AND OBJECTIVE
The toxicokinetics of the main degradation product of the notified chemical was tested rather than the notified chemical due to the rapid breakdown of the notified chemical in biological fluids.

Six female CD rats were topically treated with approximately 1.12mg (117 µg/cm^2) of test substance in 50 % ethanol and the treated site occluded (Group I). Six other females were similarly treated but a non-occlusive dressing was used (Group II). After 8 hours the treated sites of group II animals were rinsed and recovered with a non-occlusive dressing. After 48 hours all covering were removed (group I and II) and the test sites rinsed. Urine and faeces were collected/sampled from both groups as follows:
Urine: At 8, 24 and 48 hours

Faeces: At 24 and 48hours

Two rats from group I were weighed and sacrificed and prepared for whole body autoradiography. Heart blood was withdrawn from the remaining animals (group I and II), whose carcasses were prepared for ^{14}C analysis. The coverings were prepared for solvent extraction.

Throughout the study ^{14}C activity was determined by liquid scintillation counting. Urine samples and skin rinsings were analysed by TLC for the detection of metabolites.

RESULTS

Group I

Approximately 8.5% of the applied dose (9.9 µg/cm^2) was absorbed through the skin within 48 hours. Of this, approximately 84% was excreted in the urine, 7% in the faeces, with 8.5% being retained in the carcase. Blood levels were below the level of detection. Of the non-absorbed ^{14}C, approximately 69% was rinsed from the skin, with approximately 16% still associated with the skin. Over a 48 hour period approximately 4% of the applied dose had become transferred to the covering. The total recovery was approximately 97%.

The whole body autoradiogram demonstrated that only a very low level of ^{14}C labelled material was seen in the body confined to the kidney and intestinal contents.

Group II

Approximately 3.5% of the applied dose (4.1 µg/cm^2) was absorbed through the skin. Of this, approximately 82% was excreted in the urine, 8% in the faeces, with 6% being retained in the carcase. Blood levels were below the level of detection. Of the non-absorbed 14C, approximately 71% and 1% was rinsed from the skin after 8 hours and 48 hours, respectively, with approximately 13% still associated with the skin. Over a 48 hour period approximately 4% of the applied dose had become transferred to the covering. The total recovery was approximately 93%.

Metabolites

TLC of the 8 –24 hour urine of one rat showed there to be at least five metabolites (two major) present. The identity of the metabolism products was not established. TLC analysis of the skin rinsings showed that approximately 2% and 9% of the test substance had broken down on the skin surface under occlusive and non-occlusive conditions, respectively.

CONCLUSION

Under conditions of occlusion, penetration showed moderate levels of absorption equivalent to 9.9 µg/cm^2. Under more consumer-like conditions (non-occlusive dressing, skin rinsing after 8 hours), percutaneous absorption was reduced to a level of 4.1 µg/cm^2. Under both conditions, excretion was rapid and mainly in the urine. Tissue accumulation (very low levels) was confined to those tissues associated with excretion. Breakdown of the test substance on the skin was approximately five times greater under non-occlusive conditions than occlusive conditions.

TEST FACILITY	Unpublished report provided by notifier

7.18.4 Pharmacokinetic/toxicokinetic

TEST SUBSTANCE	Main degradation product of the notified chemical
METHOD	Toxicokinetics in the rat after administration by gavage (low/high dose) – in house

STUDY DESIGN AND OBJECTIVE

The toxicokinetics of the main degradation product of the notified chemical was tested rather than the notified chemical due to the rapid breakdown of the notified chemical in biological fluids.

Groups of five male CD rats were dosed by gavage with the test substance at a low dose level (approximately 12 mg/kg bw) or at a high dose level (approximately 172 mg/kg bw). Expired air, urine and faeces were collected/sampled as follows:
Urine: At 8, 24, 72 and 96 hours

Faeces: At 24, 48, 72 and 96 hour.

After 96 hours, heart blood was withdrawn from the remaining animals, whose carcasses were prepared for ^{14}C analysis.

Throughout the study ^{14}C activity was determined by liquid scintillation counting. Urine samples from each treatment group were analysed by TLC and HPLC for the detection of metabolites. HPLC analysis was also carried out on a solvent extraction of faeces from the high level dose group. GC-MS and ion mass spectrometry were used to identify the primary metabolites.

RESULTS
In both treatment groups excretion of ^{14}C was mainly via the urine with 80% (low dose group) and 68% (high dose group) being excreted in the first 24 hours. The rate of urinary excretion of ^{14}C was, however, different between the two groups.

	% of ^{14}C excreted in urine		
	0-8 hours	*8-24 hours*	*24–96 hours*
Low dose group	56	24	2
High dose group	17	51	12

Faecal excretion accounted for approximately 4% of the ^{14}C from the low level dose group and approximately 19% from the high level dose group with the majority excreted in the first 48 hours.

Blood levels were below the limit of detection and carcass levels were < 1% in both treatment groups.

HPLC analysis of the urine of both treated groups showed two major metabolites with several minor metabolites. No parent test substance was excreted in the urine or faeces. HPLC analysis of the faeces of the high dose group also indicate two major metabolites. The primary urinary metabolite was identified as the β-oxidation of the test substance and a second 'metabolite' as the hydrolysis product of this metabolite.

CONCLUSION
The test substance was extensively absorbed from the intestinal tract and excreted mainly in the urine. There was a slower rate of urinary excretion over the first 8 hours in the high dose treated animals. Metabolism was shown to be complete and via β-oxidation of the test substance.

TEST FACILITY Unpublished report provided by notifier

7.18.5 Pharmacokinetic/toxicokinetic

TEST SUBSTANCE Main degradation product of the notified chemical

METHOD Pharmacokinetics in the rat after single and repeated oral administration – in house

STUDY DESIGN AND OBJECTIVE
5 rats/sex/group (Crl:CD SD (BR) rats) were administered via gavage daily with 300 mg/kg/day unlabelled test substance for 14 consecutive days. A control group (5/sex) were treated with vehicle (0.5% methylcellulose) only. On day 15, both groups were dosed with a single dose of 300 mg/kg/day ^{14}C-labelled test substance. After the last dosage, urine samples were collected after 4 and 8 hours in the 1st day and daily for the following week. Faeces were collected daily for one week. Afterwards, all animals were sacrificed and blood, organs and tissues were collected. ^{14}C-content in organs and biological fluids was analysed by liquid scintillation counting. The number and the amount of metabolites were detected and measured by TLC in the urine samples.

