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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Arlasolve DMI

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Director
Chemicals Notification and Assessment

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FULL PUBLIC REPORT

Arlasolve DMI

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Symex Holdings Limited
14 Woodruff Street
PORT MELBOURNE VIC 3207

and

Uniqema Australia Pty Ltd
c/o Blake Dawson Waldron
Level 39, 101 Collins Street
Melbourne VIC 3000

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:

- Spectral data
- Import volume
- Client details

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

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Johnson & Johnson Pacific Pty Ltd hold a Commercial Evaluation Chemical permit for this chemical at the time of this assessment.

NOTIFICATION IN OTHER COUNTRIES

2. IDENTITY OF CHEMICAL

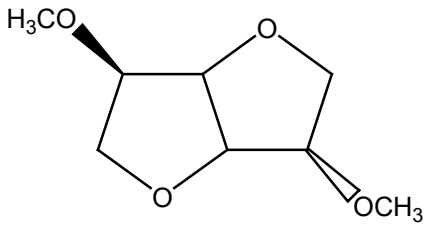
CHEMICAL NAME
1,4:3,6-dianhydro-2,5-di-O-methyl-D-glucitol

OTHER NAME(S)
Dimethyl isosorbide
Arlasolve DMI

CAS NUMBER
5306-85-4

MOLECULAR FORMULA
$C_8H_{14}O_4$

STRUCTURAL FORMULA



MOLECULAR WEIGHT
174.2

METHODS OF DETECTION AND DETERMINATION
The notified chemicals has been characterised using NMR, IR, and MS. Analytical techniques such as gas chromatography could be used for its detection and determination.

3. COMPOSITION

DEGREE OF PURITY
96%

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical will be introduced as a component of finished personal care product, and in the future, as a raw ingredient for reformulation by local manufacturers.

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

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

USE
The notified chemical is used as a skin emollient in personal care products at concentrations up to 25%.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, Transport and Storage

PORT OF ENTRY
Not known

IDENTITY OF MANUFACTURER/RECIPIENTS

TRANSPORTATION AND PACKAGING
The notified chemical will imported in 200L drums and/or 20L pails. It will also be imported as a component of packaged personal care products.

5.2. Operation Description

Importation
The notified chemical will be imported neat in 200 L drums or 20 L pails. It will also be imported as a component of packaged personal care products. Following importation, the notified chemical or product containing it will be delivered to the notifiers' sites for reformulation or distribution to customers.

Reformulation
The drums/pails containing the notified chemical will be transferred from storage to the manufacturing area. The notified chemical is then either decanted or pumped into the mixer where it is combined with other ingredients of the cosmetic product. The mixing vessels used in this process may by open or closed depending on the formulation being prepared.

The final product containing the notified chemical at concentrations up to 25% is then transferred to the packaging line where it is packaged in plastic and glass containers and distributed for sale.

End-use
The products containing the notified chemical will be sold through retails outlets to consumers or distributed to personal care salons such as hairdressers, cosmetologists or sunless tanning studios. In some cases retail workers may demonstrate the products at the point-of-sale.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Importation	10	4 hours/day	40 days/year
Storage & Transport	100	6 hours/day	240 days/year
Formulation Preparation	200	6 hours/day	240 days/year
Point of Sale	1000	6 hours/day	240 days/year

Exposure Details
Importation, Transport and Storage
Workers involved in the importation, storage, and transport of the notified chemical or products containing it are not expected to be exposed to the notified chemical except in the event of an accident where the packaging may be breached.

Formulation
Dermal exposure to the notified chemical (96%) may occur during reformulation during transfer of the notified chemical from drums and pails to the mixing vessel. Following reformulation any exposure will be to products containing up to 25% notified chemical and may occur during packaging and unitising of finished consumer products.

Retail
Retail workers involved in the shelf filling and sale of the final consumer product are not expected to be exposed to the notified polymer except in cases of an accident where the packaging may be breached. Sales representatives demonstrating the products will be dermally exposed to the products containing 0.1 – 25% through application of the products to potential consumers or themselves.

End-Use
Dermal, and inadvertent ocular exposure may occur in those professions where the services provided involve the application of personal care products. Examples include hairdressers, cosmeticians, and beauticians. Inhalation exposure may also occur during the use of products which are applied as a spray.

5.4. Release

RELEASE OF CHEMICAL AT SITE
The notified chemical will not be manufactured in Australia but will be reformulated into personal skin care products. Waste notified chemical will be generated during reformulation via:

- Spills up to 1% maximum 100 kg,
- Import container residues up to 1% maximum 100 kg,
- Process Equipment cleaning up to 1.5% maximum 150 kg.

RELEASE OF CHEMICAL FROM USE

Approximately 1% of the contents of the end-product container will remain in it when it is disposed of to landfill, generally in domestic rubbish. This equates to approximately 100 kg of notified chemical annually. Since the notified chemical is a component in skin care products ultimately the majority of the notified chemical will be washed into the sewer.

5.5. Disposal

Reformulation solid wastes, including spills and import containers and any residues present, will be disposed of to landfill. This represents up to 200 kg per year of the notified chemical. A further 100 kg will be disposed of to landfill in end-user containers.

The process equipment cleaning effluent containing 1.5% (150 kg) of notified chemical will be disposed of to sewer. Approximately 95.5% of the notified chemical will end up in the sewer due to use of the end-product. A total of 97% of the imported volume of notified chemical will go to sewer, ie up to 9700 kg per annum.

5.6. Public exposure

Personal care products containing the notified polymer at concentrations of up to 25% are for sale to the general public. Members of the public will make dermal contact and possibly accidental ocular contact with products containing the notified polymer. In most cases exposure is expected to be limited to 1-10 grams of product, 1-2 times per day. Inhalation exposure may occur during use of spray products.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa Colourless liquid with a mild odour

Boiling Point 234-242 °C

METHOD Not stated
Remarks From MSDS
TEST FACILITY Not stated

Density 1160 kg/m^3 at 25°C

METHOD Not stated
Remarks From MSDS
TEST FACILITY Not stated

Vapour Pressure 0.013 kPa at 25°C

METHOD The estimation method, MPBPWIN in the EPIWIN package, uses the composition and structure of the chemical to estimate its melting point, boiling point and vapour pressure.
Remarks Antoine method – VP= 0.104 mm Hg
Modified Grain method – VP= 0.094 mm Hg
Mackay method – VP= 0.104 mm Hg
Mean of results – VP = 0.1 mm Hg

These results indicate that the notified chemical is volatile (Mensink, 1995).
TEST FACILITY Not stated

Water Solubility 1×10^3 g/L at 25°C

METHOD Estimation method
Remarks The estimation method, WSWIN in the EPIWIN package, uses the composition and structure of the chemical to estimate its water solubility. As this value is derived from the log P_{ow} of −1.6, which was estimated by the fragment method, the result is relatively reliable.

This estimation indicates that the notified chemical is readily soluble (Mensink, 1995).

TEST FACILITY Not stated.

Hydrolysis as a Function of pH Not attempted.

The notified chemical is not expected to hydrolyse in the environmental pH range 4-9.

Partition Coefficient (n-octanol/water) Log Pow = -2.1 at 20ºC

METHOD Fragmentation technique (part of OECD TG 117)

Remarks This method entails the addition or subtraction of known structures and their fragmental constants to produce the structure of the test chemical, and consequently its partition coefficient.

This result indicates that the notified chemical will partition into water.

TEST FACILITY Brixham Environmental Laboratory, 1993a.

Partition Coefficient (n-octanol/water) log Pow = -1.6 at 20ºC

METHOD Estimation method.

Remarks The estimation method, KOWWIN in the EPIWIN package, uses the composition and structure of the chemical to estimate its partition coefficient by the fragment method.

TEST FACILITY Not stated.

Adsorption/Desorption log K_{oc} = 1 (temperature not specified)

METHOD Estimation method.

Remarks The estimation method, KOCWIN in the EPIWIN package, uses the composition and structure of the chemical to estimate its adsorption/desorption coefficient.

A K_{oc} of 10 indicates that the notified chemical is very highly mobile. (McCall et al, 1981).

TEST FACILITY Not stated.

Dissociation Constant Not attempted.

The notified chemical does not contain any groups that would dissociate.

Particle Size Not applicable as chemical is liquid.

Flash Point >110ºC

METHOD ASTM D3278-73

Remarks From MSDS

TEST FACILITY Not stated

Flammability Limits Not flammable. Combustible.