RESULTS
The excretion study showed that excretion is predominantly (approximately 75-80%, both sexes) by the urinary route and occurs mainly (>90%) within 24 hours. Faecal excretion (13-16% males, 9-10% females) was considered complete within 48-72 hours of dosing. A very low rate of urinary excretion was still going on after 144-186h (0.3-0.5 % of the dose). Low (up to 0.02% of the dose), but still detectable ^{14}C-levels were measured

in plasma 168 hours after the last administration. Tissue levels were 0.1 to 1.3 times the plasma level. No significant differences between single and repeated dosing group was observed, either in excretion pattern or in tissue distribution or metabolism.

No parent test substance was present in the urine. In the 0 – 4 hour urine sample, a major metabolite (Rf 0.5: 50 – 60% of total radioactivity) was detected, together with a lesser metabolite (Rf 0.9: ca 20%); in the following 4 – 8 hour sample, the Rf 0.5 metabolite diminished to ca 20 – 30% and that of Rf 0.9 increased to 30 – 40%. Between 8 and 24 hours, the Rf 0.5 metabolite disappeared while that of Rf 0.9 increased further, accounting for 60 –80% of total urinary radioactivity.

CONCLUSION

The test substance was extensively absorbed from the intestinal tract and excreted mainly in the urine. Pre-feeding rats did not induce a change which affected the test substance's metabolism, disposition and excretion. No tissue accumulation was observed although the presence of plasma levels at 168 hours after dosing is an indication for slow release from a tissue compartment.

TEST FACILITY Unpublished report provided by notifier

8. ENVIRONMENT

8.1. Environmental fate

8.1.1.1 Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I).
Inoculum	Mixed Liquid Suspended Solids (Chemical Biotesting Centre, Inspection and Testing Institute, Japan)
Exposure Period	28 Days
Analytical Monitoring	TOC for analyse of DOC HPLC for analysis of test substance
Remarks - Method	The test substance was exposed to the activated sludge in a closed-system oxygen consumption measuring apparatus. Initial concentration of test substance was 100 mg/L. Initial concentration activated sludge concentration was 30 mg/L. Initial aniline concentration was 100 mg/L. Growth of sludge was observed in each sample containing activated sludge. The BOD was measured for 28 days, the DOC and residual test substance concentration was measured at the 28 day.

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	5.7	7	62
14	20.0	14	76
21	34.7	21	77
28	44.3	28	76

Remarks - Results	pH ranging from 6.7 7.1 was measured in the test substance samples exposed to inoculum. A pH 4.7 was measured in the test substance sample in pure water. The degree of degradability based on the residual test substance concentration was all over 99 %. The test substance was detected at concentration of 1 mg/L or less on samples containing activated sludge, and 94.5 mg/L in the control sample. The normal notified chemical peaks at retention time 5.9 and 6.9 min disappeared, and new peaks appeared at retention time 2.8 and 3.7 for each sample containing test substance and activated sludge. LC-MS analysis demonstrated that these new peaks were notified chemical degradation by-products and notified chemical sodium adducts. Sludge activity was satisfactory as the degradability of aniline, based on the BOD was 62% after 7 days. From the degradability results based on the BOD and DOC, it is concluded that the test substance was not readily biodegradable under the conditions of this test.
CONCLUSION	While 99% had degraded, the test substance was not ready biodegradable under the conditions of the test.
TEST FACILITY	Two unpublished reports provided by notifier

8.1.1.2 Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 301 B Ready Biodegradability: Modified Sturm Test.
Inoculum	Activated Sludge (Municipal sewage treatment plant of Hildesheim, Ge)
Exposure Period	28 Days
Analytical Monitoring	Titration with standardised HCl
Remarks - Method	Two concentrations were selected as appropriate: 10 and 20 mg/L. Because the test substance was not soluble at the test concentration, ultra sound dispersion had been used to achieve a good dispersion of the test material. Initial concentration Sodium Acetate concentration was 20 mg/L. Biodegradability was expressed as a percentage of theoretical CO_2. The amount of CO_2 produced by the test substance during the test was measured by titration and expressed as percentages of the theoretical CO_2 calculated from carbon content of the test substance. Non adapted activated sludge was used as study system.

Test substance			*Sodium Acetate*	
Day	*% Degradation 10 mg/L*	*% Degradation 20 mg/L*	*Day*	*% Degradation*
7	15	6	7	38
14	17	7	14	61
21	22	15	21	71
28	25	16	28	76

Remarks - Results	The total CO_2 evolution of the blank at the end of the test did not exceed 50 mg per 3 litres medium. The functional control gave a yield > 60% CO_2 within 28 days, verifying the test conditions.
CONCLUSION	The test substance was not considered readily biodegradable.
TEST FACILITY	Unpublished report provided by notifier

8.1.1.3 Ready biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	Based on OECD TG 301 B Ready Biodegradability: Sealed Vessel Test for CO_2 production.
Inoculum	Activated Sludge (non-adapted secondary effluent of a sludge treatment plant at URL North, UK)
Exposure Period	28 Days
Analytical Monitoring	Ionic 555 Inorganic Carbon Analyser
Remarks - Method	Recent studies conducted by OECD aimed at harmonising the various tests for ready biodegradability also was used. The test used was the sealed vessel test which is suitable for determining the ready and ultimate biodegradability of organic substances. The notified chemical organic carbon concentration was 3.0 mg/L. Sodium Benzoate organic carbon concentration was 10.03 mg/L The pH of the solution was not adjusted to 7 – 8 since it was a working solution containing such a small quantity of test material (0.006 mg/L) that the addition of NaOH may have resulted in overshooting the required pH and therefore altering the sample irreversible. The inoculum used was 10% by volume of activated sludge plant secondary effluent. The level of dissolved inorganic carbon was reduced by sparging the filtered effluent with nitrogen after prior adjustment of the pH to 6.5. Analysis of both the headspace gas and the liquid medium for CO_2 and

DIC was measured respectively in each sample.