Autoignition Temperature No data available

Explosive Properties None known

METHOD None

Remarks

TEST FACILITY None

Reactivity

Remarks	Can react with oxidising agents

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral	LD50 6530.8 mg/kg bw - low toxicity
Rat, acute intravenous (1)	LD50 5836 mg/kg bw (both sexes)
Rat, acute intravenous (2)	LD50 5369 mg/kg bw (both sexes)
Mouse, acute intravenous (1)	LD50 6895 mg/kg bw (both sexes)
Mouse, acute intravenous (2)	LD50 5416 mg/kg bw (both sexes)
Rat, 14-day ocular toxicity	Low acute ocular toxicity NOAEL (systemic toxicity) 630 mg/kg/day
Rabbit, skin irritation (1)	very slightly irritating
Rabbit, skin irritation (2)	non-irritating
Rabbit, ear irritation	non-irritating
Rabbit, eye irritation - 40%, 100%	inconclusive
Rabbit, eye irritation – 60%, 80%	slightly-irritating
Rabbit, eye irritation – 100%	slightly-irritating
Rat, repeat dose oral toxicity - 90 days.	NOAEL 375 mg/kg/bw day
Beagle, repeat dose oral toxicity - 90 days	NOAEL 100 mg/kg/bw day
Rabbit, repeat dose oral toxicity - 8 days	NOAEL 300 mg/kg/bw day
Genotoxicity - bacterial reverse mutation (1)	non mutagenic
Genotoxicity - bacterial reverse mutation (2)	non mutagenic
Genotoxicity – in vitro human lymphocyte chromosome aberration	non genotoxic
Skin sensitisation – human volunteers	No evidence of sensitisation
Developmental toxicity - rabbit	NO(A)EL 300 mg/kg/bw/day No evidence of maternal or foetal toxicity
Developmental toxicity - rat	NO(A)EL 300 mg/kg/bw/day No evidence of maternal or foetal toxicity
Oral tolerance, human	No treatment related effects up to 25%
Rat, percutaneous absorption	32% absorbed in 12 hours
Mouse, skin penetration enhancement	Enhanced absorption of glycerol

7.1. Acute toxicity – oral

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 401 Acute Oral Toxicity.

Species/Strain — Rat/Holtsman
Vehicle — Distilled water
Remarks - Method

RESULTS

Group	*Number and Sex of Animals*	*Dose mL/kg bw*	*Mortality*
I	5M	10.0 (11600 mg/kg)	5
II	5M	6.81 (7899.6 mg/kg)	5
III	5M	4.64 (5382.4 mg/kg)	0
IV	5M	3.16 (3665.6 mg/kg)	0
V	5M	2.15 (2494 mg/kg)	0
VI	5M	1.47 (1705.2 mg/kg)	0

LD50 — 5.63 mL/kg bw (6530.8 mg/kg bw)
Signs of Toxicity — Within five to 10 minutes following oral administration of the test substance, the animals at each dosage level appeared depressed and showed lacrimation, laboured respiration, tachycardia, and ataxia. The above listed gross signs of systemic toxicity continued throughout the

	remainder of the day in animals dosed with the lowest dosage level (1.47 mL/kg bw). Within one hour or less following dosage and generally throughout the remainder of the day, remaining animals showed the following additional signs: chromodacryorrhoea, slow and laboured respiration, and depressed or placement, righting, and pain reflexes. Animals at the three higher dosage levels also showed bloated abdomens. Death was immediately preceded by coma and a profuse bloody discharge from the eyes. Animals at the lower two dosage levels exhibited normal appearance and behaviour at 24 hours after dosage and thereafter. At 24 hours the remaining survivors appeared depressed and showed a bloody discharge around the eyes and laboured respiration, while those at 4.64 and 6.81 mL/kg levels also showed bloated abdomens, tachycardia, and depressed or absent placement and righting reflexes. These animals gradually recovered within an additional one to three days after which they appeared normal.
Effects in Organs	Gross autopsies performed upon the animals that died showed hyperaemic and inflated lungs, slight irritation of the small intestine and congested kidneys and adrenals. In addition the blood appeared to have a thin consistency and did not clot readily. No gross pathological findings were observed at autopsy of the surviving animals.
Remarks - Results	
CONCLUSION	The notified chemical is of low toxicity via the oral route.
TEST FACILITY	Hazleton Laboratories (1957)

7.2. Acute toxicity - intravenous

TEST SUBSTANCE	Notified chemical.
METHOD	
Species/Strain	Rat-Sprague Dawley Mouse- Swiss Webster
Vehicle	0.9% sodium chloride solution
Remarks - Method	14 day study period

RESULTS

Group	*Conc. (% v/v)*	*Dose (mg/kg)*	*Number and Sex of Animals*	*LD50 (both sexes)*
Rat I	20	3160	10M/10F	5836
		3980	10M/10F	
		5010	10M/10F	
		6310	10M/10F	
		7940	10M/10F	
Rat II	40	3160	10M/10F	5369
		3980	10M/10F	
		5010	10M/10F	
		6310	10M/10F	
		7940	10M/10F	
Mouse I	20	4470	10M/10F	6895
		5620	10M/10F	
		7080	10M/10F	
		8910	10M/10F	
		11200	10M/10F	

Mouse II	40	2820	10M/10F	5416
		3550	10M/10F	
		4470	10M/10F	
		5620	10M/10F	
		7080	10M/10F	

LD50 — All of the 14-day LD50 values in both sexes of mice and rats for 20% and 40% notified chemical indicate a low order of intravenous toxicity in both rats and mice.

Signs of Toxicity - Local — Following a single toxic intravenous dose of the notified chemical, both sexes of rats and mice displayed initial stimulation, demonstrated by rapid shallow breathing and rapid heartbeat. This was followed by a prolonged depression phase characterised by loss of righting reflex, laboured respiration, narcosis and death. Death was attributed to respiratory depression. A few rats and mice chewed the tips of their tails off, which was probably a response to irritation induced by notified chemical that had leaked from the vein into the tissues of the tail.
Other signs of toxicity seen only in rats were lacrimation, coolness to the touch, and white froth around the mouth and nose. Several rats had bloody urine, and small dull spots on the eyeball surface were seen in about 14 of 119 survivors. A dose related decrease in bodyweight gain was noted in rats which was probably related to the lack of feeding during long period of narcosis or decreased motor activity. Several mice had urine stained abdomens and a few had small patches of fur missing from the top of their heads.

Remarks - Results — No marked difference in toxicity between 20% and 40% solutions.

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

TEST FACILITY — ICI Americas Inc (1981a)

7.3.1 Irritation – skin

TEST SUBSTANCE — Notified chemical

METHOD — Primary irritation to the rabbit skin was tested and scored in accordance with the procedure outlined in Association of Food and Drug Officials, US (1959)

Species/Strain — Rabbit/New Zealand White
Number of Animals — 30
Vehicle — Water
Observation Period — 72 hours
Type of Dressing — Occlusive
Remarks - Method — 6 rabbits were used, three with skin intact and three with the skin abraded. Dermal scores were at 24h and 72h only.

RESULTS

Lesion	*Mean Score**	*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
Erythema/Eschar	0.083	1	<72	0
Oedema	0	0	-	0

*Calculated on the basis of the scores at 24and 72 hours for ALL animals.

Remarks - Results — At 24 hours none of the three intact skin areas showed any irritation while one of the three abraded skin areas showed slight erythema. At 72 hours

no irritation at all was observed on any of the skin tested.

CONCLUSION The notified chemical is mildly irritating to skin.

TEST FACILITY Atlas Chemical Industries (1968a)

7.3.2 Irritation – skin

TEST SUBSTANCE Notified Chemical

METHOD Primary irritation to the rabbit skin was tested and scored in accordance with the procedure outlined in Association of Food and Drug Officials, US (1959)

Species/Strain	Rabbit/New Zealand White
Number of Animals	30
Vehicle	Water
Observation Period	72 hours
Type of Dressing	Occlusive
Remarks - Method	6 rabbits were used for each material or preparation that was tested, three with skin intact and three with the skin abraded.

RESULTS

Lesion	*Mean Score*. Conc %*					*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	100	80	60	40	20			
Erythema/Eschar	0	0	0	0	0	0	-	0
Oedema	0	0	0	0	0	0	-	0

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

Remarks - Results All individual dermal irritation scores observed on each rabbit, with intact or abraded skin, at 24 hours and 72 hours were zero.

CONCLUSION The notified chemical is non-irritating to skin.

TEST FACILITY Atlas Chemical Industries (1963)

7.4. Irritation – External auditory canal

TEST SUBSTANCE Notified chemical

METHOD The test substance (0.25 mL) was introduced into the external auditory canal so that it wet the integument from the external orifice to the tympanaum. The two ears, after installation of the test material, were taped together to in an upright position with masking tape to prevent the ears from "flopping" independently when the rabbit shook its head. Tape was removed at two hours and the canal observed for signs of irritation. The canal was observed again at 24 and 72 hours. After five days each rabbit was sacrificed and the auditory canal dissected from the external orifice to the tympanum. The tissue was observed, grossly, for signs of irritation.

Species/Strain	Rabbit/New Zealand White
Number of Animals	16

Vehicle	Water
Observation Period	72 hours
Type of Dressing	None
Remarks - Method	4 rabbits were used for each material or preparation that was tested. The notified chemical was instilled into the right ear of each of the four rabbits; Tween 80, in comparable concentration, was instilled into the left ear of each of the same four rabbits and served as a control.

RESULTS

Remarks - Results	No signs of irritation to the integument of the external auditory canal of the was observed in any of the rabbits treated with the notified chemical either undiluted or as a 40% w/v aqueous solution, or with Tween 80, undiluted or as a 40% w/v aqueous solution. The dissection of the canal revealed no visible signs of irritation to either the tympanum or the integument of the canal.

CONCLUSION	The notified chemical is not irritating to the ear of rabbits.
TEST FACILITY	Atlas Chemical Industries (1963)

7.5.1 Irritation - eye

TEST SUBSTANCE	Notified chemical
METHOD	Primary irritation to the rabbit eye was tested and scored in accordance with the procedure outlined in Association of Food and Drug Officials, US (1959)
Species/Strain	Rabbit/New Zealand White
Number of Animals	4F/7M, 5F4M
Observation Period	7 days
Remarks - Method	Results were interpreted using the methods of Kay and Calandra (1962) and Larrick (1963).

RESULTS

Concentration %	Methods of interpretation			
	Kay and Calandra	Conclusion	Larrick	Conclusion
100	Cannot be classified	None	4/6 positive	Positive test
100	Non-irritating	Non-irritating	0/6 positive	Negative test
40	Non-irritating	Non-irritating	0/6 positive	Negative test

Remarks - Results	Testing of undiluted test substance on the cornea and mucosa of the rabbit eye produced a range of irritation so varied (scores ranging from 0 to 64 at 24 hours) that a retest was indicated. The notified chemical was retested undiluted and as a 40% w/v aqueous solution, each on 6 unwashed eyes and 3 receiving a wash 2 seconds after instillation. In all tests whether made with undiluted or the 40% w/v aqueous solution, no irritation was observed.
CONCLUSION	Overall the study was inconclusive. However, based on the results of the retests, the notified chemical is non-irritating to the eye
TEST FACILITY	Atlas Chemical industries Inc. (1964a)

7.5.2 Irritation - eye

TEST SUBSTANCE	Notified chemical

METHOD — Primary irritation to the eye mucosa of the rabbit was tested and scored in accordance with the procedure outlined in AFDO, US (1959)

Species/Strain	Rabbit/New Zealand White
Number of Animals	9 (male and female – relative numbers not clear)
Observation Period	7 days
Remarks - Method	

RESULTS

Remarks - Results	Tested on the eye mucosa of albino rabbits as an 80% and 60% w/v aqueous solution, the notified chemical did not cause irritation to the washed or unwashed eyes. All scores were zero.

CONCLUSION — The notified chemical is non-irritating to the eye.

TEST FACILITY — Atlas Chemical industries Inc. (1964b)

7.5.3 Irritation - eye

TEST SUBSTANCE — Notified chemical

METHOD — Primary irritation to the eye mucosa of the rabbit was tested and scored in accordance with the procedure outlined in AFDO, US (1959)

Species/Strain	Rabbit/New Zealand White
Number of Animals	4F/5M
Observation Period	7 days
Remarks - Method	0.1 mL instilled into eye- 6 unwashed, 3 washed for 2 seconds with 20 mL water.

RESULTS

Concentration (%)	Condition of eye in regard to wash after instillation	Classification		
		Kay and Calandra	Code of Federal regulations	No of eyes Positive/No. Tested
100	Unwashed	Mildly irritating	Negative	0/6
	2 second wash	Mildly irritating	Negative	0/3

Remarks - Results	The notified chemical, tested on the eye mucosa of albino rabbits as a 100% w/v aqueous solution, was classified as mildly irritating according to the interpretation of Kay and Calandra.

CONCLUSION — The notified chemical is slightly irritating to the eye.

TEST FACILITY — Atlas Chemical industries Inc. (1968)

7.6.1 13-Week repeat dose oral toxicity

TEST SUBSTANCE — Notified chemical

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

Species/Strain	Rat – Sprague Dawley.
Route of Administration	Oral – gavage/diet/drinking water.
Exposure Information	Total exposure days: 13 weeks Dose regimen: 7 days per week Post-exposure observation period: None

Vehicle Water
Remarks - Method

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	20M/20F	0	1M
II	20M/20F	30	0
III	20M/20F	100	0
IV	20M/20F	375	1M

Mortality and Time to Death
Two males died during the 13 week treatment period. One control male dies shortly after withdrawal of a blood sample during week 12. A high dose male was found dead during week 13 of treatment with no significant prior clinical history.

Clinical Observations
No clinical signs considered to be treatment related were noted during the 13 week treatment period.

Body Weights
There was no indication of a treatment related effect on body weights.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis
Clinical biochemistry
Isolated increases in serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) levels were obtained at week 6 from 1 high-dose and 1 mid-dose female, and at week 12 from 1 high-dose male and SGPT levels for 2 mid-dose females when compared with controls. These differences were however considered of doubtful toxicological significance given their small magnitude and the inherent variability of these parameters.

Marginally increased levels of chloride were recorded for all females receiving 375 mg/kg/day, a large proportion of females and 1 male receiving 100 mg/kg/day, and occasional males and females receiving 30 mg/kg/day. In light of the lack of disturbance in other electrolyte levels, the small magnitude of differences in chloride levels, and the individual variability between sampling occasions, the toxicological significance of these marginally higher chloride levels is uncertain.

Urinalysis
No changes in quantity and quality of urine voided by treated rats when compared with controls which could be attributed to treatment with the test substance.

Haematology
There was no indication of any adverse treatment related changes in haematological results obtained from control and DMI treated rats receiving the test substance at a level of 375 mg/kg/day.

Pathology – Organ weights, Macroscopic changes, Histopathology
Organ weights
A small but statistically significant increase in absolute and relative liver weights among males and females receiving 375 mg/kg/day compared to controls was recorded. Absolute and relative liver weights for other treated rats were comparable with controls.

A small but statistically significant increase in absolute kidney weights is was also noted for males receiving 375 mg/kg/day, with an associated increase in relative liver weights when compared with controls. Females receiving 375 mg/kg/day and all other rats treated with lower doses showed no significant change in kidney weights.

Macroscopic changes
Gross pathology examination of rats found dead during the course of the study revealed no consistent changes that could be associated with treatment. Additionally, examination of those rats surviving to termination revealed a low incidence of commonly occurring pathology changes with no indication of any disturbance attributable to treatment.

Histopathology
Histopathological examination of controls and rats at 375 mg/kg/day revealed a low incidence of commonly occurring changes which showed no evidence of any treatment related disturbance.

Remarks – Results
The small increases in absolute and relative liver and kidney weights for males and females receiving 375 mg/kg/day were not associated with any morphological changes and therefore believed to be adaptive in nature.

CONCLUSION
The No Observed (Adverse) Effect Level (NO(A)EL) was established as 375 mg/kg bw/day in this study, based on the absence of any consistent effect on survival, clinical signs, growth rate, food intake, haematology, clinical chemistry, urinalysis, gross pathology or histopathological findings. Small increase in liver and kidney weights at the 375 mg/kg/day level is considered to be adaptive in nature. The NOEL was established as 100 mg/kg/day.

TEST FACILITY Bio-Research Laboratories Ltd. (1987a).

7.6.2. 13-Week repeat dose oral toxicity

TEST SUBSTANCE Notified chemical

METHOD OECD TG 409 Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents.

Species/Strain	Dog – Canis familiaris (Beagle)
Route of Administration	Oral – gelatin capsule
Exposure Information	Total exposure days: 13 weeks Dose regimen: 7 days per week Post-exposure observation period: None
Vehicle	Water
Remarks - Method	

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	3M/3F	0	0
II	3M/3F	30	0
III	3M/3F	100	0
IV	3M/3F	700	0

Mortality and Time to Death
No deaths occurred during the course of the study.