Test substance		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	4	7	97
14	23	14	93
21	71	21	96
28	70	28	96

Remarks - Results: Sodium benzoate was rapidly biodegraded and it achieved the 60% pass level by the first analysis point (3 days) confirming the suitability of the inoculum and culture conditions. NOTIFIED CHEMICAL achieved 69.9% biodegradation after 28 days and passed the 10 days window criterion of > 60% within 10 days of reaching 10% degradation. Therefore it can be classified as being readily and ultimately biodegradable.

CONCLUSION: The test substance was considered readily biodegradable, based on the test conditions.

TEST FACILITY: Unpublished report provided by notifier

8.1.1.4 Ready biodegradability

TEST SUBSTANCE: Main degradation product of the notified chemical

METHOD: OECD TG 301 B Ready Biodegradability: Modified Sturm Test.
Inoculum: Activated Sludge (Municipal sewage treatment plant of Hildesheim, Ge)
Exposure Period: 28 Days
Analytical Monitoring: Titration with standardised HCl - CO_2 evolution
Remarks - Method: Two concentrations were selected as appropriate: 10 and 20 mg/L. Because the test substance was not soluble at the test concentration, ultra sound dispersion had been used to achieve a good dispersion of the test material.
Biodegradability was expressed as a percentage of theoretical CO_2. The amount of CO_2 produced by the test substance during the test was measured by titration and expressed as percentages of the theoretical CO_2 calculated from carbon content of the test substance.
Non adapted activated sludge was used as study system.

Test substance			*Sodium Acetate*	
Day	*% Degradation 10 mg/L*	*% Degradation 20 mg/L*	*Day*	*% Degradation*
7	14	10	7	66
14	22	32	14	89
21	36	42	21	99
28	85	67	28	100

Remarks - Results: The total CO_2 evolution of the blank at the end of the test did not exceed 50 mg per 3 litres medium. The functional control gave a yield > 60% CO_2 within 28 days

CONCLUSION: The test substance was considered readily biodegradable after an adaptation phase of 11 days. However, the 10 days window criterion was not met.

TEST FACILITY: Unpublished report provided by notifier

8.1.1.5 Ready biodegradability

TEST SUBSTANCE	Main degradation product of the notified chemical
METHOD	Based on OECD TG 301 B Ready Biodegradability: Sealed Vessel Test for CO_2 production.
Inoculum	Activated Sludge (non-adapted secondary effluent of a sludge treatment plant at URL North, UK)
Exposure Period	28 Days
Analytical Monitoring	Ionic 555 Inorganic Carbon Analyser
Remarks - Method	Recent studies conducted by OECD aimed at harmonising the various tests for ready biodegradability also was used. The test used was the sealed vessel test which is suitable for determining the ready and ultimate biodegradability of organic substances. The test substance organic carbon concentration was 3.03 mg/L. Sodium benzoate organic carbon concentration was 10.03 mg/L The pH of the solution was adjusted to 7 – 8 by the addition of 1 M NaOH. The inoculum used was 10% by volume of activated sludge plant secondary effluent. The level of dissolved inorganic carbon was reduced by sparging the filtered effluent with nitrogen after prior adjustment of the pH to 6.5. Analysis of both the headspace gas and the liquid medium for CO_2 and DIC was measured respectively in each sample.

Test substance		*Sodium Benzoate*	
Day	*% Degradation*	*Day*	*% Degradation*
7	20	7	97
14	100	14	93
21	114	21	96
28	101	28	96

Remarks - Results	Sodium benzoate was rapidly biodegraded and it achieved the 60% pass level by the first analysis point (3 days) confirming the suitability of the inoculum and culture conditions. The test substance achieved 101.0% biodegradation after 28 days and passed the 10 days window criterion of > 60% within 10 days of reaching 10% degradation. Therefore can be classified as being readily and ultimately biodegradable.
CONCLUSION	The test substance was considered readily biodegradable based on test conditions.
TEST FACILITY	Unpublished report provided by notifier

8.1.2.1 Inherent biodegradability

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 302C, Inherent Biodegradability. Modified MITI Test (II)
Inoculum	Mixed Liquid Suspended Solids (Chemical Biotesting Centre, Inspection and Testing Institute, Japan)
Exposure Period	28 days
Analytical Monitoring	TOC for analysed of DOC HPLC for analysed of residual test substance
Remarks – Method	The test substance was exposed to the activated sludge in a closed-system oxygen consumption measuring apparatus. Initial concentration of test substance was 30 mg/L. Initial concentration activated sludge concentration on samples containing test substance was 100 mg/L.

Initial concentration aniline concentration was 100 mg/L.
Growth of sludge was observed in each sample containing activated sludge.
The BOD was measured for 28 days, the DOC and residual test substance concentration was measured at 28 days.
A sample containing the test substance in pure water was included to estimate the parallel abiotic degradation.

RESULTS

Test substance		*Aniline*	
Day	*% Degradation*	*Day*	*% Degradation*
7	25	7	56
14	91	14	68
21	96	21	69
28	92	28	70

Remarks – Results: Sludge activity was satisfactory as the degradability of aniline, based on the BOD was 56% after 7 days.
From the degradability results based on the BOD and DOC, it is concluded that the test substance was inherently biodegradable under the conditions of this test.

CONCLUSION: The test substance was inherent biodegradable under the conditions of this test.

TEST FACILITY: Unpublished report provided by notifier

8.1.2.2. Inherent biodegradability

TEST SUBSTANCE: Main degradation product of the notified chemical

METHOD: OECD TG 302A, Inherent Biodegradability. Modified Semi-continuous Activated Sludge

Inoculum: Unacclimatised Activated Sludge (non-adapted secondary effluent of a sludge treatment plant at URL North, UK)

Exposure Period: 83 days

Analytical Monitoring: Organic Carbon Analyser

Remarks – Method: Acclimatization of the microorganisms to the test chemical was done for up to 3 months.
The test substance initial concentration was 31.7 mg/L (equivalent to 21.7 mg/L of organic carbon).
The water solubility of the free acid was low, and suitable stock solution could not be prepared. To overcome the problem the test chemical was converted to the sodium salt during solution preparation. It was assumed that the sodium salt, like the free acid is stable in aqueous solution.
The effluent dissolved organic carbon levels were determined over the 12 week test period.