Clinical Observations
Brown or yellow and or white mucoid material in cage trays was noted on one or two occasions among 1 control female, 2 females receiving 30 mg/kg/day, 1 male and 1 female receiving 100 mg/kg/day, and 1 male and 1 female receiving 700 mg/kg/day. This finding was also observed on three occasions in 1 female receiving 100 mg/kg/day, four occasions in one female receiving 700 mg/kg/day, and on six occasions in one male receiving 700 mg/kg/day. Rare occasions of sporadic vomiting was noted before or after the daily

treatment. Mucous deposition and vomiting were noted with a low incidence and showed no consistent pattern attributable to the notified chemical.

Salivation during or shortly after treatment was noted once in 2 females receiving 100 mg/kg/day and on five occasions in 1 female receiving 700 mg/. During week 12 salivation was also noted following ocular administration of atropine for ophthalmoscopic examination, in all males receiving 30 mg/kg/day, 2 males and 1 female receiving 100 mg/kg/day and 1 male and 2 females receiving 700 mg/kg/day.

Body Weights

Negligible weight gain or a small weight loss over the 13-week treatment period compared with control weights was observed in dogs treated at 700 mg/kg/day. This reduction in weight body weight gain was noted from the second week of treatment and resulted in slightly lower weekly group mean body weights for the high dose animals compared with controls or dogs receiving 30 mg/kg/day.
Similarly, dogs receiving 100 mg/kg/day showed marginally lower overall body weight gains, compared with controls, for the 13 –week treatment period. Weekly group mean body weights and overall body weight gains for animals receiving 30 mg/kg/day were comparable with those of controls.

Food consumption and conversion ratios

A consistent small reduction in food intake was noted from week 2 of treatment in dogs treated with 700 mg/kg/day compared with controls. Males and females treated at this level also recorded a marked reduction in food utilisation throughout the treatment period. Food conversion ratios for dogs receiving 100 mg/kg/day were also slightly higher than controls for the first 8 weeks of the treatment period. These dogs, however, also exhibited slightly higher pre-treatment values and showed overall values similar to that of controls and the 30 mg/kg/day group. The toxicological significance of food this result for the 100 mg/kg/day group is of doubtful toxicological significance.

Ophthalmoscopy

No toxicologically significant ocular findings were observed.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

Clinical biochemistry

Alkaline phosphatase levels were markedly higher in dogs treated at 700 mg/kg/day at weeks 7/8 and 12. A marked increase in glutamic pyruvic transaminase (GPT) levels was also noted in 1 male and all females receiving 700 mg/kg/day at weeks 7/8 and 12. A less marked increase was also noted for an additional two males in the 700 mg/kg/day group. Increased glutamic oxaloacetic transaminase (GOT) values were also noted at 7/8 and 12 for 2 high dose males as compared with controls. Increase GOT values were also noted at weeks 7/8 and 12 for one male and at week 7 for one female as compared with controls and other treated dogs. At weeks 7/8 and 12, a trend to slightly lower values for cholesterol, total protein, albumin and A/G ratio was noted for females receiving 700 mg/kg/day compared to controls. One male receiving this dose level also showed slightly lower total protein at week 12 and slightly lower albumin at weeks 7/8 and 12 compared with controls.

Urinalysis

No changes in quantity and quality of urine voided by treated rats when compared with controls which could be attributed to treatment with DMI.

Haematology

Haematology data obtained at weeks 7/8 and 12 revealed slightly lower red cell parameters for one male and 2 females receiving 700 mg/kg/day. Compared with controls. One additional female also showed slightly lower red cell parameters at week 12 when compared with controls. The red cell parameters in affected individuals were also slightly reduced when compared with pre-treatment values.
No other toxicologically significant haematological values were observed.

Pathology – Organ weights, Macroscopic findings, Histopathology

Organ weights

Increased absolute and relative liver weights were observed in dogs receiving 700 mg/kg/day compared with controls. Liver weights were comparable with controls for other treated dogs. Higher relative and absolute spleen weights were observed in females receiving 700 mg/kg/day while males receiving these levels tended to show lower spleen weights. This parameter is however considered to be of doubtful toxicological significance given the inherent variability in this parameter due to differences in the degree of exsanguination (blood

content), inconsistency with respect to sex, and absence of histopathological change.

Macroscopic findings
Gross pathology examination of all dogs killed after 13 weeks of treatment revealed macroscopically observed liver enlargement in 1 male receiving 700 mg/kg/day compared with controls. No other significant gross pathology observations were made.

Histopathology
Histopathological evaluation revealed no evidence of treatment related effects.

Remarks – Results

CONCLUSION
The NO(A)EL level is established as 100 mg/kg/day based on signs of general toxicity at 700 mg/kg/day. This included reduced body weight gain, haematological and blood biochemistry changes and liver effects at 700 mg/kg/day.

TEST FACILITY Bio-Research Laboratories Ltd. (1987b).

7.7. 8-day repeat dose oral toxicity

TEST SUBSTANCE Notified chemical

METHOD

Species/Strain	Rabbit/New Zealand White
Route of Administration	Oral – gavage
Exposure Information	Total exposure days: 8 days Dose regimen: Once daily for eight days Post-exposure observation period: None
Vehicle	Water
Remarks - Method	

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I	5F	300	0

Mortality and Time to Death
No premature deaths occurred during the course of the study.

Clinical Observations
There were no changes in clinical condition observed during the dosing period or on the days of necropsy.

Body Weights
Slight retardation of mean bodyweight gain to slight bodyweight loss in some cases was observed during the first five days of dosing, however this is considered usual when dosing naïve animals. Bodyweight gain during the remainder of the dosing period was similar to that of the pre-dosing period. There was no effect of treatment on bodyweight.

Food consumption
Slight reduction in the food consumption of 3 of the five animals was observed over days 3 to 5 however this was considered to be related to the dosing of naïve animals rather than a direct effect of the notified chemical. Food consumption for all five animals was similar to that during the pre-dosing period on the other days of the study.

Necroscopy
There were no macroscopic abnormalities observed at necroscopy in any of the treated females.

Remarks – Results

CONCLUSION
The NO(A)EL level is established as 300 mg/kg/day based the lack of evidence of toxicity at this dose level.

TEST FACILITY Toxicol. (1993a).

7.8.1 Genotoxicity - bacteria

TEST SUBSTANCE Notified chemical

METHOD Not stated
Species/Strain *S. typhimurium*:
G46, TA1535, TA1537, TA 1538, TA98, TA100, D3052, C3076.
E. coli: WP2, WP2 uvrA$^-$
Metabolic Activation System S9
Concentration Range in Main Test a) With metabolic activation: 0.1-1000 µg/plate.
b) Without metabolic activation: 0.1-1000 µg/plate.
Vehicle Water

Remarks - Method Positive controls are 2-acetylaminofluorene and Streptozotocin.

RESULTS No mutagenic activity was observed at any concentration in any of the strains tested.

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

TEST FACILITY Not provided (RE Macmahon, 1979)

7.8.2 Genotoxicity - bacteria

TEST SUBSTANCE Notified Chemical

METHOD Maron and Ames (1983)
Species/Strain *S. typhimurium*:
TA1538, TA1535, TA1537, TA98, TA100.
Metabolic Activation System Araclor 1254–induced liver S9
Concentration Range in Main Test a) With metabolic activation: 1.6 - 5000 µg/plate.
b) Without metabolic activation: 1.6 - 5000 µg/plate.
Vehicle Dimethyl sulphoxide
Remarks - Method

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in PreliminaryTest	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1		None	-	No
Test 2		None	-	No
Test 3		None	-	No
Present				
Test 1		None	-	Slight (TA 1535 only)

Test 2	None	-	No
Test 3	None	-	Slight (TA 1538 only)

Remarks - Results

In the first experiment, a slight positive response was observed for TA 1535 in the presence of S9. Data obtained for strain TA1537 in the absence of S9 was insufficient due to the level of contamination observed. Data for strain TA 1538 (+S9) was discounted due to the lack of response observed with the positive control 2-Aminoanthracene, in this strain. It is believed the S9-mix was omitted from these plates during pouring.
In the second experiment, the notified chemical gave a negative response in both the presence and absence of an auxiliary metabolising system (S9) in all strains, when tested to a maximum dose of 5000g/plate.

CONCLUSION

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

TEST FACILITY

Imperial Chemical Industries P.L.C. (1986)

7.9. Genotoxicity – in vitro cytogenics assay

TEST SUBSTANCE

Notified chemical

METHOD

OECD TG 473 In vitro Mammalian Chromosomal Aberration Test.

Species/Strain: Human
Cell Type/Cell Line: Lymphocyte
Metabolic Activation System: Aroclor 1254 Induced Rat liver – S9
Vehicle: Water
Remarks - Method:

Metabolic Activation	*Test Substance Concentration (μg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	34.45, 49.21, 70.30, 100.4, 143.5, 204.9, 292.8, 418.3, 597.5, 853.6*, 1219*, 1742*	20 hours	20 hours
Test 2	73.57, 98.10, 130.8, 174.4, 232.5, 310.0, 413.4, 551.2, 734.9, 979.9*, 1307*, 1742*	44 hours	44 hours
Present			
Test 1	34.45, 49.21, 70.30, 100.4, 143.5, 204.9, 292.8, 418.3, 597.5, 853.6*, 1219*, 1742*	3 hours	20 hours
Test 2	73.57, 98.10, 130.8, 174.4, 232.5, 310.0, 413.4, 551.2, 734.9, 979.9*, 1307*, 1742*	3 hours	44 hours

*Cultures selected for metaphase analysis.

RESULTS

Metabolic Activation	*Test Substance Concentration (μg/mL) Resulting in:*			
	Cytotoxicity in PreliminaryTest	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	-	None	-	No
Test 2	-	None	-	No
Present				
Test 1	-	None	-	No
Test 2	-	None	-	No

Remarks - Results	No mitotic inhibition was apparent in Experiment 1 after treatment in either the absence or presence of S9. A similar mitotic inhibition result was seen in experiment 2 with no evidence of an effect on proliferation at the delayed harvest time.
CONCLUSION	The notified chemical was not clastogenic to human peripheral blood lymphocytes when tested in vitro under the conditions of the test.
TEST FACILITY	Hazelton Microtest (1993)

ADDITIONAL INVESTIGATIONS

7.10T. 14-day Ocular toxicity - intravenous

TEST SUBSTANCE	Notified chemical.

METHOD

Species/Strain	Rat (strain not stated)
Vehicle	Not stated
Remarks - Method	14 day study period/14 day recovery period

RESULTS

Group	*Number and Sex of Animals*	*DMI Conc. (mg/kg/day)*	*Mortality*
I	10M	0	0
II	10M	200	0
III	10M	630	0
IV	10M	2000	0

Signs of Toxicity	No ocular lesions were observed at any dose either by ophthalmoscopic examination or gross and microscopic pathology. General signs of toxicity observed were restricted to the high-dose group and reversed during the 14-day recovery period. Rats dosed at 2000 mg/kg/day produced a depressant effect on the central nervous system as well as decreased body tone, heart palpitation, lacrimation, and shaking of the head. Rats in the high dose group showed significantly retarded weight gain during the dosing period however no significant effects on body weight or weight gain were noted for the low and mid-dose groups. The mid dose of 630 mg/kg/day produced minimal toxic signs in a few animals only on the first day of dosing and there was no apparent adverse effect on the health of the animals. The NOEL was established as 200 mg/kg/day, based on minor effects at 630 mg/kg/day. Based on severe toxicity at the high dose, the NOAEL is 630 mg/kg/day.
Remarks - Results	

CONCLUSION	The notified chemical is of low ocular toxicity via the intravenous route.
TEST FACILITY	ICI Americas Inc (not stated)

7.11T. Skin sensitisation – human volunteers

TEST SUBSTANCE	Notified chemical

METHOD

Study Design	Two hundred human volunteers were tested by application of the substance to the skin under a closed patch employing cotton felt circles.
Study Group	188 F / 12 M Ages: 16-65 years
Vehicle	None
Induction Procedure	Cotton felt circles impregnated with undiluted test substance were applied for 3 days and then removed.
Rest Period	2 weeks
Challenge Procedure	Cotton felt circles impregnated with undiluted test substance were applied for 3 days and then removed.
Remarks - Method	

RESULTS

Remarks - Results	All skin sites were negative except for 2 subjects who showed questionable reactions. These subjects were immediately retested by application of the substance to another skin site by a semi-closed patch (gauze impregnated with the substance and secured only by tape above and below) and the usual closed patch. Both of these subjects were negative in each of the retested sites after 48 hours.
CONCLUSION	A human patch test was conducted using 100% notified chemical under occlusive dressing. The notified chemical was non-irritating and non-sensitising under the conditions of the test.
TEST FACILITY	Atlas Chemical Industries (1968)

7.12T. 1 Developmental toxicity

TEST SUBSTANCE	Notified chemical

METHOD

Species/Strain	Rabbit – New Zealand White
Route of Administration	Oral – gavage
Exposure Information	Exposure period: 13 days
Vehicle	Water
Remarks - Method	

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
1	18	0	0
2	18	30	0
3	18	100	0
4	19	300	1(1*)

Mortality and Time to Death

One female rabbit from group 4 was found dead on day 8 following a dosing intubation error and another rabbit* from group 4 was prematurely killed following abortion of nine foetuses.

Effects on Dams

Reduced faeces production was observed in eight to ten rabbits in each treatment group after commencement of treatment compared to three in the control group. All other clinical signs such as alopecia were minor in nature and considered not to be treatment-related.

There was no effect of treatment on either maternal bodyweight or food consumption. There were no macroscopic abnormalities detected at necropsy that were indicative of an effect of treatment at any dose level.

Effects on Foetus

Major skeletal abnormalities were observed in the control group including scoliosis, missing ribs, and major fusion of sternabrea. In the group dosed with 30 mg/kg/day, major external, visceral, and skeletal abnormalities were observed in one foetus, while another was observed to have major visceral abnormalities, and two others were observed to have major skeletal abnormalities. In the group dosed with 100 mg/kg/day, a total of two foetuses from separate litters had major external, visceral and skeletal abnormalities. In the group dosed at 300 mg/kg/day a total of four foetuses from separate litters had major abnormalities. One foetus had major visceral and skeletal abnormalities, two foetuses had major skeletal abnormalities, and one foetus had major visceral abnormalities.

Abnormalities were therefore observed in 2, 4, 2 and 4 foetuses with major abnormalities in the control group and the groups dosed with 30, 100 and 300 mg/kg/day respectively. As some of the observations were present in the control group and there was little consistency of findings in treatment groups, the observations were

considered not to be treatment related.
There were two statistically significant differences in the incidence of minor abnormalities between treatment groups and control group. At 100 mg/kg/day, the incidence of abnormal parietals was significantly higher than in the control group. At 30 and 300 mg/kg/day, the incidence of non-ossified metacarpals was greater than control group. In both cases however, not all dosage groups were affected, and neither observation was therefore considered treatment related.

Remarks – Results

CONCLUSION
Based on the lack of evidence of maternal toxicity or developmental toxicity at any of the dosage levels investigated., the NOAEL was 300 mg/kg/day.

TEST FACILITY Toxicol Laboratories Ltd. (1993b)

7.12T. 2 Developmental toxicity

TEST SUBSTANCE Notified chemical

METHOD

Species/Strain	Rat – Sprague Dawley
Route of Administration	Oral – gavage
Exposure Information	Exposure period: 10 days
Vehicle	Water
Remarks - Method	

RESULTS

Group	*Number of Animals*	*Dose mg/kg bw/day*	*Mortality*
1	24	0	0
2	24	30	0
3	24	100	0
4	24	300	0

Mortality and Time to Death
No rats died during the observation period or were prematurely killed.

Effects on Dams
There were no treatment related changes in clinical condition observed. No effect on either maternal body weights or food consumption were observed. Macroscopic examination revealed no treatment related abnormalities at necropsy. Pregnancy incidence, corpora lutea numbers and pre-implantation losses were similar in all groups. Litter size, post-implantation losses, foetal sex ratio and foetal weights were also unaffected at all treatment levels.

Effects on Foetus
No major abnormalities were observed in the foetuses of the 30 mg/kg/day treatment group. An unusually high incidence of major abnormalities occurred in the group dosed at 100 mg/kg/day, however only 2 of 23 litters were affected, one of which contained five affected foetuses from a total of seven. Abnormalities observed were external/visceral and skeletal including micrognathia, cleft palate, protruding tongue, hypoplastic lung lobes, short body (and associated movement restriction), short mandible, and retarded ossification of the long bones and misshapen long bones in both fore- and hind limbs. At 300 mg/kg/day one foetus was observed with major external/visceral abnormalities which were domed head, umbilical hernia, and short body (and associated movement restriction).