RESULTS

Day	*Control 1*	*Control 2*	*Control Mean*	*Test Item*	*Mean Control - Test item*	*% Removal*
1	10.6	11.0	10.8	27.4	16.6	76.5
8	9.1	9.7	9.4	23.3	13.9	64.1
13	8.7	9.3	9.0	16	7.0	32.3
16	8.0	8.6	8.3	9.5	1.2	5.5
27	9.0	9.3	9.2	10.4	1.3	5.8
43	7.1	7.2	7.2	7.9	0.8	3.5

55	7.4	7.4	7.4	7.8	0.4	1.8
62	6.8	7.0	6.9	10.2	3.3	15.2
78	7.5	7.5	7.5	7.3	-0.2	-0.9
83	6.7	6.9	6.8	6.7	-0.1	-0.5

Remarks – Results: Over the first week of the test the removal of the test substance was poor but by the end of the second week it began to steadily improve. Taking the calculation period from 3 weeks onward, 95% confidence limits for the improve removal were 95.5 to 102.1 per cent. The report concludes the test material may be classed as being inherently, ultimately biodegradable and on the basis of this results, there is no evidence that any water soluble residue is formed.

CONCLUSION: The test substance was inherently biodegradable under the conditions of this test.

TEST FACILITY: Unpublished report provided by notifier

8.1.3. Bioaccumulation

No bioaccumulation study is available.

The notified chemical and its main degradation product can be regard as low bioaccumulative chemicals, by considering the following points:

- The fat solubility of THE NOTIFIED CHEMICAL at 37^0C was determined by Hoechst (1992a) by HPLC analysis. An average low solubility was (693 mg/100 g fat) observed.
- Low log Kow of 2.2 and 2.0 were determined for the notified chemical and its main degradation product, respectively.
- A bioconcentration factor of 9.86 was estimated for THE NOTIFIED CHEMICAL by BCF program v2.15 (EPIWIN, US EPA).

8.2. Ecotoxicological investigations

8.2.1.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 203 Fish, Acute Toxicity Test –semi static test

Species	Zebrafish, *Brachydanio rerio*
Exposure Period	96 hours
Auxiliary Solvent	0.01% methylcellulose
Water Hardness	50 mg $CaCO_3$/L
Analytical Monitoring	HPLC-UV/Vis

Remarks – Method: One group of 20 animals was treated only with water (negative control).
One group of 20 animals was treated with 0.01% methylcellulose water solution (vehicle control group).
Groups of 10 animals were treated with the notified chemical.
Treatment solutions were changed every 24 hours over a period of 96 hours. Animals were inspected every 24 hours. pH, temperature and dissolved oxygen of the test solution were monitored at each time point, before and after solution renewal.

RESULTS

Concentration mg/L		*Number of Fish*				
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
0.0		20	0	0	0	0
0.1	0.093	10	0	0	0	0

0.17		10	0	0	0	1
0.31		10	0	0	2	3
0.53		10	1	4	5	6
0.90	0.882	10	9	10	10	10

LC50 0.7 mg/L at 24 hours.
0.5 mg/L at 72 hours.
0.4 mg/L at 96 hours.
NOEC 0.1 mg/L at 96 hours.
Remarks – Results At all concentration before dying fish showed severe redness of the gills.
The NOTIFIED CHEMICAL actual concentration was calculated for 0.1 and 0.9 mg/L at 0 hours and 24 hours only.
In the analysis negligible notified chemical decomposition takes place in the column in concentrated solutions, while very dilute solutions the decomposition is quite significant. However, the sum concentrations detected for the notified chemical and its main degradation product correspond to that of the notified chemical initially injected.
The highest concentration causing no mortality was 0.1 mg/L, the lowest concentration causing 100% mortality was 0.9 mg/L. No animal died either in the negative control or in the control vehicle group.

CONCLUSION The notified chemical is very toxic to *Brachydanio rerio* (United Nations, 2003).

TEST FACILITY Unpublished report provided by notifier

8.2.1.2. Acute toxicity to fish

TEST SUBSTANCE Notified chemical

METHOD OECD TG 203 Fish, Acute Toxicity Test – semi static test
Species Zebrafish, *Brachydanio rerio*
Exposure Period 96 hours
Auxiliary Solvent methylcellulose
Water Hardness 245 mg $CaCO_3$/L
Analytical Monitoring
Remarks – Method One group of 7 animals was treated only with water (negative control).
One group of 7 animals was treated with 0.01% methylcellulose water solution (vehicle control group).
Groups of 7 animals were treated with notified chemical.
The notified chemical actual concentration was not determined.
Treatment solutions were changed every 24 hours over a period of 96 hours. Animals were inspected every 24 hours. pH, temperature and dissolved oxygen of the test solution were monitored at each time point, before and after solution renewal.

RESULTS

Concentration mg/L		*Number of Fish*				
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
0.0		14	0	0	0	0
0.1		7	0	0	0	0
0.17		7	0	0	0	0
0.31		7	0	1	1	1
0.53		7	0	0	0	1
0.90		7	6	7	7	7

LC50 0.7 mg/L at 24 hours.
0.6 mg/L at 96 hours.
NOEC 0.17 mg/L at 96 hours.

Remarks – Results	No animal in the control and positive control groups showed visible signs of abnormalities. Six animals in the group treated at 0.31 mg/L at 72 hours, all the animals in the group treated at 0.53 mg/L and one animal treated at 0.90 mg/L at 24 hours showed signs of reduced escape reflex. No animal in the control and positive control groups died. Six animals in the group treated at 0.90 mg/L died at 24 hours, the last one died in this group died at 48 hours. One animal in the group treated at 0.31 mg/L died at 48 hours. One animal in the group treated at 0.53 mg/L died at 96 hours.
CONCLUSION	The notified chemical is very toxic to *Brachydanio rerio* (United Nations, 2003)
TEST FACILITY	Unpublished report provided by notifier

8.2.1.3. Acute toxicity to fish

TEST SUBSTANCE	Main degradation product of the notified chemical
METHOD	OECD TG 203 Fish, Acute Toxicity Test – semi static test
Species	Zebrafish, *Brachydanio rerio*
Exposure Period	96 hours
Auxiliary Solvent	0.01% methylcellulose
Water Hardness	50 mg $CaCO_3$/L
Analytical Monitoring	HPLC
Remarks – Method	One group of 10 animals was treated only with water (negative control). One group of 10 animals was treated with 0.01% methylcellulose water solution (vehicle control group). Groups of 10 animals were treated with the test substance. The actual concentration of the test substance was calculated at 0 hours and 24 hours only.