As there were no dose related trends and since all abnormalities were of a type and incidence that can occur spontaneously in this strain of rat, none of the observed effects were considered to be treatment related.

The incidence of abnormal parietals was significantly higher than in the control group, and at 30 and 300 mg/kg/day the incidence of non-ossified metacarpals was greater than in the control group. However, as in both cases, not all doage groups were affected, neither observation is considered to be treatment related.
There were no treatment related differences in the incidences of specific types of foetal external and visceral abnormalities or skeletal variants at any of the dose levels investigated.

Remarks – Results

CONCLUSION
Based on the lack of evidence of maternal toxicity or developmental toxicity at any of the dosage levels investigated, the NOAEL was 300 mg/kg/day.

TEST FACILITY Toxicol Laboratories Ltd. (1993c)

7.13T. Oral tolerance of teeth cleaning gels containing Notified Chemical – Human

TEST SUBSTANCE Notified Chemical

METHOD 15 male volunteers took part in the study which involved brushing with toothpaste formulations containing varying concentrations of the test chemical. Initial and weekly examination of participants was undertaken in order to determine the extent, if any, of toxic effects.

STUDY DESIGN AND OBJECTIVE
The study design was designed to have four two week brushing sessions each separated by a one week hiatus to avoid any possible carry over effect. The distibution of teeth cleaning gels was as follows:

Session	I	Placebo dental gel
Session	II	Dental gel with 5% notified chemical
Session	IV	Dental gel with 10% notified chemical
Session	V	Dental gel with 25% notified chemical

Initial and weekly clinical evaluations included thorough observations of the soft tissues of the mouth including:

1. Oral mucosa
2. Gingiva
3. Tongue
4. Tonsillar area
5. Lips

RESULTS
No adverse tissue reactions were observed or reported except for one subject who developed a chapped lower lip during the second week use of the 10% gel. This condition persisted to the end of the study. This subject had, however a prior history of frequent episodes of chapped lips which were unrelated to the use of the notified chemical. At the outset of the study, one subject presented with geographic tongue, which remained unchanged throughout the test periods with all concentrations of the notified chemical. The oral mucosa of two subjects showed evidence of cheek biting which was present at the outset of the study and unrelated to the use of the notified chemical.

CONCLUSION
No treatment related effects were observed following the use of the notified chemical in concentrations up to 25% in the gels with the possible exception of one case of chapped lips which may have been aggravated by notified chemical.

TEST FACILITY Forsyth Dental Centre (1985)

7.14T. Absorption after percutaneous admninistration.

TEST SUBSTANCE	Notified chemical
METHOD	A 100 mg/kg dose of 14C-DMI was applied dorsally to a 4 × 3 cm shaved skin area of eight male rats. The skin of four of the rats was further prepared by stripping stratum corneum cells from the epidermal layer of the skin with Scotch Tape prior to dosing. Small beads of the test material were applied to the skin and spread evenly using a small glass rod. The glass rod was rinsed with acetonitrile and the dose corrected by the ^{14}C measured in the rinse. Urine was collected over dry ice for 12 hours, and stored frozen prior to analysis. Faeces were collected for 12 hours. The animals were killed 12 hours after dosing. The tongue and oesophagus were excised and later assayed to determine if the animal had licked the treated area. The treated skin and surrounding perimeter were removed and the body stored prior to assay. Samples collected were analysed for total 14C by liquid scintillation counting. The body except for the tongue and oesophagus, was ground and homogenised. Aliquots were prepared for LSC by combustion. The tongue and oesophagus were combusted separately.

STUDY DESIGN AND OBJECTIVE
The objective of the study was to determine the percutaneous absorption of ^{14}C-DMI in male rats.

RESULTS
The percentage of dose measure in the excretion products and in the body as 14C after the percutaneous administration of 14C-DMI was determined to be an average of 31.8% ± 7.6% absorbed dose in 12 hours. The kidney was the major excretory path for total ^{14}C. Tongue and oesophagus tissue to body ratios obtained in the percutaneous study were not significantly different to ratios obtained in a pilot study using intraperitoneal-dosed rats

CONCLUSION
The notified chemical is absorbed through the skin.

TEST FACILITY Stuart Pharmaceuticals (1984)

7.15T. Skin penetration enhancement.

TEST SUBSTANCE	Notified chemical
METHOD	^{14}C radiolabeled glycerol was applied to the skin of hairless mice in the presence of water alone and in water plus the notified chemical. Depth of penetration was measured by serially stripping back stratum corneum and analysing for radiolabelled ^{14}C glycerol, with and without the notified chemical. The notified chemical enhancement was evaluated by comparing absolute and relative depth profiles of radiolabeled ^{14}C glycerol, with and without the notified chemical in aqueous solution.

STUDY DESIGN AND OBJECTIVE
The objective of the study was to determine effect of the notified chemical on enhancing the penetration of glycerin in hairless mice.

RESULTS

The radiolabelled ^{14}C glycerol was applied and tracked through the stratum corneum of hairless mice with the concentration profiles analysed by tape stripping of the stratum corneum at 1, 5, 10, and 15 layers. The notified chemical raised absolute concentration and relative concentrations at 1 and 12 hours post application. Absolute concentration at 12 hours was about 1/10 that measured at 1 hour. Depletion of surface activity from about 400 000 to 20 000 units of activity occurred within 1 hour.
The glycerol with notified chemical in aqueous solution was found to penetrate the stratum corneum at a greater rate than that of glycerol without notified chemical.

CONCLUSION
The notified chemical enhances the penetration of glycerol through the stratum corneum.

TEST FACILITY Xienta Institute for Skin Research (1989)

7.16T. In Vitro Blood Compatability

TEST SUBSTANCE Notified chemical

METHOD The notified chemical was prediluted with saline to achieve concentrations of 2, 10, 20, 40, 60, and 100% (v/v). 0.5 mL of test solution was mixed with 0.5 mL of blood from rats, dogs, and drug free humans. The final concentrations in blood were 0, 1, 5, 10, 20, 30 and 50%. The tubes were vortexed and read macroscopically and microscopically for agglutination. Following centrifugation, supernatants were graded for haemolysis compared with negative controls. Phytohaemaglutinin served as a positive control for Phytohaemaglutinin.

STUDY DESIGN AND OBJECTIVE
The objective of the study was to determine the maximum concentration of notified chemical compatible with blood from rats, dogs, and humans, when used as a solvent in parenteral formulations of pharmaceuticals.

RESULTS
Rat
Agglutination was absent and hemolysis was graded as equal to the negative control in all rat specimens at 20% notified chemical. At 30% notified chemical, no changes in pH were observed. Five of 10 and 9 of 10 samples showed agglutination and hemolysis, respectively, at 30% notified chemical. Significant changes in pH were observed at concentrations of 50% notified chemical.

Dog
One of 10 and two of ten dog samples showed agglutination at 10% and 20% respectively, however the sample which showed minimal agglutination at 10% was negative at 20%. Two of 10 dog samples had haemolysis gradings greater than the negative control at 20% concentration. A difference from control of greater than 0.10 pH units was noted for female means at 5%. However at 10%, the pH change was within 0.10 pH units, therefore the 5% change in pH was dismissed.

Humans
Eight of 10 human bloods were agglutinated at 30% and three of 10 human specimens were haemolysed at this concentration. Cloudy supernatants were observed during hemolysis evaluation at 20% concentration and 30% concentration of all human samples. No significant change in pH means was noted in any human specimen at 30% concentration.

CONCLUSION
In vitro data indicates the compatibility with blood of a notified chemical concentration of 10% or less in dogs and humans and 20% or less in rats. There was no apparent sex difference in any of the species when tested with the notified chemical.

TEST FACILITY ICI Americas (1981)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE	Dimethyl Isosorbide
METHOD	OECD TG 301 F Ready Biodegradability: Manometric Respirometry Test.
Inoculum	Activated sludge from Buckland Sewage Treatment Works which mainly treats domestic effluent.
Exposure Period	28 days
Auxiliary Solvent	None
Analytical Monitoring	None
Remarks - Method	Reference substance – sodium acetate Temperature 20±2ºC Treatments: - bottles 1-3 control blanks - bottles 4-6 reference substance, 200 mg/L - bottles 7-9 test material, 100 mg/L Oxygen uptake was measured daily.

RESULTS

Control		*Sodium Acetate*		*Dimethyl Isosorbide*	
Day	*% degradation*	*Day*	*% degradation*	*Day*	*% degradation*
5	0	5	67	5	0
10	0	10	76	10	0
15	0	15	78	15	0
20	0	20	78	20	0
25	0	25	78	25	0
28	0	28	78	28	0

Remarks - Results	The reference substance degradation exceeded 60% thus indicating that the study was valid.
CONCLUSION	The test material, dimethyl isosorbide, is not readily biodegradable under the study conditions.
TEST FACILITY	Brixham Environmental Laboratory, 1993b.

8.1.2. Bioaccumulation

METHOD	Estimation method
Remarks	The estimation method, BCF program in the EPIWIN package, uses the composition and structure of the chemical to estimate its bioaccumulation.
Estimations	Log BCF = 0.5 (BCF = 3.162) The estimation indicates that the notified chemical is slightly concentrating (Mensink, 1995).
TEST FACILITY	Not stated.

8.1.3 Fugacity model

METHOD	Estimation method		
Remarks	The estimation method, BIOWIN in the EPIWIN package, uses the composition and structure of the chemical to estimate its fate in the environment.		
Estimations	Compartment	Distribution in environment (%)	Half Life (hr)
	Air	0.003	5.33

	Water	45.4	360
	Soil	54.6	360
	Sediment	0.08	1440

TEST FACILITY Not stated.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE Dimethyl Isosorbide

METHOD Estimation Method.

Remarks – Method The estimation method, ECOSAR in the EPIWIN package, uses the composition and structure of the chemical to estimate its potential toxicity to various trophic levels and based on a log P_{ow} of –1.62.

Results Fish: 96 hr LC_{50} $3.26X10^5$ mg/L
Fish Saltwater: 96 hr LC_{50} $1.2991\ X10^4$ mg/L

COMMENT/CONCLUSION The estimation indicates that the notified chemical may be slightly more toxic to saltwater fish, but in both cases appears to be practically non-toxic to fish.

8.2.2. Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Dimethyl Isosorbide

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

Species *Daphnia magna*
Exposure Period 48 hours
Auxiliary Solvent None
Water Hardness 173 mg $CaCO_3$/L
Analytical Monitoring None
Remarks - Method

RESULTS

Concentration mg/L Nominal	*Number of D. magna*	*Number Immobilised*	
		24 h	*48 h*
0	20	0	0
1000	20	0	0

LC_{50} > 1000 mg/L at 48 hours
NOEC (or LOEC) > 1000 mg/L at 48 hours
Remarks - Results

CONCLUSION Under the conditions of the limit test, the test material was practically non-toxic to daphnia.

TEST FACILITY Brixham Environmental Laboratory, 1993c.

Acute toxicity to aquatic invertebrates

TEST SUBSTANCE Dimethyl Isosorbide

METHOD Estimation Method.

SPECIES Daphnid

Remarks – Method	The estimation method, ECOSAR in the EPIWIN package, uses the composition and structure of the chemical to estimate its potential toxicity to various trophic levels and based on a log P_{ow} of –1.62.
Results	48 hr LC_{50} 2.72X10^5 mg/L
COMMENT/CONCLUSION	The estimation indicates that the chemical may be practically non-toxic to Daphnid. This estimation is in agreement with the above study.

Acute toxicity to aquatic invertebrates

TEST SUBSTANCE	Dimethyl Isosorbide
METHOD	Estimation Method.
SPECIES	Mysid shrimp
Remarks – Method	The estimation method, ECOSAR in the EPIWIN package, uses the composition and structure of the chemical to estimate its potential toxicity to various trophic levels and based on a log P_{ow} of –1.62.
Results	96 hr LC_{50} 1.25X10^6 mg/L
COMMENT/CONCLUSION	The estimation indicates that the chemical may be practically non-toxic to Mysid shrimp.

8.2.3. Algal growth inhibition test

TEST SUBSTANCE	Dimethyl Isosorbide
METHOD	Estimation Method.
Remarks - Method	The estimation method, ECOSAR in the EPIWIN package, uses the composition and structure of the chemical to estimate its potential toxicity to various trophic levels.
Results	Green Algae: 96 hr EC_{50} 1.38X10^5 mg/L
COMMENT/CONCLUSION	The estimation indicates that the chemical may be practically non-toxic to algae.

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE	Dimethyl Isosorbide
METHOD	Based on method described by Bringman and Kuehn and modified by Slabbert. This method measures the degree of inhibition of a pure culture of *Pseudomonas putida* during a 6 hour period when the cells are in the logarithmic growth phase.
Inoculum	*Pseudomonas putida*/growth medium solution with an optical density with an absorbance of 0.8 at 600 nm.
Exposure Period	6 hours
Concentration Range Nominal	100 mg/L
Remarks – Method	Reference substance – 3,5-dichlorophenol, 18 mg/L. Treatments: - 3 flasks with 100 mg/L Dimethyl Isosorbide - 3 flasks with 18 mg/L 3,5-dichlorophenol - 3 flasks as control blanks Each flask had 4 mL of growth medium concentrate and 1 mL of inoculum (except to the blank and chemical controls) added and were made up to 50 mL with deionised water. The flasks were shaken at 150

	rpm for 6 hours at 25°C, after which the optical density at 600 nm of each flask was measured. An 8% v/v growth medium solution was used as the reference cell.
RESULTS	
EC_{50}	>100 mg/L
NOEC	>100 mg/L
Remarks – Results	The reference substance, 3,5-dichlorophenol, produced a 96% inhibition of growth.
CONCLUSION	The test material is practically non-toxic to *Pseudomonas putida* bacterium.
TEST FACILITY	Brixham Environmental Laboratory, 1993d.

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The majority of the notified chemical (up to 9700 kg annually) will eventually be released into the environment via discharge into sewerage systems during personal washing. It is expected that up to 100 kg per annum will remain in the consumer product containers and be disposed of to landfill, along with 200 kg from end-user product formulation.

The notified chemical is expected to be highly soluble in water and have a low Pow. Therefore it will be mobile in both the aquatic and terrestrial compartments. It will not readily hydrolyse in natural waters at environmental pH values and is not readily biodegradable. However, the notified chemical will degrade through biological and abiotic processes to water and oxides of carbon. Residual chemical disposed of to landfill with empty containers is also expected to slowly degrade by similar mechanisms.

As the majority of the notified chemical in the skin care products will eventually be released into the aquatic environment via the sewerage systems, the predicted environmental concentration (PEC) in the aquatic environment is estimated using a worst-case scenario assuming all the notified chemical is released to sewer, where there is no removal and it is used across Australia:

Amount released to sewer	10000 kg
Population	20 million
Water use per person	200 L
Number of days used	365
PEC_{sewer}	$\frac{10\,000\,000\,000}{365X200X20\,000\,000}$ = 0.0068 mg/L = 6.8 µg/L
PEC_{inland} (dilution factor 1)	6.8 µg/L
PEC_{ocean} (dilution factor 10)	0.68 µg/L

The ready biodegradability test results showed that the notified chemical was not readily biodegradable. The SIMPLETREAT model (European Commission, 1996) for modelling partitioning and losses in sewage treatment plants (STP) was used to estimate the proportions of the chemical partition into the different environmental compartments. The results indicate that when the chemical is released into the aqueous phase of a STP, all of it will partition into the water compartment with no removal or degradation. Thus, there will be no change to the above estimated PECs.

STP effluent re-use for agricultural irrigation occurs throughout Australia The following calculation is undertaken assuming an application rate of 1000 L/m^2/year (10 ML/ha/year) and that any notified chemical in the water is assumed to infiltrate and accumulate in the top 0.1 m of

soil (density 1000 kg/m^3).

Concentration in effluent	6.8 µg/L	
Soil concentration, PECsoil (mg/kg) (assumes no degradation)		
	1 year	0.068
	5 years	0.34
	10 years	0.68

Bioaccumulation is not expected due to the high water solubility and low log P_{ow} of the notified chemical, which indicates a poor affinity to lipids.

9.1.2. Environment – effects assessment

The results of the aquatic toxicity tests are listed below.

Organism	*Duration*	*End Point*	*mg/L*
Fish	96 h	LC_{50}	3.26×10^5 est.
			1.29×10^4 est.
Daphnia	48 h	EC_{50}	>1000 actual
			2.72×10^5 est.
Algae	96 h	EC_{50}	1.38×10^5 est.
Microbial activity	6 h	EC_{50}	> 100 actual

ECETOC (2003) states that non-ionic chemicals with a narcotic mode of action can be predicted reliably with relatively simple QSARs (based on log P_{ow}) for fish, invertebrates and algae. The actual daphnia study results support the estimated results, thus in this situation the use of QSAR is acceptable.