RESULTS

Concentration mg/L		*Number of Fish*				
Nominal	*Actual*		*24 h*	*48 h*	*72 h*	*96 h*
0		20	0	0	0	0
500	485	10	0	0	0	0

LC50	> 500 mg/L at 96 hours.
NOEC (or LOEC)	500 mg/L at 96 hours.
Remarks – Results	No animal showed abnormalities and no animal died in any group. The LC_{50} was not calculated and was estimated to be higher than 500 mg/L.
CONCLUSION	The main degradation product of the notified chemical was found not to be toxic to fish up to a nominal 500 mg/L.
TEST FACILITY	Unpublished report provided by notifier

8.2.2.1. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – static.
Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	0.01% methylcellulose

Water Hardness	Not stated
Analytical Monitoring	HPLC-UV-Vis
Remarks - Method	One group of 20 animals was treated only with water (negative control). One group of 20 animals was treated with 0.01% methylcellulose water solution (vehicle control group). Groups of 20 animals were treated with THE NOTIFIED CHEMICAL. A stock solution was prepared by suspending a weighed amount of test article with 0.01% methylcellulose water solution in order to obtain a concentration of 50 mg/L. Suitable volumes of this solution were then diluted with water in order to obtain the concentrations of 8.9, 13.3, 20, 30, and 45 mg/L. The actual concentration of the notified chemical was calculated for 8.9 and 45 mg/L at 0 hours and 48 hours only. Animals were inspected at 24 and 48 hours. pH, temperature and dissolved oxygen of the test solution were monitored at the beginning and at the end of the exposure.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0.0		40	0	0
8.9	8.8	20	0	0
13.3		20	3	7
20		20	7	11
30		20	10	18
45	44.9	20	20	20

LC50	24.8 mg/L at 24 hours (95% c.l. 21.5-28.7) 17.6 mg/L at 48 hours (95% c.l. 15.5-20.0)
NOEC	8.9 mg/L at 48 hours
Remarks - Results	In the analysis negligible notified chemical decomposition takes place in the column in concentrated solutions, while very dilute solutions the decomposition is quite significant. However, the sum concentrations detected for the notified chemical and its main degradation product correspond to that of the notified chemical initially injected. The highest concentration causing no mortality was 8.9 mg/L, the lowest concentration causing 100% mortality was 45 mg/L. No animal died either in the negative control or in the control vehicle group.

CONCLUSION The notified chemical is harmful to *Daphnia magna* (United Nations, 2003).

TEST FACILITY Unpublished report provided by notifier

8.2.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Main degradation product of the notified chemical

METHOD OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	0.01% methylcellulose
Water Hardness	Not stated
Analytical Monitoring	HPLC-UV-Vis
Remarks - Method	One group of 20 animals was treated only with water (negative control). One group of 20 animals was treated with 0.01% methylcellulose water solution (vehicle control group). Groups of 20 animals were treated with the test substance.

The actual concentration of the test substance was calculated at 0 hours and 48 hours only.
Animals were inspected at 24 and 48 hours.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0		40	0	0
500	500	20	0	0

LC50 > 500 mg/L at 48 hours.
NOEC 500 mg/L at 48 hours.
Remarks - Results No animal of the group treated at 500 mg/L was immobilized. No animal of the negative group neither of the vehicle control group was immobilized. The LC_{50} was not calculated and was estimated to be higher than 500 mg/L.

CONCLUSION The main degradation product of the notified chemical was found not to be toxic to *Daphnia magna* up to a nominal 500 mg/L.

TEST FACILITY Unpublished report provided by notifier

8.2.3.1. Algal growth inhibition test

TEST SUBSTANCE Notified chemical

METHOD OECD TG 201 Alga, Growth Inhibition Test.
Species *Selenastrum capricornutum*
Exposure Period 72 hours
Concentration Range Nominal: 1, 1.8, 3.2, 5.6 and 10 mg/L
Actual: not determined
Water Hardness 40 mg $CaCO_3$/L
Remarks - Method Initial cell concentration was 10^4 cell/mL. Microscope with counting chamber was used to determine cell concentration.
One control only with algal growing medium was tested.
The actual concentration of the notified chemical was calculated at 0 hours and 24 hours only.

RESULTS

Biomass		*Growth*	
E_bC50 (95% CL) mg/L (0-24 h)	*NOEC* mg/L	*$E_\mu C50$ (95% CL)* mg/L (0-24 h)	*NOEC* mg/L
2.23 (2.09-2.38)	1	3.17 (2.97-3.48)	1

Biomass		*Growth*	
E_bC50 (95% CL) mg/L (24-48 h)	*NOEC* mg/L	*$E_\mu C50$ (95% CL)* mg/L (24-48 h)	*NOEC* mg/L
1.24 (1.01-1.38)	<1	3.66 (3.31-4.10)	<1

Biomass		*Growth*	
E_bC50 (95% CL) mg/L (48-72 h)	*NOEC* mg/L	*$E_\mu C50$ (95% CL)* mg/L (48-72 h)	*NOEC* mg/L
1.33 (1.15-1.44)	<1	3.15 (2.93-3.59)	<1

Remarks - Results	No growth rate inhibition was observed on the control sample up to 72 hours. E_bC50 at 24, 48, 72 hours were 2.23, 1.24 and 1.33 mg/L respectively. E_uC50 at 24, 48, 72 hours were 3.17, 3.66 and 3.15 mg/L respectively. $NOEC_b$ at 24, 48, 72 hours were 1, <1, <1 mg/L respectively. $NOEC_\mu$ at 24, 48, 72 hours were 1, <1, <1 mg/L respectively.
CONCLUSION	The notified chemical is harmful to algal cells (United Nations, 2003).
TEST FACILITY	Unpublished report provided by notifier

8.2.3.2. Algal growth inhibition test

TEST SUBSTANCE	Main degradation product of the notified chemical
METHOD	OECD TG 201 Alga, Growth Inhibition Test.
Species	*Selenastrum capricornutum*
Exposure Period	96 hours
Concentration Range	Nominal: 32, 56, 100, 180 and 320 mg/L Actual: 0.2, 0, 39.1, 90.2, and 225 mg/L
Water Hardness	Not reported
Analytical Monitoring	HPLC
Remarks - Method	Concentration of the test substance in samples taken from each test concentration were analysed at 0 and 96 hours. Analysis at 0 hours indicated a mean measured concentration of 90% (range 87 to 94%) of nominal. At 96 hours mean measured concentration had fallen, on overage, to 36% (range 0 to 79%) of 0 hours measured concentration.

RESULTS

Biomass		*Growth*	
E_bC50 (95% CL) mg/L (0-24 h)	*NOEC* mg/L	*$E_\mu C50$ (95% CL)* mg/L (0-24 h)	*NOEC* mg/L
180 (130-270)		280 (200-480)	

Biomass		*Growth*	
E_bC50 (95% CL) mg/L (24-48 h)	*NOEC* mg/L	*$E_\mu C50$ (95% CL)* mg/L (24-48 h)	*NOEC* mg/L
150 (120-210)		290 (200-540)	

Biomass		*Growth*	
E_bC50 (95% CL) mg/L (48-72 h)	*NOEC* mg/L	*$E_\mu C50$ (95% CL)* mg/L (48-72 h)	*NOEC* mg/L
140 (110-180)		>320	

Biomass		*Growth*	
E_bC50 (95% CL) mg/L (72-96 h)	*NOEC* mg/L	*$E_\mu C50$ (95% CL)* mg/L (72-96 h)	*NOEC* mg/L
130 (110-150)	56	>320	

Remarks - Results	There was a 414 fold mean increase in the cell density of control cultures over 96 hours. The control growth was therefore qualitatively acceptable. Since the concentrations decreases substantially during the 96 hour exposure period, effect concentrations based on nominal concentrations (as given above) are probably an underestimate of the toxicity of the substance. A more relevant assessment would be base the effect on mean measured concentrations. Although in this test assessment is limited

	because the two lowest concentrations had fallen to zero, it is considered acceptable since inhibition of growth was probably only significant at 100 mg/L and above. Based on mean measured concentrations the 96 hour EC50s are 79 mg/L (95% fiducial limits 65 to 97 mg/L) for biomass and >256 mg/L for growth rate. The 96 hour NOEC was 25 mg/L also using mean measured values.
CONCLUSION	The main degradation product of the notified chemical is harmful to algal cells (United Nations, 2003).
TEST FACILITY	Unpublished report provided by notifier

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 209 Activated Sludge, Respiration Inhibition Test. EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test
Inoculum	Activated Sludge (Municipal sewage treatment plant of Hildesheim, Ge)
Concentration Range	Nominal: 10 to 100 mg/L
Remarks – Method	The results of a respiration inhibition test, carried out as part of a biodegradation study, are reported in the ready biodegradability study (Noack, 1992a). No details of the test conduct are reported.
RESULTS	
NOEC	10 mg/L
Remarks – Results	0% and 39% of inhibition were observed for the notified chemical at 10 and 100 mg/L, respectively.
CONCLUSION	The notified chemical at 100 mg/L moderately inhibited the microbial activity. No inhibition was observed at 10 mg/L.
TEST FACILITY	Unpublished report provided by notifier

8.2.5. Acute study in earthworm

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 207 Earthworms, Acute toxicity test
Species	*Eisenia foetida*
Exposure Period	14 days
Remarks – Method	The actual concentration of the notified chemical was not calculated. The study was performed on *Eisenia foetida*. 40 animals were subjected to single exposure to nominal concentrations and observed for the following 14 days. The animals were observed on day 7 and 14 and mortality and other visible behavioural or pathological signs were reported. Bodyweight was measured on day 0 and 14. LC50 was calculated at day 7 and 14.

RESULTS

Concentration mg/kg		*Number of Earthworms*		
Nominal	*Actual*		*7 days*	*14 days*
0		40	1	1
200		40	0	8

300	40	5	10
447	40	9	15
668	40	19	28
1000	40	37	40

LC50	619.8 mg/kg at 7 days. 491.7 mg/kg at 14 days
LOEC	200 mg/kg at 14 days
Remarks – Results	No animals of control group showed visible signs of abnormalities. The LC_{50} at 7 days was 619.82 mg/kg (95% confidence limit 556.81 – 689.96) and at 14 days was 491.69 mg/kg (95% confidence limit 417.95 – 578.43)
CONCLUSION	The notified chemical is slightly toxic to *Eisenia foetida* (Mensink, 1995).
TEST FACILITY	Unpublished report provided by notifier

8.2.6. Terrestrial plant growth

TEST SUBSTANCE	Notified chemical
METHOD	OECD TG 208, Terrestrial plant growth test
Species	*Oat, lettuce, turnip*
Exposure Period	14 days
Remarks – Method	The number of seedlings emerging from the soil surface was counted and recorded from the day when the first seedling appeared until the day when no more seedlings appeared. Seeds of each species were sown in treated soil. Their germination was observed until 50% of the seeds of control group had germinated, and then their growth was monitored for 14 days.
RESULTS	
LC50	> 100 mg/kg at 14 days
LOEC	> 100 mg/kg at 14 days
Remarks – Results	The results examined with Dunnett's procedure showed that none of the rates applied affected significantly the number of seedlings which emerged Oat: In the controls and in the groups treated at 10 and 100 mg/kg the period of germination lasted for 4 and 6 days respectively, meanwhile in the group treated with 1 mg/kg the germination period lasted 3 days. Lettuce: In the controls the period of germination lasted 7 days, in the groups treated with 1 and 10 mg/kd the germination period lasted for 6 days, in the group treated with 100 mg/kg the germination period lasted 4 days. Turnip: The germination period lasted 5 days for the control and for the groups treated at 1 and 10 mg/kg, meanwhile it lasted 4 days for group treated at 10 mg/kg. The growth of none of the species of plants used as test system was affected from any of the test substance rate applied. The results showed that none of the rate tested displays inhibition effect neither on seedlings emergence nor on final dry weight in any plant species tested.
CONCLUSION	No seeds of any of the species tested showed signs of phytotoxicity.
TEST FACILITY	Unpublished report provided by notifier

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The notified chemical will be imported into Australia as a finished product. No reformulation occurs in Australia. The finished product containing the notified chemical will be sold to retail outlets. Consumers will then use the finished product by placing one tablet per wash load in the appliance dispenser. Nearly all of the notified chemical may potentially be disposed of to sewer after use, with only small quantities, including that proportion remaining as residual in containers and major spills, being disposed of to landfill.