Using the lowest EC_{50} actual datum (ie. > 100 mg/L) and a safety factor of 1000 (OECD) since there is actual data for only one trophic level, a predicted no effect concentration (PNEC) for aquatic ecosystems of <0.1 mg/L has been determined (EC_{50}/1000).

9.1.3. Environment – risk characterisation

The risk of the release of all the imported notified chemical can be estimated by determining the aquatic risk quotient (RQ = PEC/PNEC).

Location	PEC	PNEC	Risk Quotient (RQ)
Australia-wide STPs			
Aquatic			
Ocean outfall	0.00068 mg/L	<0.1 mg/L	<0.0068
Inland River	0.0068 mg/L	<0.1 mg/L	<0.068

Since the RQ values are less than 1, the proposed use of the notified chemical is unlikely to pose an unacceptable risk to the aquatic life.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

Reformulation

Skin contact will be the main route of exposure, although eye contact is also possible. Given the molecular weight distribution of the polymer, absorption through intact skin cannot be excluded. Exposure to the notified polymer may occur during transfer of neat chemical from the 20 L pails and 200 L drums into the mixing vessel via residual or leaking chemical from hoses, fittings and/or pumps.

Mixing occurs mechanically in a closed or open system and thus exposure may occur when open

systems are used. Exposure to the chemical during manufacturing is controlled through the use of semi-automatic equipment, engineering control measures, such as sealed vessels and the use of PPE such as safety glasses, gloves, protective clothing and respirator if required. Inhalation exposure is expected to be low, given the chemical's low vapour pressure.

Exposure to the notified chemical in the reformulated product is not expected to occur during automated filling and packaging activities, however incidental exposure to small amounts of product containing up to 25% notified chemical may occur as a result of faulty plant and equipment, or damaged packaging. Maintenance personnel may also be exposed to small amounts of these products in the event of any unscheduled repairs. The use of personal protective equipment such as safety glasses, gloves, and protective clothing is sufficient to mitigate any such exposure.

Retail
Sales representatives demonstrating the products in shopping centres and other points-of sale will be dermally exposed to the notified chemical several times per day, several days per week through application of the products to potential consumers or themselves. Inadvertant ocular exposure may also occur. The notified chemical is non-volatile, however, if it is present in product applied as a mist or aerosol, inadvertent inhalation of the notified chemical may also occur.

End-Use
Intermittent, wide-dispersive use with direct handling is expected to occur among hairdressers, cosmeticians, and beauticians. According to EASE (1997) modelling of this work environment, exposure in the range of 1-5 mg/cm^2/day of products containing up to 0.5-1.2% of the notified chemical could result. Dermal exposure is expected during application of certain products and accidental ocular exposure may also occur. The notified chemical is non-volatile, however, if it is present in product applied as a mist or aerosol, inadvertent inhalation of the notified polymer may also occur.

9.2.2. Public health – exposure assessment

Personal care products containing the notified chemical at concentrations of up to 25% are for sale to the general public. Members of the public will make dermal contact and possibly accidental ocular contact with products containing the notified chemical. In most cases exposure is expected to be limited to 1-10 grams of product, 1-2 times per day. Inhalation exposure may also occur during application of a spray product containing the notified chemical. Potentially all the notified chemical will be released to the environment however no significant indirect exposure to the general population is expected.

9.2.3. Human health - effects assessment

The notified chemical has a molecular weight of 174, a high degree of water solubility, and is expected to cross biological membranes readily. A study conducted using a radio-labelled dose of the notified chemical demonstrated a high degree (31.8 % ± 7.6%) of percutaneous absorption in 12 hours. Additionally, the notified chemical was shown to increase the penetration of the stratum corneum by glycerol.

A study designed to determine the maximum concentration of the notified chemical compatible with blood from rats, dogs, and humans indicated that the notified chemical is compatible with blood at concentrations up to 10% or less in dogs and humans and up to 20% in rats.

The acute oral toxicity of the notified chemical was determined to be low in rats, with an LD50 of 6531 mg/kg bw. In an acute intravenous toxicity study using mice and rats, the 14-day LD50s for the notified chemical using both 20% and 40% aqueous solutions were greater than 5000 mg/kg (for combined sexes), with no marked difference between LD50s for the two concentrations. Females were slightly more affected, with the difference more apparent in rats. In a separate 14-day intravenous study in rats, no ocular toxicity was observed, however, severe

effects on the central nervous system were observed at the highest dose, 2000 mg/kg/day. The NOAEL was 630 mg/kg/day.

Acute dermal toxicity studies were not conducted, however on the basis of the data supplied for acute oral toxicity and acute intravenous toxicity, the notified chemical is not expected to be acutely toxic by the dermal route.

Several skin and eye irritation studies in the rabbit were provided. The studies were conducted several decades ago, however, the results indicated that the notified chemical was slightly irritant to both skin and eye of the rabbit. An additional rabbit study indicated that the notified chemical was not irritating to the skin of the external auditory canal. The notified chemical was also found to be non-irritating and non-sensitising in a human patch test.

In a 13-week repeated dose oral toxicity study in rats, the NOAEL was 375 mg/kg/day, the top dose. Only adaptive changes in the liver and kidney were observed at this dose. In a similar study in beagle dogs, the NOAEL was 100 mg/kg/day, based on signs of general toxicity, including reduced body weight gain and food consumption, liver effects and clinical chemistry changes (increased alkaline phosphatase levels and reduced red blood cell parameters) at the top dose (700 mg/kg/day).

Two developmental toxicity studies failed to produce evidence of maternal or developmental toxicity at concentrations up to 300 mg/kg bw/day in the rabbit or rat.

The notified chemical was not mutagenic in an Ames test nor clastogenic in an *in vitro* human lymphocyte chromosomal aberration test.

No treatment related effects were observed or reported in a study which tested the human oral tolerance to teeth-cleaning gels containing up to 25% of the notified chemical.

Based on the above toxicological information, the notified chemical is not determined to be hazardous in accordance with the *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 2002).

9.2.4. Occupational health and safety – risk characterisation

The notified chemical is a slight skin and eye irritant and may be absorbed through the skin. Intermittent dermal exposure to the notified chemical may occur during the reformulation of the notified chemical into personal care products and during unscheduled maintenance of automated filling lines. However as the notified chemical is of overall low toxicity, the OHS risk presented by the notified polymer during reformulation is expected to be low. However, due to the chemical's irritant properties, PPE consisting of eye protection, gloves, and protective clothing should be worn. Workers involved in the transport and storage of the notified chemical are not expected to be exposed to the notified chemical except in the event of accidental spillage.

Potential for occupational exposure occurs in professions such as hairdressing and beauty therapy, where workers may apply cosmetic products containing the notified chemical several times each working day. Dermal exposure is the main route of exposure although inadvertent ocular and inhalation exposure may also occur. However, the notified chemical is of low toxicity, and only used in small amounts, therefore the risk to these workers is considered low.

9.2.5. Public health – risk characterisation

The products containing the notified chemical will be used by the general public applying the products themselves, and also by those having products applied during professional hairdressing or cosmetic applications. The notified chemical is readily absorbed by the skin but will be used infrequently in small amounts. Despite the potential widespread use, the risk to public health is considered low due to the low toxicity nature of the notified chemical and the small amounts of product applied.

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

10.1. Hazard classification

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

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

10.2. Environmental risk assessment

The chemical is not considered to pose a risk to the environment.

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 low concern to public health when used in the intended manner.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

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

11.2. Label

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

12. RECOMMENDATIONS

CONTROL MEASURES

Occupational Health and Safety

- Employers should implement the following safe work practices to minimise occupational exposure during handling of the notified chemical.
  - Avoid skin and eye contact

- Employers should ensure that the following personal protective equipment is used by workers to minimise occupational exposure to the notified chemical as introduced:
  - Protective clothing
  - Chemically resistant gloves or gauntlets
  - Chemical goggles or safety glasses

  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.

Environment

- The following control measures should be implemented by reformulator to minimise environmental exposure during (reformulation and use) of the notified chemical:
  - Ensure all process areas and storage areas are properly bunded;
  - Storm drains should not be within processor storage areas, to avoid any of the notified chemical entering the storm drains.

Disposal

- The notified chemical should be disposed of to an approved landfill or incineration.

Emergency procedures

- Spills/release of the notified chemical should be handled by containment with absorbent material, collection and storage in sealable labelled container.

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(2) of the Act:
  - if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

No additional secondary notification conditions are stipulated.

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