Based on the worst-case scenario of 100% notified chemical being released to the aquatic environment via the sewer, with nil removal, a predicted environmental concentration (PEC) of the notified chemical has been calculated:

Process or Dilution Factor	
Typical notified chemical use expected per day	30000 kg
Number of day used	365 days
Australian population	20 million people
Water consumed average	200/L/person
STP daily Volume	4000 ML
Concentration in effluent from sewage treatment plant	20.55 µg/L
PEC Ocean (Dilution Factor 1:10)	2.05 µg/L
PEC River (Dilution Factor 1:1)	20.55 µg/L

The low Koc value and the water solubility test results indicate that the test substance has a low adsorption potential to sludge. Therefore, the notified chemical will remain in the water column.

The potential for bioaccumulation is also low due to the high water solubility, low log Kow and low fat solubility of the notified chemical.

STP effluent re-use for irrigation occurs throughout Australia. The agricultural irrigation application rate is assumed to be 1000 L/m^2/year (10 ML/ha/yr). The notified chemical in this volume is assumed to infiltrate and accumulate in the top 0.1 m of soil (density 1000 kg/m^3). Using these assumptions, irrigation with a concentration of 20.55 µg/L may potentially result in a soil concentration of approximately 205.5 µg/kg. Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil in 5 and 10 years may be approximately 1.03 and 2.05 mg/kg respectively.

9.1.2. Environment – effects assessment

The results of the aquatic toxicity tests for the notified chemical are listed below.

Organism	*Duration*	*End Point*	*Result (mg/L)*
Fish	96 h	LC_{50}	0.4
Daphnia	48 h	LC_{50}	17.5
Algae	0-72 h	E_bC_{50}	1.24
		E_uC_{50}	3.15

Notified chemical: Using the lowest value of 0.4 mg/L and a safety factor of 100 (based on 3 experimental results) for fish/*Daphnia*/algal acute toxicity endpoints, a Predicted No Effect Concentration (PNEC) for aquatic ecosystems of 0.004 mg/L is estimated.

Main degradation product: Using the lowest value of 100 mg/L and a safety factor of 100 (base on 3 experimental results) for fish/*Daphnia*/algal acute toxicity endpoints, a Predicted No Effect

Concentration (PNEC) for aquatic ecosystems of 1 mg/L is estimated, using an assessment factor of 100.

9.1.3. Environment – risk characterisation

		Location	*PEC* µg/L*	*PNEC µg/L*	*Risk Quotient (RQ)**
Notified (100%)	chemical	Ocean outfall	2.05	4	0.51
		Inland River	20.55	4	5.14

* The worst-case PEC and the RQ values calculated assuming the notified chemical is not removed during the wastewater treatment process

The resulting risk quotient (RQ = PEC/PNEC) values for the aquatic environment, assuming that the chemical is not removed in the communal STP, is less than 1 for marine environment indicating no concern. However, RQ is above 1 for freshwater water, indicating immediate concern to this aquatic compartment. The notified chemical is unstable and is expected to degrade in the dish water. The notifier indicates 99% degradation but support data for this exact figure is lacking. However, the half life to hydrolysis is < 24 hours at pH 9 and the notified chemical has also been show to be ready biodegradable under the right conditions. Thus extensive degradation may be expected.

Using the SIMPLETREAT model (European Commission, 2003) to Predicted Environmental Concentration (PEC) Values. With ready biodegradability assumed and that:

- log Kow is 2.2; and
- log H is assumed to be < 0 (while calculation of Henry's Law Constant is not possible as a vapour pressure result is not available, log H may be expected to be low)

results in 13% in the water column and 87% degraded. Therefore, the PEC for the river is reduced to 2.67 µg/L and the Q = 0.67. Considering that only 25% of Australian sewage is released to fresh water (reducing the Q to < 0.2) and taking into account the much
lower toxicity of the break down product, an acceptable risk to the aquatic environment is indicated.

Assuming accumulation of the notified chemical in soil for 5 and 10 years under repeated irrigation, the concentration of notified chemical in the applied soil may be approximately 1.03 and 2.05 mg/kg respectively. However, acute toxicity study to earthworm showed a LOEC of 200 mg/kg, indicating no concern to the terrestrial environment.

Based on the proposed use pattern the notified chemical is expected not to pose a risk to the health of aquatic or terrestrial life.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Occupational exposure to the notified chemical is only expected for laboratory chemists through incidental dermal and ocular contact with aqueous solutions of the notified chemical (concentration < 10%) when carrying out testing. The estimated dermal exposure is 0.21 mg/day, based on EASE model (EASE) using reasonable worst case defaults for the exposure scenario 'quality control sampling of liquids' (European Commission, 2003a) and assuming the notified chemical is present at concentration of 10%. Therefore, for a 70 kg worker and a worstcase 100% dermal absorption factor, systemic exposure is estimated to be 0.003 mg/kg bw/day. Based on the toxicokinetic studies the dermal absorption and hence the exposure is expected to be lower than this estimate. In addition exposure would be limited by the use of PPE.

9.2.2. Public health – exposure assessment

Formulated products containing the notified chemical will be sold to the public and as such widespread public exposure is expected. Since these products will be stored and used in a domestic environment, there is also the possibility for children to be exposed to the notified chemical by accidental ingestion.

Direct exposure to the notified chemical from the handling of the dishwasher tablet is not expected due to the presence of the resin coating. Even if this coating layer is breached, negligible exposure is expected due to the short contact time, the expected very small skin contact area and the low concentration of the notified chemical. Dermal exposure is expected to only potential route of exposure.

9.2.3. Human health – effects assessment

Toxicokinetics, metabolism and distribution.
The notified chemical was demonstrated to rapidly break down in biological fluids to one main breakdown product. As such three toxicokinetic and one pharmacokinetic study was conducted on the main breakdown product with oral and dermal routes of exposure assessed. In all studies the test substance was extensively absorbed from the intestinal tract and excreted mainly by the urine with secondary excretion in the faeces. The majority of the absorbed test substance was excreted in the first 24 hours although low levels remained in the blood and urine after 96 hours. A slower rate of urinary excretion was observed when a higher dose was administered. No tissue accumulation was observed. Metabolism was shown to be complete and likely to be via a β-oxidation mechanism. When the test substance was applied topically 8.5% of the applied dose was absorbed under occlusive conditions with 3.5% absorbed under non-occlusive conditions.

Acute toxicity.
The notified chemical is of low toxicity via the oral and dermal routes.

Irritation and Sensitisation.
Based on the studies provided the notified chemical is non-irritating to skin, severely irritating to eyes and not likely to induce skin sensitisation. At the concentration at which the notified chemical is introduced (<10%) it is likely to be irritating to eyes.

Repeated Dose Toxicity.
A NOAEL for the notified chemical was established as 100 mg/kg bw/day in a 28-day oral repeat dose study in rats, based on treatment related effects on the liver and stomach observed at 300 mg/kg bw/day. In order to avoid the local effects observed in the stomach of administered animals, attributable to the peroxidic moiety of the notified chemical, a 90-day oral repeat dose study in the rats was carried out using the main degradation product of the notified chemical. The NOAEL was established as 100 mg/kg bw/day in this study, based on treatment related effects on the liver.

Mutagenicity.
The notified chemical was negative in two Ames tests, in an *in vitro* chromosome aberration test with human lymphocytes, an *in vivo* mouse micronucleus test and an *in vivo* unscheduled DNA synthesis (UDS) test.

Toxicity for reproduction.
In a developmental toxicity study in rabbits, the Maternal No Observed Adverse Effect Level (NOAEL) was established as 50 mg/kg bw/day in this study, based on significantly lower bodyweight gain and food and water intake observed at doses ≥ 100 mg/kg bw/day. The Foetal No Observed Adverse Effect Level (NOAEL) was established as 50 mg/kg bw/day in this study, based on the decreased foetal weight observed at 300 mg/kg bw/day and the possible treatment related increase in the number of early resorptions at doses ≥ 100 mg/kg bw/day. No evidence of teratogenic potential was indicated by this study.

In a one generation reproduction study in rats, a NOAEL for F0 males was set at 100 mg/kg/day, due to the decreased bodyweight gain observed at 300 mg/kg/day and a NOAEL of 50 mg/kg/day was established for the F1 generation, due to the significant increase in post implantation loss and decrease in number of live born per litter at the higher doses. No NOAEL could be established for F0 females, due to the elongation of the gestation period, although 50 mg/kg bw/day could be considered as the LOAEL (Low Observed Adverse Effect Level) as gestation length was still within historical controls and was the only effect observed at this dose. As such another one generation study was conducted at lower doses. In this study the maternal

NOAEL was established as 25 mg/kg bw/day based on the absence of treated related effects.

Hazard classification for health effects.
Based on the available data, the notified chemical is classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004).

9.2.4. Occupational health and safety – risk characterisation

Reasonable worst-case exposure to the notified chemical for laboratory chemists was estimated to be 0.003 mg/kg bw/day. Based on a NOAEL of 25 mg/kg bw/day, derived from the one generation reproduction study the margin of exposure (MOE) is calculated as 8300. MOE greater than or equal to 100 are considered acceptable to account for intra- and inter-species differences. Therefore, the risk of systemic effects using modelled worker data is acceptable for laboratory chemists. The notified chemical is a severe eye irritant and as such an aqueous solution of the notified chemical is considered to be irritating to eyes. As there is the potential for ocular exposure during testing of the finished product and hence the risk of an irritant effect, it is recommended that eye protection be worn.

9.2.5. Public health – risk characterisation

Due to the negligible exposure to the notified chemical expected during use of the dishwasher tablet, the risk to public health is considered to be negligible.

Since products formulated with the notified chemical will be stored and used in a domestic environment, there is also the possibility for children to be exposed to the notified chemical by accidental ingestion. However, as the notified chemical is considered to be of low acute toxicity the risk of lethal effects as a result of accidental ingestion of the notified chemical is considered to be low. In addition, the dishwasher tablet has a resin coating.

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

10.1. Hazard classification

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

R41 Risk of serious damage to eyes

and

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

	Hazard category	***Hazard statement***
Acute toxicity	5	May be harmful if swallowed (oral)
Serious eye damage	1	Causes serious eye damage
Chronic hazards to the aquatic environment	1	Very toxic to aquatic life with long lasting effects

10.2. Environmental risk assessment

Based on its reported use pattern, the chemical is considered not to pose a risk to the health of aquatic or terrestrial life.

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 No Significant Concern to public health when used in the proposed manner.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of the products containing the notified chemical provided by the notifier were in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 2003). They are 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 products containing the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

REGULATORY CONTROLS
Hazard Classification and Labelling

- The ASCC Chemicals Standards Sub-committee should consider the following health hazard classification and safety phrases for the notified chemical:
  - R41 Risk of serious damage to eyes
  - S25 Avoid contact with eyes
  - S26 In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
  - S39 Wear eye/face protection

- Use the following risk phrases for products/mixtures containing the notified chemical:
  - Conc $\geq$ 10%: R41
  - 5% $\leq$ Conc < 10%: R36

- The notified chemical should be classified as follows under the ADG Code:
  - Class 5.2 Organic Peroxides

CONTROL MEASURES
Occupational Health and Safety

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified when carrying out product testing:
  - *Wear protective eye wear*

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

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

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

Disposal

- The notified chemical should be disposed of as described in safety data sheet: destroy by treatment with dilute alkali solution. Dispose of in authorized depuration plants or incineration according to local laws and regulations.

Emergency procedures

- Spills or accidental release of the notified chemical should be handled as described in safety data sheet: collect the product with suitable equipment avoiding dust formation. The containers should be clean, vented, dry, labelled and isolated in a safe place. Wash the contaminated area with plenty of water or with buffered alkali solution.

Transport and Packaging

- The Dangerous Goods classification of formulations containing the notified chemical should be established and should be transported and packaged consistent with the provisions of State and Territory legislation.

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 Section 64(1) of the Act; if
- the importation volume exceeds 50 tonne per annum notified chemical; or
- the notified chemical is introduced other than in a dishwasher tablet

or

(2) Under 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. If the importable volume exceeds 50 tonnes per annum, more accurate estimations of degradation of the notified chemical during dish washing and in the sewer systems will required to be submitted.

13. BIBLIOGRAPHY

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